Clarivate Analytics

FILE HISTORY
US 11,878,049

PATENT:	11,878,049
INVENTORS:	IYER VARSHA VENKATACHALAM PRAKASH CHANDRA AGARWAL YANG HUA
TITLE:	Mitapivat therapy and modulators of cytochrome P450
APPLICATION NO:	US16900610A
FILED:	12 JUN 2020
ISSUED:	23 JAN 2024
COMPILED:	27 MAY 2026

Agios Pharmaceuticals, Inc.
Exhibit 2001
Apotex v. Agios
IPR2026-00351
Ex. 2001-0001

11,878,049

MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

Transaction History

Date	Transaction Description
06-12-2020	PGPubs nonPub Request
06-12-2020	Claim Preliminary Amendment
06-12-2020	PTO-SB-69-Authorize EPO Access to Search Results
06-12-2020	Applicants have given acceptable permission for participating foreign
06-12-2020	Entity Status Set To Undiscounted (Initial Default Setting or Status Change)
06-12-2020	Initial Exam Team nn
06-19-2020	Electronic Review
06-19-2020	Email Notification
06-19-2020	Email Notification
06-19-2020	Application ready for PDX access by participating foreign offices
06-19-2020	Corrected Paper
06-19-2020	Filing Receipt
08-19-2020	Patent Term Adjustment - Ready for Examination
08-19-2020	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic
08-19-2020	Additional Application Filing Fees
08-19-2020	Applicant has submitted new drawings to correct Corrected Papers problems
08-24-2020	Email Notification
08-24-2020	Notice of Incomplete Reply
08-28-2020	Sent to Classification Contractor
08-28-2020	FITF set to YES - revise initial setting
08-31-2020	Email Notification
08-31-2020	Email Notification
08-31-2020	Application Is Now Complete
08-31-2020	Filing Receipt - Updated
08-31-2020	Application Is Now Complete
08-31-2020	Mail Pre-Exam Notice
09-01-2020	Electronic Review
09-29-2020	Application Dispatched from OIPE
10-21-2020	Email Notification
10-21-2020	Change in Power of Attorney (May Include Associate POA)
04-12-2021	Information Disclosure Statement (IDS) Filed
04-12-2021	Information Disclosure Statement (IDS) Filed
04-12-2021	Information Disclosure Statement (IDS) Filed
04-12-2021	Information Disclosure Statement (IDS) Filed
04-12-2021	Information Disclosure Statement (IDS) Filed
04-12-2021	Information Disclosure Statement (IDS) Filed
08-20-2021	Case Docketed to Examiner in GAU
05-14-2022	Case Docketed to Examiner in GAU
07-08-2022	Information Disclosure Statement considered
07-08-2022	Information Disclosure Statement considered
07-12-2022	Non-Final Rejection
07-18-2022	Electronic Review
07-18-2022	Email Notification
07-18-2022	Mail Non-Final Rejection
10-10-2022	Correspondence Address Change
11-18-2022	Response after Non-Final Action
11-18-2022	Request for Extension of Time - Granted
12-02-2022	Date Forwarded to Examiner
01-30-2023	Final Rejection
02-07-2023	Mail Final Rejection (PTOL - 326)
02-28-2023	Email Notification
03-08-2023	Mail Post Card

04-07-2023	Response after Final Action
04-12-2023	Date Forwarded to Examiner
04-18-2023	Interview Summary - Examiner Initiated - Telephonic
04-18-2023	Information Disclosure Statement considered
04-18-2023	Information Disclosure Statement considered
04-30-2023	Notice of Allowance Data Verification Completed
05-03-2023	Electronic Review
05-03-2023	Electronic Review
05-03-2023	Email Notification
05-03-2023	Mail Notice of Allowance
08-02-2023	Amendment after Notice of Allowance (Rule 312)
08-02-2023	Issue Fee Payment Verified
08-02-2023	Issue Fee Payment Received
08-03-2023	Pubs Case Remand to TC
08-04-2023	Request for Continued Examination (RCE)
08-04-2023	Workflow - Request for RCE - Begin
08-04-2023	Mail-Record Petition Decision of Granted to Withdraw from Issue
08-04-2023	Record Petition Decision of Granted to Withdraw from Issue
08-04-2023	Petition Entered
08-11-2023	Date Forwarded to Examiner
08-11-2023	Disposal for a RCE - CPA - R129
08-28-2023	Notice of Allowance Data Verification Completed
08-30-2023	Mail Notice of Allowance
11-29-2023	Issue Fee Payment Verified
11-29-2023	Issue Fee Payment Received
12-06-2023	Dispatch to FDC
12-06-2023	Application Is Considered Ready for Issue
01-03-2024	Issue Notification Mailed
01-04-2024	Email Notification
01-23-2024	Recordation of Patent Grant Mailed
01-23-2024	Email Notification
01-23-2024	Mail Patent eGrant Notification
01-23-2024	Patent eGrant Notification
01-23-2024	Recordation of Patent eGrant
01-23-2024	Patent Issue Date Used in PTA Calculation
02-05-2024	Post Issue Communication - Certificate of Correction
02-27-2024	Email Notification
02-27-2024	Mail Patent eCofC Notification
02-27-2024	Patent eCofC Notification
02-27-2024	Recordation of Patent eCertificate of Correction
05-18-2026	Petition Requesting Trial

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	45	F	2013-01-01
A61K	/	45	/	06	A	2013-01-01
C12Y	/	207	/	0104	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621	18 April 2023	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628	24 April 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	ONE	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20230418

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K38/45	/	38	/	45	
A61K45/06	/	45	/	06	

NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621 (Assistant Examiner)	18 April 2023 (Date)	**Total Claims Allowed:** 19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628 (Primary Examiner)	24 April 2023 (Date)	O.G. Print Claim(s) ONE	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	59	10	68	19	77										
2	60	11	69												
3	61	12	70												
4	62	13	71												
5	63	14	72												
6	64	15	73												
7	65	16	74												
8	66	17	75												
9	67	18	76												

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621	18 April 2023	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628	24 April 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	ONE	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20230418

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	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	45	F	2013-01-01
A61K	/	45	/	06	A	2013-01-01
C12Y	/	207	/	0104	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621	18 August 2023	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628	23 August 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	ONE	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20230818

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K38/45	/	38	/	45	
A61K45/06	/	45	/	06	

NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621	18 August 2023	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628	23 August 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	ONE	NONE

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	Examiner	**Art Unit**
	GEORGE W KOSTURKO	1621

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	59	10	68	19	77										
2	60	11	69												
3	61	12	70												
4	62	13	71												
5	63	14	72												
6	64	15	73												
7	65	16	74												
8	66	17	75												
9	67	18	76												

/GEORGE W KOSTURKO/ Examiner, Art Unit 1621	18 August 2023	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/THEODORE R. HOWELL/ Primary Examiner, Art Unit 1628	23 August 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	ONE	NONE

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	Art Unit
	GEORGE W KOSTURKO	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/08/2022								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	-								
	7	-								
	8	-								
	9	-								
	10	-								
	11	✓								
	12	✓								
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	15	✓								
	16	✓								
	17	✓								
	18	-								
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	20	-								
	21	-								
	22	✓								
	23	-								
	24	-								
	25	-								
	26	-								
	27	-								
	28	-								
	29	-								
	30	-								
	31	-								
	32	✓								
	33	-								
	34	✓								
	35	-								
	36	✓								
	37	✓								
	38	✓								
	39	-								
	40	-								
	41	-								
	42	-								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
	GEORGE W KOSTURKO	1628

CLAIM		DATE								
Final	Original	07/08/2022								
	43	-								
	44	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	Art Unit
	GEORGE W KOSTURKO	1628

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/4709, 31/496	07/07/2022	G.K.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E-OC SEARCH: Inventors: H. Yang, C. Prakash, V. Iyer; AG-348 /mitapivat for treating pyruvate kinase disorders; CYP3A4 metabolism of AG-348/mitapivat; combinations of CYP3A4 inhibitors with CYP3A4 inducers;	07/07/2022	G.K.
STN SEARCH HISTORY: AG-348/mitapivat for treating pyruvate kinase disorders; CYP3A4 metabolism of AG-348/mitapivat; combinations of CYP3A4 inhibitors with CYP3A4 inducers;	07/07/2022	G.K.

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/4709, 31/496	07/07/2022	G.K.

/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

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	GEORGE W KOSTURKO	1628

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Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/4709, 31/496	07/07/2022	G.K.

/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

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	Examiner	Art Unit
	GEORGE W KOSTURKO	1621

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/4709, 31/496	07/07/2022; 04/14/2023	G.K.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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Search Notes	Date	Examiner
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Interference Search			
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A61K	31/4709, 31/496	07/07/2022 ; 04/14/2023	G.K.

/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

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	Examiner	Art Unit
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/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
	GEORGE W KOSTURKO	1621

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/4709, 31/496	07/07/2022; 04/14/2023	G.K.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
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* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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STN SEARCH HISTORY: AG-348/mitapivat for treating pyruvate kinase disorders; CYP3A4 metabolism of AG-348/mitapivat; combinations of CYP3A4 inhibitors with CYP3A4 inducers;	07/07/2022 ; 01/20/2023 ; 04/14/2023	G.K.

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/4709, 31/496	07/07/2022 ; 04/14/2023	G.K.

/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/900,610	Iyer et al.
	Examiner	Art Unit
	GEORGE W KOSTURKO	1621

/GEORGE W KOSTURKO/ Examiner, Art Unit 1628	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:30 AM
L2	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L3	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L4	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT,	OR	ON	ON	2022/07/07 11:31 AM

			JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L5	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L6	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L7	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:57 PM
L8	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:58 PM
L9	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2022/07/07 01:01 PM

			JPO; DERWENT)				
L10	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:02 AM
L11	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L12	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L15	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:05 AM
L16	12	L5 AND L15	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:05 AM
L17	18	L5 AND L15	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L18	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L19	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK,	OR	ON	ON	2022/07/08 10:06 AM

Ex. 2001-0020

			TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L20	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L21	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L22	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L23	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L24	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L25	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH,	OR	ON	ON	2022/07/08 10:06 AM

		("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L26	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L27	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L28	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L29	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L30	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L31	156	(("zankel") near2 ("todd")).in.	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/11 02:01 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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 NEWS  2  NOV  9  RDISCLOSURE Reload Expands Searching Capabilities and
                  Introduces Numeric Property Searching
 NEWS  3  NOV 12  PATGENE database provides updated BLAST and GETSIM versions,
                  new searching capabilities and data quality improvements
 NEWS  4  DEC 16  Latest INPADOCDB and INPAFAMDB Enhancements Focus on Patent
                  Status Information
 NEWS  5  JAN  4  Reloaded GENESEQ database provides updated BLAST and GETSIM
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                  Life Sciences Researchers
 NEWS 10  MAR 25  New Get Prior Art Analysis Feature in CA/CAplus Provides
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 NEWS 11  MAR 25  Searching Chemical Compounds with Fragmentation Codes in
                  Derwent World Patents Index (R) Subscriber Files
 NEWS 12  MAR 30  New Projects Feature Allows STNext Users to Define and
                  Manage Search Projects
 NEWS 13  APR  4  The enhanced Derwent World Patents Index(R) is now
                  available on STNext
 NEWS 14  APR  4  The Derwent Chemistry Resource (DCR) is now available as
                  a standalone database on STNext
 NEWS 15  JUN  3  Latest Update to Emtree(R) Now Available in Embase(R)
 NEWS 16  JUN 22  CAS Customer Center Hours Expanded!
 NEWS 17  JUN 22  Claims for Four Additional Patent Authorities Added to
                  CA/CAplus
 NEWS 18  JUN 24  SMARTracker SDI Option Now Supported in Derwent Files
 NEWS 19  JUN 24  Expanded Claims Coverage and Enhanced HIT Displays of
                  Claims Data in Derwent World Patents Index(R)

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=> s (("pyruvate kinase"))

         90594 "PYRUVATE"
          1226 "PYRUVATES"
         91097 "PYRUVATE"
                 ("PYRUVATE" OR "PYRUVATES")
        912915 "KINASE"
        122970 "KINASES"
        934487 "KINASE"
                 ("KINASE" OR "KINASES")
L1       17762 (("PYRUVATE KINASE"))
                 ("PYRUVATE"(W)"KINASE")

=> s (("CYP 3A4") or ("CYP3A5") or ("CYP 3A4") or ("CYP 3A5") or ("cytochrome P450
3A4") or ("cytochrome P450 3A5"))

         19232 "CYP"
          3675 "CYPS"
         20545 "CYP"
                 ("CYP" OR "CYPS")
         12614 "3A4"
          1213 "CYP 3A4"
                 ("CYP"(W)"3A4")
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          3675 "CYPS"
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          2999 "3A5"
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        267471 "CYTOCHROME"
         21933 "CYTOCHROMES"
        271554 "CYTOCHROME"
                 ("CYTOCHROME" OR "CYTOCHROMES")
         56367 "P450"
         12614 "3A4"
          3744 "CYTOCHROME P450 3A4"
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         267471 "CYTOCHROME"
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         271554 "CYTOCHROME"
                ("CYTOCHROME" OR "CYTOCHROMES")
          56367 "P450"
           2999 "3A5"
            153 "CYTOCHROME P450 3A5"
                ("CYTOCHROME"(W)"P450"(W)"3A5")
L2         7877 (("CYP 3A4") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5") OR ("CY
               TOCHROME P450 3A4") OR ("CYTOCHROME P450 3A5"))

=> s L1 and L2

L3          10 L1 AND L2

=> display L3 1-10 ibib abs hitstr


L3   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER:         2022:1351823  CAPLUS Full-text
DOCUMENT NUMBER:          179:56776
TITLE:                    Flurochloridone induces responses of free radical
                          reactions and energy metabolism disorders to BRL-3A
                          cell
AUTHOR(S):                Xue, Liming; Xu, Jiale; Feng, Chao; Zhou, Zhijun; Jin,
                          Yu'e; Lu, Dasheng; Wang, Guoquan
CORPORATE SOURCE:         Division of Chemical Toxicity and Safety Assessment,
                          Peop. Rep. China
SOURCE:                   Ecotoxicology and Environmental Safety (2022), 239,
                          113647
                          CODEN: EESADV; ISSN: 0147-6513
DIGITAL OBJECT ID:        10.1016/j.ecoenv.2022.113647
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal; (online computer file)
LANGUAGE:                 English
AB   Flurochloridone (FLC), a wildly used herbicide, could induce
     hepatotoxicity after long-term exposure to male rat, in addn. to its
     reactive oxygen species (ROS)-dependent reproductive toxicity.  The
     hepatotoxicity effect and mechanism was investigeted using 1, 10 and
     100μmol L-1 FLC treated BRL-3A liver cell in this study.  The function
     of mitochondrial respiration, glycolysis rate and real time ATP prodn.
     rate are detd. by seahorse XF analyzer, and the bio-transformers of FLC,
     intermediates of TCA cycle and glycolysis, and related amino acids are
     detd. and identified by [U-13C] Glucose metabolic flux technol. based on
     UPLC-HRMS.  The mRNA expression of cytochrome P450s and the key regulatory
     enzymes of glucose metab. and γ- glutamyl cycle pathway.  The
     protein expressions of protein kinase B (AKT) and glycogen synthase
     kinase-3 beta (GSK-3β) were detd.  The results show dechlorination
     and glutathione (GSH) conjugate products of FLC are predominant
     bio-transformmers after 24 h treatment in BRL-3A cell.  FLC could enhance
     glycolysis function and inhibit mitochondrial aerobic respiratory, which
     is accompanied by the decreased total ATP level and ATP produced rate.
     Increased glucose-6-phosphate, fructose-6-phosphate, pyruvate and lactate
     levels, and elevated level of GSH and its precursor 5-glutamate-cysteine
     (γ-Glu-Cys) are obsd. in FLC treated cells, which indicates that
     energy metab. dysfunction and GSH accumulation could be potentially
     mediated by activating γ- Glutamyl cycle pathway.  Conclusively, FLC
     induced hepatotoxicity could be potentially related to some free radical
     reactions, including inhibiting mitochondrial function, glucose metab. via
     glycolysis, regulating γ- glutamyl cycle pathway to promote reactive
     oxygen species (ROS) level, and then induced cell apoptosis by inhibiting
     AKT/GSK-3β signal.
REFERENCE COUNT:          37    THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
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L3   ANSWER 2 OF 10  CAPLUS  COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER:         2019:1939154  CAPLUS Full-text
DOCUMENT NUMBER:          175:475992
TITLE:                    Integration of metabolomic and transcriptomic
                          profiling to compare two protocols of differentiation
```

of human induced pluripotent stem cells into hepatocytes

AUTHOR(S): Jellali, Rachid; Poulain, Stephane; Bernier, Myriam Lereau; Gilard, Francoise; Tauran, Yannick; Kato, Sachi; Danoy, Mathieu; Segard, Bertrand David; Kido, Taketomo; Miyajima, Atsushi; Plessy, Charles; Sakai, Yasuyuki; Leclerc, Eric

CORPORATE SOURCE: Laboratoire de Biomecanique et Bioingenierie, Sorbonne universites, Universite de Technologies de Compiegne, CNRS UMR 7338, Fr.

SOURCE: Process Biochemistry (Oxford, United Kingdom) (2020), 88, 138-147
CODEN: PBCHE5; ISSN: 1359-5113
DIGITAL OBJECT ID: 10.1016/j.procbio.2019.09.034
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Human hepatocyte-like cells derived from human induced pluripotent stem cells (hiPSC) may provide an unlimited supply of cells for in vitro liver models. However, hiPSC differentiation remains a major challenge due to immaturity of the hepatocytes obtained and the high cost of differentiation protocols currently proposed. Here, we studied the efficacy of new protocol, with redn. of growth factors, for the generation of hepatocyte-like cells from hiPSC. We performed metabolomic and mRNA anal. by RTqPCR and nanoCAGE processing to identify and understand key metabs. during differentiation. By reducing the change frequency of the culture medium in the new protocol, we successfully generated hepatocyte-like cells producing albumin, urea, and CYP3A4 pos. The metabolomic anal. successfully extd. both signatures, common and specific, for each differentiation step. Integrating the metabolomic data with transcriptomic contributed to explaining the kinetics of carbohydrate, lipid and nitrogen metab. throughout differentiation. The information extd. during differentiation showed that the cells moved from an aerobic-like respiration pattern to a mitochondrial oxidative respiration pattern in both protocols. Reducing culture medium renewal led to reduced glucose consumption, followed by fructose prodn. and significant extracellular lipogenesis throughout differentiation. We believe that the overall dataset can provide information on the sequence of process.

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L3 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2019:335335 CAPLUS Full-text
DOCUMENT NUMBER: 172:209640

TITLE: Generation of insulin-producing hepatocyte-like cells from human Wharton's jelly mesenchymal stem cells as an alternative source of islet cells

AUTHOR(S): Beikmohammadi, Leila; Bandehpour, Mojgan; Hashemi, Seyed Mahmoud; Kazemi, Bahram

CORPORATE SOURCE: Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

SOURCE: Journal of Cellular Physiology (2019), 234(10), 17326-17336
CODEN: JCLLAX; ISSN: 0021-9541
DIGITAL OBJECT ID: 10.1002/jcp.28352
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Islet cell transplantation, as a treatment of type 1 diabetes, has a lot of complexity such as allograft rejections and an insufficient no. of donors. The liver can be used as a replacement for endogenous insulin prodn. Hepatocytes can inherently respond to glucose levels and secrete proteins. Utilization of mesenchymal stem cells for curing diabetes represents a major focus of recent investigations. As a new choice for transplantation, we have proposed glucose-regulated insulin-producing hepatocyte-like cells, which produce insulin dependent on glucose levels. We have transfected human Wharton's jelly mesenchymal stem cells with the special construct, which included homol. arms and glucose-responsive

elements upstream of the min. liver-type pyruvate kinase promoter-directed insulin gene. Then, we have differentiated these transfected cells to hepatocyte-like cells by using serial exposure of different inducing material and exogenous growth factors. Immunofluorescence analyses have demonstrated the expression of albumin, cytokeratin-18, Hep-Par1, α-fetoprotein, and insulin. The expression of hepatocyte marker genes in the differentiated cells was confirmed by reverse-transcription polymerase chain reaction. Interestingly, flow cytometry results showed that approx. 60% of the insulin-producing hepatocyte-like cells were simultaneously cytochrome P 450 3A4 (CYP3A4) and insulin pos. CYP3A4 is a significant enzyme found in mature liver tissue. This confirmed that the differentiation and the transfection procedures were done correctly. They were functionally active by releasing insulin in response to elevated glucose concns. in vitro. These applicable cells could be used in the liver for cell therapy of diabetes.

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L3 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2019:59789 CAPLUS Full-text
DOCUMENT NUMBER: 171:405724
TITLE: Targeting a phospho-STAT3-miRNAs pathway improves vesicular hepatic steatosis in an in vitro and in vivo model
AUTHOR(S): Belloni, Laura; Di Cocco, Silvia; Guerrieri, Francesca; Nunn, Abigail D. G.; Piconese, Silvia; Salerno, Debora; Testoni, Barbara; Pulito, Claudio; Mori, Federica; Pallocca, Matteo; Sacconi, Andrea; Vivoli, Elisa; Marra, Fabio; Strano, Sabrina; Blandino, Giovanni; Levrero, Massimo; Pediconi, Natalia
CORPORATE SOURCE: Center for Life Nano, Rome, Italy
SOURCE: Scientific Reports (2018), 8(1), 1-12
CODEN: SRCEC3; ISSN: 2045-2322
DIGITAL OBJECT ID: 10.1038/s41598-018-31835-2
PUBLISHER: Nature Research
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Non-alc. fatty liver disease (NAFLD) is a leading cause of chronic liver disease. Although genetic predisposition and epigenetic factors contribute to the development of NAFLD, our understanding of the mol. mechanism involved in the pathogenesis of the disease is still emerging. Here we investigated a possible role of a microRNAs-STAT3 pathway in the induction of hepatic steatosis. Differentiated HepaRG cells treated with the fatty acid sodium oleate (fatty dHepaRG) recapitulated features of liver vesicular steatosis and activated a cell-autonomous inflammatory response, inducing STAT3-Tyrosine-phosphorylation. With a genome-wide approach (Chromatin Immunopptn. Sequencing), many phospho-STAT3 binding sites were identified in fatty dHepaRG cells and several STAT3 and/or NAFLD-regulated microRNAs showed increased expression levels, including miR-21. Innovative CARS (Coherent Anti-Stokes Raman Scattering) microscopy revealed that chem. inhibition of STAT3 activity decreased lipid accumulation and deregulated STAT3-responsive microRNAs, including miR-21, in lipid overloaded dHepaRG cells. We were able to show in vivo that reducing phospho-STAT3-miR-21 levels in C57/BL6 mice liver, by long-term treatment with metformin, protected mice from aging-dependent hepatic vesicular steatosis. Our results identified a microRNAs-phosphoSTAT3 pathway involved in the development of hepatic steatosis, which may represent a mol. marker for both diagnosis and therapeutic targeting.

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L3 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2018:1014808 CAPLUS Full-text

DOCUMENT NUMBER: 170:545474
TITLE: Immortalized common marmoset (Callithrix jacchus) hepatic progenitor cells possess bipotentiality in vitro and in vivo
AUTHOR(S): Guo, Zhenglong; Jing, Renwei; Rao, Quan; Zhang, Ludi; Gao, Yimeng; Liu, Fengyong; Wang, Xin; Hui, Lijian; Yin, Hai Fang
CORPORATE SOURCE: Department of Cell Biology, Tianjin Medical University, Tianjin, 300070, Peop. Rep. China
SOURCE: Cell Discovery (2018), 4(1), 1-14
CODEN: CDEIBM; ISSN: 2056-5968
DIGITAL OBJECT ID: 10.1038/s41421-018-0020-7
PUBLISHER: Nature Research
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Common marmoset (Callithrix jacchus) is emerging as a clin. relevant nonhuman primate model for various diseases, but is hindered by the availability of marmoset cell lines, which are crit. for understanding the disease pathogenesis and drug/toxicol. screening prior to animal testing. Here we describe the generation of immortalized marmoset hepatic progenitor cells (MHPCs) by lentivirus-mediated transfer of the simian virus 40 large T antigen gene in fetal liver polygonal cells. MHPCs proliferate indefinitely in vitro without chromosomal alteration and telomere shortening. These cells possess hepatic progenitor cell-specific gene expression profiles with potential to differentiate into both hepatocytic and cholangiocytic lineages in vitro and in vivo and also can be genetically modified. Importantly, injected MHPCs repopulated the injured liver of fumarylacetoacetate hydrolase (Fah)-deficient mice with hepatocyte-like cells. MHPCs also engraft as cholangiocytes into bile ducts of 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced bile ductular injured mice. MHPCs provide a tool to enable efficient derivation and genetic modification of both hepatocytes and cholangiocytes for use in disease modeling, tissue engineering, and drug screening.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2017:1393495 CAPLUS Full-text
DOCUMENT NUMBER: 172:88601
TITLE: Evidence-based prioritisation and enrichment of genes interacting with metformin in type 2 diabetes
AUTHOR(S): Dawed, Adem Y.; Ali, Ashfaq; Zhou, Kaixin; Pearson, Ewan R.; Franks, Paul W.
CORPORATE SOURCE: Division of Molecular and Clinical Medicine, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
SOURCE: Diabetologia (2017), 60(11), 2231-2239
CODEN: DBTGAJ; ISSN: 0012-186X
DIGITAL OBJECT ID: 10.1007/s00125-017-4404-2
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Aims/hypothesis: There is an extensive body of literature suggesting the involvement of multiple loci in regulating the action of metformin; most findings lack replication, without which distinguishing true-pos. from false-pos. findings is difficult. To address this, we undertook evidence-based, multiple data integration to det. the validity of published evidence. Methods: We (1) built a database of published data on gene-metformin interactions using an automated text-mining approach (n = 5963 publications), (2) generated evidence scores for each reported locus, (3) from which a rank-ordered gene set was generated, and (4) detd. the extent to which this gene set was enriched for glycemic response through replication analyses in a well-powered independent genome-wide assocn. study (GWAS) dataset from the Genetics of Diabetes and Audit Research Tayside Study (GoDARTS). Results: From the literature search, seven genes were identified that are related to the clin. outcomes of metformin. Fifteen genes were linked with either metformin pharmacokinetics or pharmacodynamics, and the expression profiles of a further 51 genes were found to be responsive to metformin. Gene-set enrichment anal. consisting

of the three sets and two more composite sets derived from the above three showed no significant enrichment in four of the gene sets. However, we detected significant enrichment of genes in the least prioritised category (a gene set in which their expression is affected by metformin) with glycemic response to metformin (p = 0.03). This gene set includes novel candidate genes such as SLC2A4 (p = 3.24 × 10-04) and G6PC (p = 4.77 × 10-04). Conclusions/interpretation: We have described a semi-automated text-mining and evidence-scoring algorithm that facilitates the organization and extn. of useful information about gene-drug interactions. We further validated the output of this algorithm in a drug-response GWAS dataset, providing novel candidate loci for gene-metformin interactions.

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REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2016:1003559 CAPLUS Full-text

DOCUMENT NUMBER: 169:301153

TITLE: Bisphenol a induces steatosis in HepaRG cells using a model of perinatal exposure

AUTHOR(S): Bucher, Simon; Jalili, Pegah; Le Guillou, Dounia; Begriche, Karima; Rondel, Karine; Martinais, Sophie; Zalko, Daniel; Corlu, Anne; Robin, Marie-Anne; Fromenty, Bernard

CORPORATE SOURCE: INSERM, UMR991, Universite De Rennes 1, Rennes, Fr.

SOURCE: Environmental Toxicology (2017), 32(3), 1024-1036 CODEN: ETOXFH; ISSN: 1520-4081

DIGITAL OBJECT ID: 10.1002/tox.22301

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Human exposure to bisphenol A (BPA) could favor obesity and related metabolic disorders such as hepatic steatosis. Investigations in rodents have shown that these deleterious effects are obsd. not only when BPA is administered during the adult life but also with different protocols of perinatal exposure. Whether perinatal BPA exposure could pose a risk in human is currently unknown, and thus appropriate in vitro models could be important to tackle this major issue. Accordingly, we detd. whether long-term BPA treatment could induce steatosis in human HepaRG cells by using a protocol mimicking perinatal exposure. To this end, the kinetics of expression of seven proteins differentially expressed during liver development was detd. during a 4-wk period of cell culture required for proliferation and differentiation. By analogy with data reported in rodents and humans, our results indicated that the period of cell culture around day 15 and day 18 after seeding could be considered as the "natal" period. Consequently, HepaRG cells were treated for 3 wk with BPA (from 0.2 to 2000 nM), with a treatment starting during the proliferating period. BPA was able to induce steatosis with a nonmonotonic dose response profile, with significant effects on neutral lipids and triglycerides obsd. for the 2 nM concn. However, the expression of many enzymes involved in lipid and carbohydrate homeostasis was unchanged in exposed HepaRG cells. The expression of other potential BPA targets and enzymes involved in BPA biotransformation was also detd., giving answers as well as new questions regarding the mechanisms of action of BPA. Hence, HepaRG cells provide a valuable model that can prove useful for the toxicol. assessment of endocrine disruptors on hepatic metabs., in particular in the developing liver.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2010:1412381 CAPLUS Full-text

DOCUMENT NUMBER: 154:352

TITLE: Compound Set Enrichment: A Novel Approach to Analysis of Primary HTS Data

AUTHOR(S): Varin, Thibault; Gubler, Hanspeter; Parker, Christian

N.; Zhang, Ji-Hu; Raman, Pichai; Ertl, Peter; Schuffenhauer, Ansgar
CORPORATE SOURCE: Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, CH-4056, Switz.
SOURCE: Journal of Chemical Information and Modeling (2010), 50(12), 2067-2078
CODEN: JCISD8; ISSN: 1549-9596
DIGITAL OBJECT ID: 10.1021/ci100203e
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The main goal of high-throughput screening (HTS) is to identify active chem. series rather than just individual active compds. In light of this goal, a new method (called compd. set enrichment) to identify active chem. series from primary screening data is proposed. The method employs the scaffold tree compd. classification in conjunction with the Kolmogorov-Smirnov statistic to assess the overall activity of a compd. scaffold. The application of this method to seven PubChem data sets (contg. between 9389 and 263679 mols.) is presented, and the ability of this method to identify compd. classes with only weakly active compds. (potentially latent hits) is demonstrated. The anal. presented here shows how methods based on an activity cutoff can distort activity information, leading to the incorrect activity assignment of compd. series. These results suggest that this method might have utility in the rational selection of active classes of compds. (and not just individual active compds.) for followup and validation.

OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2005:1130810 CAPLUS Full-text
DOCUMENT NUMBER: 143:403951
TITLE: Gene expression profiling for diagnosis and treatment of leiomyoma, endometriosis, ovarian hyperstimulation syndrome, adhesions, endometrial cancer and other fibrotic disorders
INVENTOR(S): Chegini, Nasser; Luo, Xiaoping; Ding, Li; Williams, R. Stan
PATENT ASSIGNEE(S): University of Florida Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005098041	A2	20051020	WO 2005-US10257		20050328
WO 2005098041	A3	20060601			
US 20080300147	A1	20081204	US 2007-590675		20071018
PRIORITY APPLN. INFO.:			US 2004-60556546	P	20040326
			US 2004-60620444	P	20041019
			US 2004-60636240	P	20041215
			WO 2005-US10257	W	20050328

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2005098041	A2	Dead	20201201
WO 2005098041	A3	Dead	20201201
US 20080300147	A1	Dead	20201120

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention provides a method for detecting a fibrotic disorder in a subject by providing a biol. sample obtained from the subject such as endometrium, peritoneal fluid, and/or smooth muscle cells and analyzing the expression of at least one gene that is differentially expressed in the fibrotic disorder of interest and correlating the expression of the genes with the presence or absence of the fibrotic disorder in the subject. The present invention also provides a method and compns. for modulating the expression of genes that are differentially expressed in

fibrotic tissues, compared to normal tissues. The present invention also includes arrays, such as microfluidic cards, for detecting differential gene expression in samples of fibrotic tissue. Diseases of the invention include leiomyoma, endometriosis, ovarian hyperstimulation syndrome, adhesions, endometrial cancer and other fibrotic disorders.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L3 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2003:97550 CAPLUS Full-text

DOCUMENT NUMBER: 138:164674

TITLE: Molecular markers for hepatocellular carcinoma and their use in diagnosis and therapy

INVENTOR(S): Debuschewitz, Sabine; Jobst, Juergen; Kaiser, Stephan

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010336	A2	20030206	WO 2002-EP8305	20020725
WO 2003010336	A3	20041229		
DE 10136273	A1	20030213	DE 2001-10136273	20010725
AU 2002333275	A1	20030217	AU 2002-333275	20020725
EP 1507871	A2	20050223	EP 2002-790191	20020725
WO 2004011945	A2	20040205	WO 2003-EP8243	20030725
WO 2004011945	A3	20040603		
AU 2003253329	A1	20040216	AU 2003-253329	20030725
EP 1525477	A2	20050427	EP 2003-771105	20030725

PRIORITY APPLN. INFO.:

DE 2001-10136273	A	20010725
WO 2002-EP8305	W	20020725
WO 2003-EP8243	W	20030725

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2003010336	A2	Dead	20201202
WO 2003010336	A3	Dead	20201202
DE 10136273	A1	Dead	20201121
EP 1507871	A2	Dead	20201202
WO 2004011945	A2	Dead	20201201
WO 2004011945	A3	Dead	20201201
AU 2003253329	A1	Dead	20201120
EP 1525477	A2	Dead	20201201

AB The invention relates to mol. markers occurring for hepatocellular carcinoma. The invention more particularly comprises gene sequences or peptides coded thereby which can be regulated upwards or downwards for hepatic cell carcinoma (HCC) in relation to healthy, normal liver cells in the expression thereof. The invention also relates to the use of said sequences in the diagnosis and/or therapy of HCC and for screening purposes in order to identify novel active ingredients for HCC. The invention also relates to an HCC specific cluster as a unique diagnostic agent for HCC.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

=> s (("phenobarbital") or ("enzalutamide") or ("carbamazepine"))

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         26240 "PHENOBARBITAL"
            26 "PHENOBARBITALS"
         26243 "PHENOBARBITAL"
                 ("PHENOBARBITAL" OR "PHENOBARBITALS")
          2462 "ENZALUTAMIDE"
         19328 "CARBAMAZEPINE"
            11 "CARBAMAZEPINES"
         19329 "CARBAMAZEPINE"
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                ("CARBAMAZEPINE" OR "CARBAMAZEPINES")
L4       45014 (("PHENOBARBITAL") OR ("ENZALUTAMIDE") OR ("CARBAMAZEPINE"))

=> s (("ketoconazole") or ("itraconazole") or ("ritonavir") or ("bocenavir") or ("v
oriconazole") or ("clarithromycin"))

         12321 "KETOCONAZOLE"
             7 "KETOCONAZOLES"
         12322 "KETOCONAZOLE"
                ("KETOCONAZOLE" OR "KETOCONAZOLES")
         10688 "ITRACONAZOLE"
             1 "ITRACONAZOLES"
         10688 "ITRACONAZOLE"
                ("ITRACONAZOLE" OR "ITRACONAZOLES")
         11229 "RITONAVIR"
             0 "BOCENAVIR"
          7284 "VORICONAZOLE"
             1 "VORICONAZOLES"
          7284 "VORICONAZOLE"
                ("VORICONAZOLE" OR "VORICONAZOLES")
         14316 "CLARITHROMYCIN"
             2 "CLARITHROMYCINS"
         14316 "CLARITHROMYCIN"
                ("CLARITHROMYCIN" OR "CLARITHROMYCINS")
L5       47838 (("KETOCONAZOLE") OR ("ITRACONAZOLE") OR ("RITONAVIR") OR ("BOCE
               NAVIR") OR ("VORICONAZOLE") OR ("CLARITHROMYCIN"))

=> s L1 and L4

L6           26 L1 AND L4

=> s L1 and L5

L7           11 L1 AND L5

=> s L6 or L7

L8           34 L6 OR L7

=> display L8 1-34 ibib abs hitstr


L8   ANSWER 1 OF 34  CAPLUS  COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER:        2022:1213351  CAPLUS Full-text
TITLE:                   Carbamazepine-modified HLA-A*24:02-bound peptidome:
                         Implication of CORO1A in skin rash
AUTHOR(S):               Min, Fuli; Fan, Cuixia; Zeng, Yuanjin; He, Na; Zeng,
                         Tao; Qin, Bing; Shi, Yiwu
CORPORATE SOURCE:        Department of Neurology, Guangzhou First People's
                         Hospital, School of Medicine, South China University
                         of Technology, Guangzhou, 510180, Peop. Rep. China
SOURCE:                  International Immunopharmacology (2022), 109, 108804
                         CODEN: IINMBA; ISSN: 1567-5769
DIGITAL OBJECT ID:       10.1016/j.intimp.2022.108804
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; (online computer file)
LANGUAGE:                English
AB   Previous studies have demonstrated that human leukocyte antigen
     (HLA)-A*24:02 is a common genetic risk factor for antiepileptic
     drug-induced skin rash, while HLA-B*15:02 is a specific risk factor for
     carbamazepine (CBZ)-induced Stevens Johnson syndrome and toxin epidermal
     necrolysis.  The HLA-B*15:02 allele can alter the repertoire of endogenous
     peptides to trigger CBZ-induced hypersensitivity.  However, it is
     uncertain whether HLA-A*24:02 could produce alterations in the peptide
     repertoire during treatment with antiepileptic drugs.We generated stable
     HMy2.  C1R cells expressing HLA-A*24:02 and HLA-B*15:02, clarified into 4
     groups according to with or without CBZ treatment.  We employed LC/MSto
     detect the HLA-bound peptides in 4 groups.  Furthermore, we conducted in
     silico anal. to seek th differential expressed genes (DEGs) assocd. with
     HLA-A*24:02 and HLA-B*15:02.  Finally, we verify the DEGs via qRT-PCR and
     Western blotting.  A total of 134 peptides were identified from the four
     groups, mainly comprising<15 mer peptides.  In CBZ-treated groups, 29 and
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30 peptides showed significantly increased resp. in HLA-A*24:02 and HLA-B*15:02 pos. cells comprising Lysine in PΩ, but the sources of these lysine peptides are different. Three peptides were exclusively detected in the HLA-A*24:02 pos. cells treated with CBZ, of which SRQVVRSSK was derived from the immune assocd. protein coronin 1A (CORO1A). CORO1A and its mRNA were significantly expressed in HLA-A*24:02 pos. cells treated with CBZ. Addnl., this significantly high expression was identified in HLA-A*24:02 pos. cells that were treated with lamotrigine (LTG). Nonetheless, CORO1A were not decreased in HLA-B*15:02 pos. cells with or without CBZ or LTG treatment. These findings confirmed that the alteration in the endogenous peptidome was a general mechanism of HLA-linked skin rashes and suggests that CORO1A is involved in HLA-A*24:02-assocd. skin rash.

IT INDEXING IN PROGRESS

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2022:688840 CAPLUS Full-text

TITLE: Reprogramming hormone-sensitive prostate cancer to a lethal neuroendocrine cancer lineage by mitochondrial pyruvate carrier (MPC)

AUTHOR(S): Xu, Huan; Liu, Zhixiao; Gao, Dajun; Li, Peizhang; Shen, Yanting; Sun, Yi; Xu, Lingfan; Song, Nan; Wang, Yue; Zhan, Ming; Gao, Xu; Wang, Zhong

CORPORATE SOURCE: Department of Urology, Shanghai Ninth People's Hospital, Shanghai, Peop. Rep. China

SOURCE: Molecular Metabolism (2022), 59, 101466
CODEN: MMOEAS; ISSN: 2212-8778

DIGITAL OBJECT ID: 10.1016/j.molmet.2022.101466

PUBLISHER: Elsevier GmbH

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Cell lineage reprogramming is the main approach for cancer cells to acquire drug resistance and escape targeted therapy. The use of potent targeted therapies in cancers has led to the development of highly aggressive carcinoma, including neuroendocrine prostate cancer (NEPC). Although metabolic reprogramming has been reported to be essential for tumor growth and energy prodn., the relationship between metabolic reprogramming and lineage differentiation which can cause hormone therapy resistance has never been reported in prostate cancer (PCa). Moreover, as there is still no efficient therapy for NEPC, it is urgent to reverse this lineage differentiation during the hormone therapy. Here for the first time, we used in vitro and in vivo human PCa models to study the effect of metabolic reprogramming on the lineage differentiation from the androgen receptor (AR)-dependent adenocarcinoma to AR-independent NEPC. This lineage differentiation leads to antiandrogen drug resistance and tumor development. This phenotype is enabled by the loss of mitochondrial pyruvate carrier (MPC), the gate for mitochondrial pyruvate influx, and can be reversed by MPC overexpression. Morphol. and cellular studies also demonstrate that the pyruvate kinase M2 (PKM2) involved epithelium-mesenchymal transition process mediated this lineage alteration. Its inhibition is a potential treatment for MPC-lo tumors. All of these results suggest that metabolic rewiring can act as a starter for increased cellular plasticity which leads to antiandrogen therapy resistance through lineage differentiation. This study provides us with a potent treatment target for therapy-induced, enzalutamide-resistant NE-like prostate cancer.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2020:1930636 CAPLUS Full-text

TITLE: Metabolic Enzymes: New Targets for the Design of Antitumor Drugs

AUTHOR(S): Braun, L. A.; Varpetyan, E. E.; Zav'yalov, G. A.; Kulikov, F. V.; Marievskii, V. E.; Tyul'ganova, D. A.; Shishnenko, A. O.; Stepanova, D. S.; Shimanovskii, N. L.

CORPORATE SOURCE: N. I. Pirogov Russian National Research Medical

University (Pirogov Medical University), Moscow, 117997, Russia
SOURCE: Pharmaceutical Chemistry Journal (2020), 54(6), 547-554
CODEN: PCJOAU; ISSN: 0091-150X
DIGITAL OBJECT ID: 10.1007/s11094-020-02238-3
PUBLISHER: Springer
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. The awareness of malignant metab. transformations has recently emerged. Since Otto Warburg found that tumor cells prefer glycolysis to oxidative phosphorylation even in the presence of oxygen, studies have shown that cancer cells also depend on upregulated fatty-acid synthesis and glutaminolysis. The present review covers the key metabolic enzymes known as metabolic oncogenes and suggests ways of modulating their activity. It is concluded that metabolic transformations during carcinogenesis present opportunities for targeted action on neoplasms and provide a new field for antitumor drug development.
IT INDEXING IN PROGRESS
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2018:1694653 CAPLUS Full-text
DOCUMENT NUMBER: 173:300835
TITLE: Environmentally relevant concentrations of carbamazepine induce liver histopathological changes and a gender-specific response in hepatic proteome of Chinese rare minnows (Gobiocypris rarus)
AUTHOR(S): Yan, Saihong; Wang, Miao; Liang, Xuefang; Martyniuk, Christopher J.; Zha, Jinmiao; Wang, Zijian
CORPORATE SOURCE: Key Laboratory of Drinking Water Science and Technology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing, 100085, Peop. Rep. China
SOURCE: Environmental Pollution (Oxford, United Kingdom) (2018), 243(Part_A), 480-491
CODEN: ENPOEK; ISSN: 0269-7491
DIGITAL OBJECT ID: 10.1016/j.envpol.2018.09.009
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB To assess hepatotoxicity and to det. the underlying mechanisms of carbamazepine (CBZ) toxicity in fish, histopathol. and the liver proteome were examd. after Chinese rare minnow (Gobiocypris rarus) were exposed to 1, 10, and 100μg/L CBZ for 28 days. Histopathol. changes included disruption of spatial structure, pyknotic nuclei, cellular vacuolization and deformation of cell nuclei, in addn. to marked swelling of hepatocytes in all treatment groups. Protein anal. revealed that there were gender-specific responses in rare minnow following exposure, and there were 47 proteins in females and 22 proteins in males identified as differentially abundant following CBZ treatments. Pathway anal. revealed that cellular processes affected by CBZ included apoptosis, cell differentiation, cell proliferation, and the respiratory chain, indicating impaired energy homeostasis. Noteworthy was that 15 proteins identified as different in abundance were assocd. with carcinogenicity. Relative mRNA levels for select transcripts were consistent with the changes of proteins N-myc downstream regulated gene (NDRG), Tropomyosin 2-Beta (TPM2) and annexin A4 (ANXA4). Protein pyruvate kinase, liver and RBC (PKLR) were increased at 1 and 100μg/L CBZ without significant difference in transcript levels. These findings characterize mol. responses and histol. changes in the liver that generate new insights into CBZ hepatotoxicity in Chinese rare minnow.
OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2018:1434336 CAPLUS Full-text

DOCUMENT NUMBER: 170:423340
TITLE: KDM8/JMJD5 as a dual coactivator of AR and PKM2 integrates AR/EZH2 network and tumor metabolism in CRPC
AUTHOR(S): Wang, Hung-Jung; Pochampalli, Mamata; Wang, Ling-Yu; Zou, June X.; Li, Pei-Shan; Hsu, Sheng-Chieh; Wang, Bi-Juan; Huang, Shih-Han; Yang, Ping; Yang, Joy C.; Chu, Cheng-Ying; Hsieh, Chia-Ling; Sung, Shian-Ying; Li, Chien-Feng; Tepper, Clifford G.; Ann, David K.; Gao, Allen C.; Evans, Christopher P.; Izumiya, Yoshihiro; Chuu, Chi-Pin; Wang, Wen-Ching; Chen, Hong-Wu; Kung, Hsing-Jien
CORPORATE SOURCE: Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli County, 35053, Taiwan
SOURCE: Oncogene (2019), 38(1), 17-32
CODEN: ONCNES; ISSN: 0950-9232
DIGITAL OBJECT ID: 10.1038/s41388-018-0414-x
PUBLISHER: Nature Research
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB During the evolution into castration or therapy resistance, prostate cancer cells reprogram the androgen responses to cope with the diminishing level of androgens, and undergo metabolic adaptation to the nutritionally deprived and hypoxia conditions. AR (androgen receptor) and PKM2 (pyruvate kinase M2) have key roles in these processes. We report in this study, KDM8/JMJD5, a histone lysine demethylase/dioxygnase, exhibits a novel property as a dual coactivator of AR and PKM2 and as such, it is a potent inducer of castration and therapy resistance. Previously, we showed that KDM8 is involved in the regulation of cell cycle and tumor metab. in breast cancer cells. Its role in prostate cancer has not been explored. Here, we show that KDM8's oncogenic properties in prostate cancer come from its direct interaction (1) with AR to affect androgen response and (2) with PKM2 to regulate tumor metab. The interaction with AR leads to the elevated expression of androgen response genes in androgen-deprived conditions. They include ANCCA/ATAD2 and EZH2, which are directly targeted by KDM8 and involved in sustaining the survival of the cells under hormone-deprived conditions. Notably, in enzalutamide-resistant cells, the expressions of both KDM8 and EZH2 are further elevated, so are neuroendocrine markers. Consequently, EZH2 inhibitors or KDM8 knockdown both resensitize the cells toward enzalutamide. In the cytosol, KDM8 assocs. with PKM2, the gatekeeper of pyruvate flux and translocates PKM2 into the nucleus, where the KDM8/PKM2 complex serves as a coactivator of HIF-1α to upregulate glycolytic genes. Using shRNA knockdown, we validate KDM8's functions as a regulator for both androgen-responsive and metabolic genes. KDM8 thus presents itself as an ideal therapeutic target for metabolic adaptation and castration-resistance of prostate cancer cells.
OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2016:307813 CAPLUS Full-text
DOCUMENT NUMBER: 166:405370
TITLE: Identifying Putative Drug Targets and Potential Drug Leads: Starting Points for Virtual Screening and Docking
AUTHOR(S): Wishart, David S.
CORPORATE SOURCE: The National Institute of Nanotechnology (NINT), National Research Council, Edmonton, AB, T6G 2E8, Can.
SOURCE: Methods in Molecular Biology (New York, NY, United States) (2015), 1215(Molecular Modeling of Proteins), 425-444
CODEN: MMBIED; ISSN: 1940-6029
DIGITAL OBJECT ID: 10.1007/978-1-4939-1465-4_19
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The availability of 3D models of both drug leads (small mol. ligands) and

drug targets (proteins) is essential to mol. docking and computational drug discovery. This chapter describes a simple approach that can be used to identify both drug leads and drug targets using two popular Web-accessible databases: (1) DrugBank and (2) The Human Metabolome Database. First, it is illustrated how putative drug targets and drug leads for exogenous diseases (i.e., infectious diseases) can be readily identified and their 3D structures selected using only the genomic sequences from pathogenic bacteria or viruses as input. The second part illustrates how putative drug targets and drug leads for endogenous diseases (i.e., noninfectious diseases or chronic conditions) can be identified using similar databases and similar sequence input. This chapter is intended to illustrate how bioinformatics and cheminformatics can work synergistically to help provide the necessary inputs for computer-aided drug design.

L8 ANSWER 7 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2015:1539854 CAPLUS Full-text
DOCUMENT NUMBER: 163:469534
TITLE: Enhanced all-trans retinoic acid (ATRA)-compounds derived from structure-activity relationships and modeling for inhibiting Pin1 and therapeutic uses thereof
INVENTOR(S): Lu, Kun Ping; Zhou, Xiao Zhen; Wei, Shuo
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, Inc., USA
SOURCE: PCT Int. Appl., 237pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2015143190	A1	20150924	WO 2015-US21522		20150319
US 20170112792	A1	20170427	US 2016-15126714		20160916
PRIORITY APPLN. INFO.:			US 2014-61968862	P	20140321
			US 2015-62177419	P	20150312
			WO 2015-US21522	W	20150319

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015143190	A1	Dead	20201201
US 20170112792	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2015:1539854
AB The invention features all-trans retinoic acid (ATRA)-related compds. capable of assocg. with Pin1 and methods of identifying the same. The invention also provides methods of treating a condition selected from the group consisting of a proliferative disorder, an autoimmune disease, and an addiction condition characterized by elevated Pin1 marker levels, Pin1 degrdn., and/or reduced Pin1 Ser71 phosphorylation in a subject by administering a retinoic acid compd. Addnl., the invention features methods of treating proliferative disorders, autoimmune diseases, and addiction conditions (e.g., diseases, disorders, and conditions characterized by elevated Pin1 marker levels) by administering a retinoic acid compd. in combination with another therapeutic compd. The invention also features a co-crystal including Pin1 and a retinoic acid compd. Finally, the invention also provides methods of developing and identifying enhanced Pin1 -targeted ATRA-related compds. based on the newly defined unique binding pockets in the Pin1 active site revealed from the co-crystal structure, structure-activity relationship, and structural modeling.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:1189036 CAPLUS Full-text
DOCUMENT NUMBER: 159:301456
TITLE: Hedgehog signaling pathway involved in energy

metabolism in relation to use of modulators of the Smoothened (Smo) receptor capable of altering cellular glucose uptake for treatment of disease

INVENTOR(S): Pospisilik, J. Andrew; Esterbauer, Harald; Penninger, Josef M.

PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany; Medizinische Universitaet Wien; IMBA-Institut fuer Molekulare Biotechnologie GmbH

SOURCE: PCT Int. Appl., 76pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013110358	A1	20130801	WO 2012-EP70186	20121011
EP 2620142	A1	20130731	EP 2012-152943	20120127

PRIORITY APPLN. INFO.: EP 2012-152943 A 20120127

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2013110358	A1	Dead	20201201
EP 2620142	A1	Dead	20201202

AB The present invention relates to a modulator of the Smoothened (Smo) receptor capable of altering cellular glucose uptake for use in the treatment of a disease, wherein (a) the modulator is an activator of the Smoothened (Smo) receptor capable of increasing cellular glucose uptake and is for use in the treatment of diabetes, glucose intolerance, hyperglycemia, obesity, overweight, sepsis and diseases assocd. therewith; or (b) wherein the modulator is an inhibitor of the Smoothened (Smo) receptor capable of decreasing cellular glucose uptake and is for use in the treatment of hypoglycemia. Further, the invention relates to a method of altering the glucose uptake, the lactate level, the NAD+/NADH ratio and/or the NADP+/NADPH ratio of a cell and a method of identifying a modulator of the Smoothened (Smo) receptor capable of altering the glucose uptake, the lactate level, the NAD+/NADH ratio and/or the NADP+/NADPH ratio of a cell. Also, the invention relates to a method of increasing uptake of glucose or a glucose analog labeled with a detectable moiety.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2013:1189026 CAPLUS Full-text

DOCUMENT NUMBER: 159:283720

TITLE: Hedgehog signaling pathway involved in energy metabolism in relation to use of modulators of the Smoothened (Smo) receptor capable of altering cellular glucose uptake for treatment of disease

PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany

SOURCE: Eur. Pat. Appl., 40pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2620142	A1	20130731	EP 2012-152943	20120127
WO 2013110358	A1	20130801	WO 2012-EP70186	20121011

PRIORITY APPLN. INFO.: EP 2012-152943 A 20120127

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
EP 2620142	A1	Dead	20201202
WO 2013110358	A1	Dead	20201201

AB The present invention relates to a modulator of the Smoothened (Smo) receptor capable of altering cellular glucose uptake for use in the treatment of a disease, wherein (a) the modulator is an activator of the

Smoothened (Smo) receptor capable of increasing cellular glucose uptake and is for use in the treatment of diabetes, glucose intolerance, hyperglycemia, obesity, overweight, sepsis and diseases assocd. therewith; or (b) wherein the modulator is an inhibitor of the Smoothened (Smo) receptor capable of decreasing cellular glucose uptake and is for use in the treatment of hypoglycemia. Further, the invention relates to a method of altering the glucose uptake, the lactate level, the NAD+/NADH ratio and/or the NADP+/NADPH ratio of a cell and a method of identifying a modulator of the Smoothened (Smo) receptor capable of altering the glucose uptake, the lactate level, the NAD+/NADH ratio and/or the NADP+/NADPH ratio of a cell. Also, the invention relates to a method of increasing uptake of glucose or a glucose analog labeled with a detectable moiety.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2012:57263 CAPLUS Full-text
DOCUMENT NUMBER: 156:167724
TITLE: Methods using antiviral agents in combination with chemotherapeutic agents for the treatment of lipogenic-adenovirus related conditions
INVENTOR(S): Atkinson, Richard L.; Lee, Zendra Pei-Lun; He, Jia
PATENT ASSIGNEE(S): Obetech LLC, USA
SOURCE: PCT Int. Appl., 74pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2012006550	A2	20120112	WO 2011-US43399		20110708
WO 2012006550	A3	20120426			
US 20130178517	A1	20130711	US 2013-13809209		20130322
PRIORITY APPLN. INFO.:			US 2010-61362915	P	20100709
			US 2011-61434984	P	20110121
			WO 2011-US43399	W	20110708

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2012006550	A2	Dead	20201201
WO 2012006550	A3	Dead	20201201
US 20130178517	A1	Dead	20201120

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2012:57263
AB Disclosed are methods of treatment for adipogenic virus-related conditions. The methods may comprise administering a compn. comprising an ED of an antiviral agent (e.g. abacavir, acyclovir, amantadine, amprenavir, cidofovir) to a subject having an adipogenic adenovirus-related condition. Administration of the antiviral agent may prevent or reduce viral proliferation in the subject. The method may also include administering a compn. comprising an ED of a therapeutic agent (e.g. cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide) known to treat the adipogenic adenovirus-related condition in conjunction with the compn. comprising an ED of an antiviral agent. Administration of the antiviral agent and the therapeutic agent may reduce or eliminate one or more symptoms of the adipogenic adenovirus-related condition more efficiently than administration of either the antiviral agent and the therapeutic agent alone.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L8 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2008:1043214 CAPLUS Full-text
DOCUMENT NUMBER: 149:299765
TITLE: Combinations of known drugs and target proteins and application to the screening of the novel drugs that can bind and/or regulate the functions and expression levels of the target proteins
INVENTOR(S): Murayama, Katsuhisa; Yamauchi, Tadakazu; Tsuchiya,

Kouichi; Komiya, Kazuo; Kito, Morikazu; Isono, Yuko; Inomata, Noriyuki; Suwa, Yorimasa; Wakamatsu, Ai; Yamamoto, Junichi; Isogai, Takao

PATENT ASSIGNEE(S): Reverse Proteomics Research Institute Co., Ltd., Japan

SOURCE: PCT Int. Appl., 532pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2008102912	A1	20080828	WO 2008-JP53345		20080220
JP 4933607	B2	20120516	JP 2009-500267		20080220
US 20110269141	A1	20111103	US 2009-528190		20090821
PRIORITY APPLN. INFO.:			JP 2007-40541	A	20070221
			WO 2008-JP53345	W	20080220

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2008102912	A1	Dead	20201202
JP 4933607	B2	Alive	20201120
US 20110269141	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The proteins that have been identified as the targets of known physiol. active substances typically drugs for clin. use are claimed with their amino acid sequences. Mol. interaction of the known drugs to their target proteins have been studied by using the SEC-MS method, etc. More than 192 combinations of known substances (drugs)-target proteins interactions that include the regulation of their gene expression levels and functions (activities) of the target protein by the drugs are claimed. More than 63 combinations of known substances (drugs)-target proteins interactions that include the binding of the known drugs to the target protein and the regulation of the functions (activities) of the target protein by the drugs are also claimed. The target proteins and the effector drugs are assocd. with certain human diseases, and therefore the substances that can bind to the target proteins or the substances that can regulate the expression levels of the genes for the target proteins are designed to be screened as the drug candidates for the corresponding diseases. Antisense nucleic acids, ribozymes, decoy nucleic acids, siRNAs, antibodies, dominant neg. mutants and the genetic vectors for the expression of these functional nucleic acids are claimed as potential regulatory substances to be screened. Genetic polymorphisms in the genes for the claimed drug target proteins can be used in the genotyping assays that is applicable to the diagnoses of the corresponding diseases. The gene promoter activity assay is claimed as one of the screening method to reveal the substances that can regulate the genes for the target proteins. The nucleotide sequences encoding two specific target proteins (plastin 3 and the Rho factor) are claimed for the drug screening assay.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2006:318526 CAPLUS Full-text

DOCUMENT NUMBER: 144:344946

TITLE: Molecular toxicity models based on gene expression profiles in isolated rat hepatocytes exposed to known hepatotoxins

INVENTOR(S): Higgs, Brandon; Elashoff, Michael; Mendrick, Donna L.; Porter, Mark W.; Castle, Arthur L.; Johnson, Kory R.

PATENT ASSIGNEE(S): Gene Logic, Inc., USA

SOURCE: PCT Int. Appl., 271 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2006037025	A2	20060406	WO 2005-US34780		20050928
WO 2006037025	A3	20060713			
PRIORITY APPLN. INFO.:			US 2004-60613292	P	20040928

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2006037025	A2	Dead	20201202
WO 2006037025	A3	Dead	20201202

AB The present invention includes methods of predicting hepatotoxicity of test agents and methods of generating hepatotoxicity prediction models using algorithms for analyzing quant. gene expression information. Isolated Sprague-Dawley rat hepatocytes exposed to known hepatotoxins were examd. to identify changes in genes expression induced by these compds. using the Affymetrix Rat Microarray. These changes in gene expression provide useful toxicity markers than can be used to monitor toxicity and/or toxicity progression by a test compd. Some of these markers may also be used to monitor or detect various disease or physiol. states, disease progression, drug efficacy, and drug metab. The invention also includes microarrays, computer systems comprising the toxicity prediction models, as well as methods of using the computer systems by remote users for detg. the toxicity of test agents.

L8 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2005:1154777 CAPLUS Full-text
DOCUMENT NUMBER: 143:433974
TITLE: Gene expression profiling and markers for use in the assessment of hepatotoxicity
INVENTOR(S): Porter, Mark; Higgs, Brandon; Mendrick, Donna; Elashoff, Michael
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005100989	A2	20051027	WO 2005-US11532		20050407
WO 2005100989	A3	20061130			
CA 2562343	A1	20051027	CA 2005-2562343		20050407
EP 1751303	A2	20070214	EP 2005-736350		20050407
JP 2007533005	T	20071115	JP 2007-507445		20050407
US 20110071767	A1	20110324	US 2008-547759		20080113
PRIORITY APPLN. INFO.:			US 2004-60559949	P	20040407
			WO 2005-US11532	W	20050407

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2005100989	A2	Dead	20201202
WO 2005100989	A3	Dead	20201202
CA 2562343	A1	Dead	20201120
EP 1751303	A2	Dead	20201202
US 20110071767	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Methods of using the effects of a substance on gene expression profiles are described for use in assessing their toxicity, esp. hepatotoxicity, are described. The invention also includes microarrays, computer systems comprising the toxicity prediction models, as well as methods of using the computer systems by remote users for detg. the toxicity of test agents. A database of gene expression profiles for rat liver using a broad range of drugs, com. chems., and known poisons is developed.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2003:951172 CAPLUS Full-text
DOCUMENT NUMBER: 140:24421

TITLE: Gene expression profiles in response to toxic compounds and their use as kidney toxicity predictive genes
INVENTOR(S): Kier, Larry; Nolan, Timothy D.; Sankar, Usha; Derbel, Maher
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, Inc., USA
SOURCE: PCT Int. Appl., 388 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003100030	A2	20031204	WO 2003-US6196		20030227
WO 2003100030	A3	20041223			
WO 2003100030	B1	20050506			
CA 2477688	A1	20031204	CA 2003-2477688		20030227
AU 2003273154	A1	20031212	AU 2003-273154		20030227
EP 1506396	A2	20050216	EP 2003-741753		20030227
PRIORITY APPLN. INFO.:			US 2002-60361128	P	20020227
			WO 2003-US6196	W	20030227

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2003100030	A2	Dead	20201202
WO 2003100030	A3	Dead	20201202
WO 2003100030	B1	Dead	20201202
CA 2477688	A1	Dead	20201121
AU 2003273154	A1	Dead	20201121
EP 1506396	A2	Dead	20201202

AB The invention provides kidney toxicity predictive genes which can be used to predict kidney toxicity in response to one or more agents. Multiple sets of kidney toxicity biomarkers are provided which are useful in the kidney toxicity prediction methods. In particular, 376 rat kidney toxicity gene expression markers demonstrate utility in predicting kidney toxicity outcomes. These biomarkers are thoroughly characterized for predictive performance; among the subsets of kidney toxicity genes provided herein are several which demonstrate prediction accuracies in the vicinity of 95%.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L8 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2003:818517 CAPLUS Full-text
DOCUMENT NUMBER: 139:321695
TITLE: Genes showing altered patterns of expression in liver necrosis and their predictive uses
INVENTOR(S): Kier, Larry; Nolan, Timothy D.; Sankar, Usha; Derbel, Maher
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, Inc., USA
SOURCE: PCT Int. Appl., 379 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003085083	A2	20031016	WO 2003-US10141		20030401
WO 2003085083	A3	20040722			
WO 2003085083	B1	20040923			
CA 2499636	A1	20031016	CA 2003-2499636		20030401
AU 2003228425	A1	20031020	AU 2003-228425		20030401
US 20040076974	A1	20040422	US 2003-404460		20030401
EP 1495419	A2	20050112	EP 2003-726177		20030401
PRIORITY APPLN. INFO.:			US 2002-60369287	P	20020401
			WO 2003-US10141	W	20030401

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

WO 2003085083	A2	Dead	20201202
WO 2003085083	A3	Dead	20201202
WO 2003085083	B1	Dead	20201203
CA 2499636	A1	Dead	20201121
AU 2003228425	A1	Dead	20201121
US 20040076974	A1	Dead	20201121
EP 1495419	A2	Dead	20201202

AB Genes that show altered levels of expression in the liver during necrosis induced by poisoning are identified for use in predicting liver poisoning by novel substances. The invention provides for a method of predicting the liver toxicity in an individual to an agent. The method comprises obtaining a biol. sample from an individual treated with the agent. The expression of one or more liver toxicity predictive genes in the sample is measured, wherein the genes are selected from a group consisting of partial gene sequences of genes identified as responsive to agents causing liver necrosis. The process generates a test expression profile using data from several points after exposure to the poison. The test expression profile is used with a set of ref. expression profiles in a Predictive Model to det. whether the agent will induce liver toxicity in the individual.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2003:76983 CAPLUS Full-text

DOCUMENT NUMBER: 138:148639

TITLE: Comparison of protein or gene expression patterns of blood cells obtained by microarray to injury database to assess injury

INVENTOR(S): Sharp, Frank R.; Tang, Yang; Lu, Aigang

PATENT ASSIGNEE(S): University of Cincinnati, USA

SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003008647	A2	20030130	WO 2001-US44278		20011128
WO 2003008647	A3	20040325			
AU 2002241520	A1	20030303	AU 2002-241520		20011128
US 20030104393	A1	20030605	US 2001-996275		20011128
EP 1425412	A2	20040609	EP 2001-988189		20011128
US 20070059745	A1	20070315	US 2006-514470		20060901
PRIORITY APPLN. INFO.:			US 2000-60253568	P	20001128
			US 2001-996275	A3	20011128
			WO 2001-US44278	W	20011128

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2003008647	A2	Dead	20201202
WO 2003008647	A3	Dead	20201201
AU 2002241520	A1	Dead	20201121
US 20030104393	A1	Dead	20201121
EP 1425412	A2	Dead	20201202
US 20070059745	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Methods of injury assessment in an individual include the steps of detg. a pattern of expression exhibited by blood cells obtained from an individual and comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury. The injury database includes genomic injury databases, proteomic injury databases, organ specific injury database, disease specific injury database. The patterns of gene or protein expression are obtained by microarray and analyzed by statistical anal., class prediction, clustering, and computer programs. The genes in the pattern of gene expression comprise acidosis-induced genes, hypoxia-induced genes, glucose-induced genes, ischemia-induced genes. The invention relates to sequences of two human genes which are expressed more highly in Parkinson's individuals. The invention also relates to genes assocd. with status epilepticus, hypoglycemia, ischemic

stroke and hemorrhagic stroke in rat model. The invention also relates to gene expression pattern in males and females, resp. The invention also relates to assessing Parkinson's disease, stroke profusion, drug, neurofibromatosis, manic bipolar depression, migraine headache, schizophrenia, and Tourettes disease based on pattern of expression.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2002:658295 CAPLUS Full-text

DOCUMENT NUMBER: 137:212221

TITLE: Rat toxicologically relevant genes and use in microarrays to evaluate toxicity of toxic agents

INVENTOR(S): Farris, Georgia; Hicken, Samuel H.; Farr, Spencer B.

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, Inc., USA

SOURCE: PCT Int. Appl., 388 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002066682	A2	20020829	WO 2002-US2935		20020129
WO 2002066682	A3	20021219			
CA 2440008	A1	20020829	CA 2002-2440008		20020129
AU 2002258387	A1	20020904	AU 2002-258387		20020129
EP 1368499	A2	20031210	EP 2002-728330		20020129
JP 2004535776	T	20041202	JP 2002-566386		20020129
PRIORITY APPLN. INFO.:			US 2001-60264933	P	20010129
			US 2001-60308161	P	20010726
			WO 2002-US2935	W	20020129

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2002066682	A2	Dead	20201202
WO 2002066682	A3	Dead	20201201
CA 2440008	A1	Dead	20201121
AU 2002258387	A1	Dead	20220203
EP 1368499	A2	Dead	20201202

AB The invention provides a set of 700 toxicol. relevant rat genes which useful for detg. toxicol. responses. The genes are discovered using empirical data from evaluation of differential expression of genes in a 17,241 gene set in response to a predetd. set of known toxic chems. in various rat tissues. The 700 genes are split into 3 groups: (1) genes discovered which match a known complete rat gene when the genes were searched in the GenBank database; (2) genes discovered which did not match a known complete rat gene; and (3) genes chosen on the basis of their possible role in crit. cellular pathways and empirical data toxicity responsiveness. Thus, the invention provides a method of evaluating the toxicity of an agent is provided by (a) exposing a test animal to the agent; (b) measuring the expression of one or more toxic response genes from a set of partial gene sequences in the test animal in response to the agent, thereby generating a test expression profile; and (c) comparing the test expression profile with a ref. expression profile indicative of toxicity. The genes corresponding to the partial gene sequences are responsive in one or more of kidney, liver, spleen, heart, lung, testis, or brain tissues.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2001:223711 CAPLUS Full-text

DOCUMENT NUMBER: 135:176591

TITLE: Induction of drug metabolism-related enzymes by methylcholanthrene and phenobarbital in transgenic

mice carrying the human prototype c-Ha-ras gene and their wild-type littermates
AUTHOR(S): Ohnishi, Yasuyuki; Arai, Toshiro; Koshirakawa, Miho; Horii, Noriko; Nakajo, Shinjiro; Urano, Kohji; Usui, Toshimi; Tamaoki, Norikazu; Ueyama, Yoshito
CORPORATE SOURCE: Central Institute for Experimental Animals, Kawasaki, 216-0001, Japan
SOURCE: Experimental Animals (2001), 50(1), 33-39
CODEN: JIDOAA; ISSN: 1341-1357
DIGITAL OBJECT ID: 10.1538/expanim.50.33
PUBLISHER: Japanese Association for Laboratory Animal Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transgenic mice hemizygously carrying the human c-Ha-ras proto-oncogene Tg-rasH2 show very sensitive and facilitated carcinogenic responses to various carcinogens. In this study, activities of certain enzymes related to drug metab. and energy metab. were measured in the microsome and cytosol fractions of the livers of Tg-rasH2-bearing mice and their wild-type littermates of both sexes treated with 3-methylcholanthrene (MC) and phenobarbital (PB). Aminopyrine N-demethylase activities increased in the livers of all mice treated with PB. MC and PB treatments increased the activities of microsomal UDP-glucuronosyltransferase and S-adenosylhomocysteinase. In the cytosol fractions, glutathione S-transferase activity was induced in the PB-treated groups. There were no significant differences in activities of lactate dehydrogenase, glucose 6-phosphate dehydrogenase, pyruvate kinase and glucose 6-phosphatase, enzymes related to energy metab., in the livers and kidneys. Tg-rasH2-bearing mice showed stable activities of enzymes related to drug detoxication and energy metab. similar to those of nontransgenic mice. These results suggest that the human c-Ha-ras transgene may not affect drug metab.-related enzymes, and the facilitated carcinogenic response in the Tg-rasH2 mouse is not due to these enzymic disorders.
OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 19 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1997:514687 CAPLUS Full-text
DOCUMENT NUMBER: 127:217361
ORIGINAL REFERENCE NO.: 127:42244h,42245a
TITLE: Activity and inducibility of drug-metabolizing enzymes in immortalized hepatocyte-like cells (mhPKT) derived from a L-PK/Tag1 transgenic mouse
AUTHOR(S): Courjault-Gautier, Francoise; Antoine, Benedicte; Bens, Marcelle; Vallet, Veronique; Cluzeaud, Francoise; Pringault, Eric; Kahn, Axel; Toutain, Herve; Vandewalle, Alain
CORPORATE SOURCE: Departement Securite Medicament, Service de Toxicologie Experimentale, Centre de Recherche de Vitry-Alfortville, Rhone-Poulenc Rorer SA, Vitry-sur Seine, Fr.
SOURCE: Experimental Cell Research (1997), 234(2), 362-372
CODEN: ECREAL; ISSN: 0014-4827
DIGITAL OBJECT ID: 10.1006/excr.1997.3626
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This report describes the establishment and characterization of the mhPKT cell line derived from the liver of a transgenic mouse harboring the simian virus (SV40) large T and small t antigens placed under the control of the 5' regulatory sequence of the rat L-type pyruvate kinase (L-PK) gene. MhPKT cells had a prolonged life span, expressed the SV40-encoded nuclear large T antigen when grown in glucose-enriched medium, and induced tumors when injected s.c. into athymic (nu-nu) mice. Growth on petri dishes or filters yielded multiple layers of cuboid cells, with numerous spaces between adjacent cells that were closed by junctional complexes. These bile canaliculi-like structures exhibited numerous microvilli in which villin, an actin-binding brush-border protein, colocalized with actin. These bile canaliculi-like structures appeared to be functional as they accumulated fluorescein. MhPKT cells conserved the expression of the

liver-specific transcription factors HNF1, HNF3, HNF4, and DBP together with substantial levels of L-PK and albumin but not α-fetoprotein mRNA transcripts. MhPKT cells mainly metabolized testosterone into androstenedione and 6β-hydroxytestosterone, as in vivo. 3-Methylcholanthrene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) markedly increased ethoxyresorufin-O-deethylase activity and the related cytochrome P 450 (CYP) 1A1/2 protein, whereas α-naphthoflavone antagonized the TCDD-elicited induction. Phenobarbital slightly increased the CYP2B-mediated activities of pentoxyresorufin-O-dependentylase, 2β- and 16β-testosterone hydroxylase. MhPKT cells also had substantial sulfotransferase, UDP-glucuronyltransferase, and glutathione S-transferase activities. This model may serve as a tool for long-term in vitro studies of xenobiotic metab., potent CYP inducers, and hepatocyte damage due to drugs and other factors.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1992:565723 CAPLUS Full-text

DOCUMENT NUMBER: 117:165723

ORIGINAL REFERENCE NO.: 117:28511a,28514a

TITLE: Hepatocarcinogenicity of PCB congeners. II. Covalent binding to liver macromolecules and modification of carbohydrate metabolism

AUTHOR(S): Braun, A.; Eigenbrodt, E.; Laib, R. J.; Brunn, H.

CORPORATE SOURCE: Staatl. Med., Lebensm. Veterinaeruntersuchungsamt Mittelhessen, Giessen, D-6300, Germany

SOURCE: Organohalogen Compounds (1990), 1(Toxicol., Environ., Food, Exposure-Risk), 67-71
CODEN: ORCOEP; ISSN: 1026-4892

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have investigated the hepatocarcinogenic mechanisms of PCB No. 49 and PCB No. 153. PCB No. 49 was incubated with isolated hepatocytes from rats and chickens that had been stimulated with phenobarbital. This low-chlorinated biphenyl is metabolically activated in the liver cells and covalently binds to nucleic acids and proteins in vitro. Enzyme activities (for pyruvate kinase, fructose 1,6-bisphosphatase, and malic enzyme), which show specific changes in tumor cells, were detd. in liver homogenates of rats and chickens treated with DENA and PCB. Apparently, tumor promotors that affect the liver, alter hepatocellular activities of key enzymes.

L8 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1992:100928 CAPLUS Full-text

DOCUMENT NUMBER: 116:100928

ORIGINAL REFERENCE NO.: 116:16925a,16928a

TITLE: Hepatocarcinogenicity of PCB congeners. II. Covalent binding to liver macromolecules and modification of carbohydrate metabolism

AUTHOR(S): Braun, A.; Eigenbrodt, E.; Laib, R. J.; Brunn, H.

CORPORATE SOURCE: Staatl. Med., Lebensmittel- Veterinaeruntersuchungsamt Mittelhessen, Giessen, D-6300, Germany

SOURCE: Toxicological and Environmental Chemistry (1991), 34(1), 23-8
CODEN: TECSDY; ISSN: 0277-2248

DIGITAL OBJECT ID: 10.1080/02772249109357773

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors investigated the hepatocarcinogenic mechanisms of 2,2',4,5'-tetrachlorobiphenyl (PCB No. 49) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB No. 153). PCB No. 49 was incubated with isolated hepatocytes from rats and chickens that had been stimulated with phenobarbital. This low-chlorinated biphenyl is metabolically activated in the liver cells and covalently binds to nucleic acids and proteins in vitro. Enzyme activities (for pyruvate kinase, fructose-1,6-biphosphatase, and malic enzyme), which show specific changes in tumor cells were detd. in liver homogenates of rats and chickens

treated with diethylnitrosamine and PCB. The results support the concept that tumor promotors that affect the liver alter hepatocellular activities of key enzymes.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L8 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1990:229556 CAPLUS Full-text
DOCUMENT NUMBER: 112:229556
ORIGINAL REFERENCE NO.: 112:38531a,38534a
TITLE: Effects of hypolipidemic drugs nafenopin and clofibrate on phenotypic expression and cell death (apoptosis) in altered foci of rat liver
AUTHOR(S): Gerbracht, Ulrich; Bursch, Wilfried; Kraus, Pavel; Putz, Barbara; Reinacher, Manfred; Timmermann-Trosiener, Irene; Schulte-Hermann, Rolf
CORPORATE SOURCE: Inst. Tumorbiol. Krebsforsch., Univ. Wien, Vienna, A-1090, Austria
SOURCE: Carcinogenesis (1990), 11(4), 617-24
CODEN: CRNGDP; ISSN: 0143-3334
DIGITAL OBJECT ID: 10.1093/carcin/11.4.617
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phenotypically altered liver foci were produced in female Wistar rats by a single dose of N-nitrosomorpholine followed by promotion with phenobarbital (PB) for 20 or 28 wk. Then treatment was changed to either hexachlorocyclohexane (HCH), or cyproterone acetate (CPA), or nafenopin (naf) or clofibrate (Clof), two hypolipidemic drugs. Foci were identified by a pos. reaction for gamma-glutamyl-transpeptidase (GGT) and other cytol. markers. HCH and CPA could substitute for PB as foci promoters; in contrast, naf and Clof decreased expression of GGT in foci resulting in a decline of no. and area of detectable foci, effects particularly pronounced with naf. Immunohistochem. investigations of serial sections revealed that naf also reduced expression of the altered phenotype when cytochrome P 450-PB and pyruvate kinase (type L) were used as foci markers, but not when glutathione-S-transferase B (GST-B) was used. Thus, the no. of foci with enhanced GST-B did not decline after the change from PB to naf treatment. Furthermore, the redn. of GGT and the decrease of foci no. during naf treatment were not assocd. with increased evidence of cell death by apoptosis in foci, in contrast to the situation after PB withdrawal. These findings strongly suggest that the disappearance of GGT-pos. foci after naf due to a phenotypic change resulting in a suppression of GGT expression rather than to phys. elimination of foci.
OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS RECORD (25 CITINGS)

L8 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1989:612388 CAPLUS Full-text
DOCUMENT NUMBER: 111:212388
ORIGINAL REFERENCE NO.: 111:35175a,35178a
TITLE: Cytochrome P450 in highly purified suspension of nonparenchymal liver cells
AUTHOR(S): Rich, K.; Lodola, A.
CORPORATE SOURCE: Biol. Lab., Univ. Kent, Canterbury/Kent, UK
SOURCE: Cell Biochemistry and Function (1989), 7(4), 275-82
CODEN: CBFUDH; ISSN: 0263-6484
DIGITAL OBJECT ID: 10.1002/cbf.290070406
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rat liver nonparenchymal cells (NPC) were prepd. by Pronase digestion and purified on discontinuous gradients on Nycodenz. Morphol. and biochem. characterization of cell suspensions showed that they were free of contamination by hepatocytes. The usefulness of pyruvate kinase activity in monitoring the degree of hepatocyte contamination of NPC was confirmed, and an equation which allows this carry-over to be calcd. was derived. By using highly purified suspensions of NPC it was shown that they contain glucose 6-phosphatase in low but detectable levels. Spectrophotometric studies showed that they contain cytochrome P 450, with a specific content of 24 mol/mg cell protein. A potential source of error

in previous studies was recognized; namely that peroxidase, present in NPC in high concn., is able to mask the absorption due to cytochrome P 450. Both the presence and inducibility of this enzyme in NPC prepd. from rats pretreated with phenobarbital or 3-methylcholanthrene were confirmed by using Western blot anal.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L8 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1989:402224 CAPLUS Full-text
DOCUMENT NUMBER: 111:2224
ORIGINAL REFERENCE NO.: 111:435a,438a
TITLE: Distribution and induction of cytochrome P-450 and two cytochrome P-450-dependent monooxygenase activities in rat liver parenchymal cell subpopulations separated by centrifugal elutriation
AUTHOR(S): Seibert, Beate; Oesch, Franz; Steinberg, Pablo
CORPORATE SOURCE: Inst. Toxicol., Univ. Mainz, Mainz, D-6500, Fed. Rep. Ger.
SOURCE: Archives of Toxicology (1989), 63(1), 18-22
CODEN: ARTODN; ISSN: 0340-5761
DIGITAL OBJECT ID: 10.1007/BF00334628
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Liver parenchymal cells from the periportal and centrilobular zones differ in their morphol., biochem. and functional characteristics. In an effort to obtain fractions enriched in either periportal or centrilobular cells, isolated rat liver parenchymal cells were sepd. into five subpopulations by centrifugal elutriation. The mean diams. of the cells present in fractions I-V were 19.6, 21.1, 21.8, 22.7 and 23.5 μm, resp. The content of cytochrome P 450 as well as benzphetamine N-demethylase and 7-ethoxyresorufin O-deethylase activities were higher in the larger parenchymal cells than in the smaller ones. After administration of phenobarbital the content of cytochrome P 450 was approx. two-fold greater in the cells present in fractions 3-5, when compared to the same subpopulations isolated from untreated rats; the activity of benzphetamine N-demethylase was enhanced to a similar extent in all five fractions. 3-Methylcholanthrene treatment resulted in a significant increase of cytochrome P 450 content and 7-ethoxyresorufin O-deethylase activity in all 5 fractions: both parameters were slightly higher in fractions 4 and 5 than in fractions 1 and 2. Evidently, the elutriated liver parenchymal cells seem to preserve the biochem. heterogeneity obsd. in the intact liver; the potential enrichment of periportal and centrilobular cells in the different fractions by centrifugal elutriation is discussed.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L8 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1988:146995 CAPLUS Full-text
DOCUMENT NUMBER: 108:146995
ORIGINAL REFERENCE NO.: 108:24063a,24066a
TITLE: The effect of azole and polyene antifungals on the plasma membrane enzymes of Candida albicans
AUTHOR(S): Surarit, Rudee; Shepherd, Maxwell G.
CORPORATE SOURCE: Sch. Dent., Univ. Otago, Dunedin, N. Z.
SOURCE: Journal of Medical and Veterinary Mycology (1987), 25(6), 403-13
CODEN: JMVMEO; ISSN: 0268-1218
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The two clin. important classes of antimycotic drugs, the polyenes and azoles, act on the plasma membrane of the cell. The primary modes of action are believed to be through interaction with sterols (polyenes) and alteration in sterol compn. of the membrane (azoles). This report shows that, at growth inhibitory concns., the polyenes (nystatin and amphotericin) and azoles (miconazole and ketoconazole) also inhibit plasma membrane enzymes. There was extensive (>75%) inhibition of the Candida albicans plasma membrane enzymes ATPase, glucan synthase, adenyl cyclase, and 5'-nucleotidase, when assayed in situ. The antifungals papulacandin and echinocandin, which inhibit glucan synthesis, also

inhibited plasma membrane enzymes in situ; glucan synthase (>90%), 5'-nucleotidase (>80%), and ATPase (70-80%). Purified plasma membrane was prepd. from yeast cells of C. albicans by 2 different techniques: concanavalin A stabilization and coating of spheroplasts with silica microbeads. In the purified plasma membrane vesicles prepd. from concanavalin A the adenyl cyclase and phosphodiesterase were extensively (>90%) inhibited by the 3 different classes of antifungal drugs; variable inhibition was obsd. with ATPase (70-100%). The 3',5'-cyclic phosphodiesterase of the plasma membrane purified by the microbead method was almost completely inhibited by all of the antifungals tested and there was partial inhibition of ATPase (20-85%) and adenyl cyclase (30-90%).
OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

L8 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1988:1977 CAPLUS Full-text
DOCUMENT NUMBER: 108:1977
ORIGINAL REFERENCE NO.: 108:387a,390a
TITLE: Immunohistochemical demonstration of decreased L-pyruvate kinase in enzyme altered rat liver lesions produced by different carcinogens
AUTHOR(S): Fischer, G.; Domingo, M.; Lodder, D.; Katz, N.; Reinacher, M.; Eigenbrodt, E.
CORPORATE SOURCE: Inst. Pathol., Univ. Goettingen, Goettingen, D-3400, Fed. Rep. Ger.
SOURCE: Virchows Archiv B: Cell Pathology Including Molecular Pathology (1987), 53(6), 359-64
CODEN: VAAZA2; ISSN: 0340-6075
DIGITAL OBJECT ID: 10.1007/BF02890264
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Preneoplastic liver lesions were produced in female rats by application of 25 mg/kg N-nitrosomorpholine (NNM) (I), 14 mg/kg DENA, 0.075 mg/kg aflatoxin B1 (AFB1), or 160 mg/kg safrole. These carcinogens were administered in 2 equal doses 12 and 24 h after partial hepatectomy. The animals then received Na phenobarbital (0.1% in tap water) for up to 410 days. Numerous altered hepatic foci (AHF) and hyperplastic nodules (HN) were detected enzyme histochem. by their neg. ATPase reaction after application of AFB1, DENA and NNM; some AHF and HN were also caused by the weak carcinogen safrole. Immunohistochem. these lesions were also L-pyruvate kinase (L-PK)-neg. with a high coincidence with regard to their no. and area. These results confirm the role of L-PK, an enzyme affecting the pentose phosphate pathway, as a neg. marker of preneoplastic liver lesions.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L8 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1987:573097 CAPLUS Full-text
DOCUMENT NUMBER: 107:173097
ORIGINAL REFERENCE NO.: 107:27735a,27738a
TITLE: Hepatic mixed function oxidase system and enzymic glucose metabolism in rats
AUTHOR(S): Karvonen, Irmeli; Stengard, Jari H.; Saarni, Hannu U.; Stenback, Frej; Sotaniemi, Eero A.
CORPORATE SOURCE: Dep. Intern. Med., Univ. Oulu, Oulu, SF-90220, Finland
SOURCE: Diabetes Research (1987), 4(4), 195-200

CODEN: DIREEM; ISSN: 0265-5985
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phenobarbital (0.5 g/L drinking water) induced liver enzymes and enhanced glucose utilization in the liver and its storage in muscles of rats. Cimetidine (1.25 g/L drinking water) decreased the activity of the mixed-function oxidase system, reduced phosphorylation of glucose, but not gluconeogenic enzymes, in the liver, and increased glycolysis in muscles. CCl_4 (1.0 mL/kg, i.p.) impaired the mixed-function oxidase system, phosphorylation of glucose, and gluconeogenesis in the liver, reduced blood glucose, and caused glycogen accumulation in muscles. The function of the liver microsomal enzyme system is closely related to enzymic glucose metab. in the liver and muscles.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L8 ANSWER 28 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1987:168438 CAPLUS Full-text
DOCUMENT NUMBER: 106:168438
ORIGINAL REFERENCE NO.: 106:27197a,27200a
TITLE: Effect of phenobarbital on the distribution of drug-metabolizing enzymes between periportal and perivenous rat hepatocytes prepared by digitonin-collagenase liver perfusion
AUTHOR(S): Bengtsson, Gunnar; Julkunen, Antero; Penttila, Kai E.; Lindros, Kai O.
CORPORATE SOURCE: Res. Lab. State Alcohol Co., Alko Ltd., Helsinki, SF-00101, Finland
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 240(2), 663-7
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intact periportal (pp) or perivenous (pv) hepatocytes were prepd. by digitonin-collagenase liver perfusion. The degree of sepn. was indicated by significant differences between the pp and pv cells in their activity of the pp markers, alanine aminotransferase, γ-glutamyltranspeptidase, and lactate dehydrogenase and pyruvate kinase. This pattern was not altered by a 3-day pretreatment with phenobarbital (PB) [50-06-6]. The hepatocytes isolated from the pv area contained higher activities of microsomal NADPH-cytochrome c reductase, 7-ethoxycoumarin O-deethylase, 7-ethoxyresorufin O-deethylase and benzo(a)pyrene hydroxylase, and of cytosolic glutathione transferase. Cytochrome P 450 and UDP-glucuronosyltransferase were slightly higher in pv cells. Treatment with PB induced NADPH-cytochrome c reductase, glutathione transferase, cytochrome P 450 and UDP-glucuronosyltransferase but the degree of induction was found to be at least as strong in pp cells as in pv cells. The induction of 7-ethoxyresorufin O-deethylase and 7-ethoxycoumarin O-deethylase was clearly more prominent in pp cells. On the other hand, PB reduced the activities of benzo(a)pyrene hydroxylase and alc. dehydrogenase in both cell types. These results demonstrate by direct enzyme assay of sepd. cells the dominance of the pv-region for metabolizing drugs in the normal liver. Contrary to several other studies, however, these data indicate that induction by PB occurs panacinarily, i.e., relatively more in the pp region, thus diminishing rather than exaggerating the original pv dominance.
OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

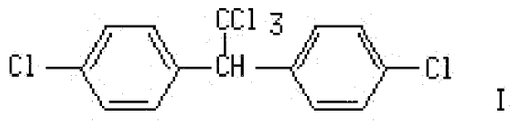
L8 ANSWER 29 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1986:588625 CAPLUS Full-text
DOCUMENT NUMBER: 105:188625
ORIGINAL REFERENCE NO.: 105:30417a,30420a
TITLE: Pyruvate kinase isoenzymes in altered foci and carcinoma of rat liver
AUTHOR(S): Reinacher, M.; Eigenbrodt, E.; Gerbracht, U.; Zenk, G.; Timmermann-Trosiener, I.; Bentley, P.; Waechter, F.; Schulte-Hermann, R.
CORPORATE SOURCE: Inst. Vet. Pathol., Univ. Giessen, Giessen, Fed. Rep. Ger.

SOURCE: Carcinogenesis (1986), 7(8), 1351-7
CODEN: CRNGDP; ISSN: 0143-3334
DIGITAL OBJECT ID: 10.1093/carcin/7.8.1351
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pyruvate kinase (PK) isoenzymes L and M2 were studied in normal rat liver, putative preneoplastic foci, neoplastic nodules, and hepatocellular carcinoma. These lesions were produced by an initiation-promotion protocol: treatment with a single dose of N-nitrosomorpholine (NNM) was followed by feeding diets contg. phenobarbital (PB) or α-hexachlorocyclohexane (α-HCH), or basal diet. Immunocytochem. showed decreases of L-PK (L-PK-) in hepatocytes of most of the foci, nodules, and carcinomas. Most L-PK- foci showed increases in γ-glutamyltransferase (γ-GT) and epoxide hydrolase (EH). PB or α-HCH treatment further decreased expression of L-PK in foci, but not in normal liver. Cells and foci with enhanced L-PK (L-PK+) were also found after carcinogen treatment. These did not show increases of γ-GT or EH or any distinct morphol. alterations with the exception of some which were basophilic (tigroid) in H and E stained sections. No L-PK+ tumors were found. The M2-type PK could not be demonstrated in parenchymal cells of liver or any of the lesions described above. This isoenzyme was restricted to stromal cells in normal rat liver and in all stages of carcinogenesis. However, stromal cells from hepatocellular carcinomas exhibited a 3-fold increase of M2-PK compared with stromal cells from normal liver. These results do not support an isoenzyme shift from L to M2-PK in the course of malignant transformation of hepatocytes as suggested previously.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L8 ANSWER 30 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1986:202001 CAPLUS Full-text
DOCUMENT NUMBER: 104:202001
ORIGINAL REFERENCE NO.: 104:31891a,31894a
TITLE: Comparative study on pyruvate kinase activity-reducing action of various promoters of hepatocarcinogenesis
AUTHOR(S): Yanagi, S.; Sakamoto, M.; Nakano, T.
CORPORATE SOURCE: Dep. Biochem., Nara Med. Coll., Kashihara, 634, Japan
SOURCE: International Journal of Cancer (1986), 37(3), 459-64
CODEN: IJCNAW; ISSN: 0020-7136
DIGITAL OBJECT ID: 10.1002/ijc.2910370319
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

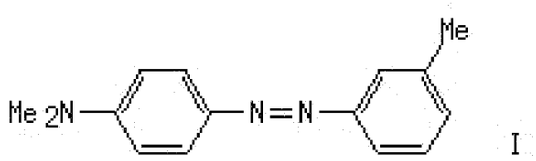


I

AB Phenobarbital (PB) [50-06-6], DDT (I) [50-29-3], ethynylestradiol (EED) [57-63-6], Na deoxycholate [302-95-4], thiobenzamide [2227-79-4], orotic acid [65-86-1], and sorbitan fatty acid ester (Sor FAE) caused a marked decrease in pyruvate kinase (PK) [9001-59-6] activity in Wistar rat liver that persisted for at least 4 wk, though the decrease caused by EED was not so marked as that caused by other hepatic promoters. Nonpromoting agents such as diphenylhydantoin (DH) [57-41-0], and some chems., such as dexamethazone [50-02-2], testosterone [58-22-0], and amobarbitol [57-43-2], which enhance the formation of γ-glutamyl transferase [9046-27-9]-pos. foci in rat livers, but do not enhance the formation of tumors or hyperplastic nodules, caused decreases in PK activity in some cases. Any such decreases, however, were only transient and normal levels were restored within 4 wk. Thus, the continuous decrease in PK activity may be a useful marker in screening tests for the

promoters of hepatocarcinogenesis.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

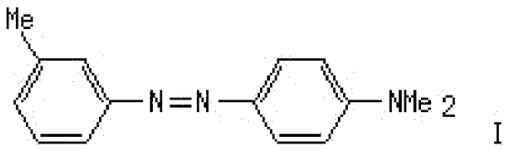
L8 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1985:500181 CAPLUS Full-text
DOCUMENT NUMBER: 103:100181
ORIGINAL REFERENCE NO.: 103:15977a,15980a
TITLE: Enhancement of hepatocarcinogenesis by sorbitan fatty acid ester, a liver pyruvate kinase activity-reducing substance
AUTHOR(S): Yanagi, Susumu; Sakamoto, Mitsuaki; Takahashi, Seiichi; Hasuike, Akikazu; Konishi, Yoichi; Kumazawa, Kyoko; Nakano, Tetsuya
CORPORATE SOURCE: Dep. Biochem., Nara Med. Coll., Nara, 634, Japan
SOURCE: JNCI, Journal of the National Cancer Institute (1985), 75(2), 381-4
CODEN: JJIND8; ISSN: 0198-0157
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Effect on hepatocarcinogenesis of dietary sorbitan fatty acid ester (SorFAE) was studied in rats fed a diet contg. 0.06% 3-methyl-4-dimethylaminoazobenzene (3'-Me-DAB)(I) [3732-90-9] for 6 wk. The incidence of hyperplastic nodules and/or hepatocellular carcinomas in the rats fed the 3'-Me-DAB diet alone was 45.0% at the end of 51 wk, whereas the incidences in the rats fed 3'-Me-DAB diet followed by 5 or 10% SorFAE or 0.1% phenobarbital (PB) diet were 76.2, 90.5, and 95.0%, resp. These incidences were significantly higher compared with the group fed 3'-Me-DAB diet alone. No tumors were obsd. in rats fed 10% SorFAE diet alone. Thus, SorFAE has an enhancing effect on hepatocarcinogenesis, although the effect was weak compared to the effective PB dose. Thus, a chem. that causes a decrease in pyruvate kinase in rat liver might promote hepatocarcinogenesis.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L8 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1985:1731 CAPLUS Full-text
DOCUMENT NUMBER: 102:1731
ORIGINAL REFERENCE NO.: 102:343a,346a
TITLE: Decrease in L-type pyruvate kinase activity in rat liver by some promoters of hepatocarcinogenesis
AUTHOR(S): Yanagi, Susumu; Sakamoto, Mitsuaki; Ninomiya, Yuko; Kamiya, Tomoya
CORPORATE SOURCE: Dep. Biochem., Nana Med. Univ., Kashihara, 634, Japan
SOURCE: JNCI, Journal of the National Cancer Institute (1984), 73(4), 887-94
CODEN: JJIND8; ISSN: 0198-0157
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A probably promoter-specific decrease of L-type pyruvate kinase (L-PK) [9001-59-6] in Wistar rat liver is described. The possibility of utilizing the decrease in L-PK activity for screening of hepatic promoters is discussed. A significantly decreased level of activity of L-PK was obsd. during continuous feedings of the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene (I) [55-80-1], which initiates and promotes hepatocarcinogenesis, and of the known hepatic promoters phenobarbital (PB) [50-06-6] and dichlorodiphenyltrichloroethane [50-29-3] for at least 4 wk. The depression of L-PK activity caused by PB was reversible, was inversely correlated with PB concn. in the diet, and seemed to be organ-specific. In contrast to L-PK activity, the activity of K-type pyruvate kinase (K-PK) was induced by injections of the carcinogen diethylnitrosamine [55-18-5] or the hepatotoxin CCl4 [56-23-5] or by the feeding of I. However, feeding of PB or 2-methyl-4-dimethylaminoazobenzene [54-88-6], which initiates but does not promote hepatocarcinogenesis, did not increase K-PK activity.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L8 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1981:582054 CAPLUS Full-text

DOCUMENT NUMBER: 95:182054

ORIGINAL REFERENCE NO.: 95:30311a,30314a

TITLE: Enzyme deviation patterns in primary rat hepatomas induced by sequential administration of two chemically different carcinogens

AUTHOR(S): Sato, Kiyomi; Hatayama, Ichiro; Hoshino, Keiji; Imai, Fusako; Tsuchida, Shigeki; Sato, Tsuyoshi; Nishimura, Koya; Tatematsu, Masae; Ito, Nobuyuki

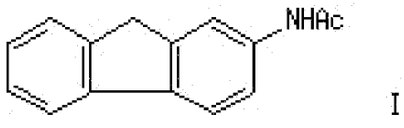
CORPORATE SOURCE: Sch. Med., Hirosaki Univ., Hirosaki, 036, Japan

SOURCE: Cancer Research (1981), 41(10), 4147-53
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Enzyme deviation were examd. in primary rat hepatomas induced by short-term sequential administration of 2 chem. carcinogens from among 2-fluorenylacetamide (FAA) (I) [53-96-3], diethylnitrosamine (DENA) [55-18-5], and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) [55-80-1] or by FAA or 3'-Me-DAB followed by phenobarbital [50-06-6] as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the 2 carcinogens in the sequence affects the patterns more. Biochem. differentiation of hyperplastic nodules and hepatomas was detd. by simultaneous assays of activities and isozyme compn. of glucose-ATP phosphotransferase [9001-36-9], pyruvate kinase [9001-59-6], glucose 6-phosphatase [9001-39-2], fructose 1,6-bisphosphatase [9001-52-9], and γ-glutamyltransferase [9046-27-9] with consideration of histol.

classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the 1st carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose of term of DENA. Thus, deviations of some enzymes, such as pyruvate kinase and fructose 1,6-bisphosphatase, as well as histol. differentiation of the primary hepatomas are more strongly influenced by the 1st carcinogen than by the 2nd under these administration schedules and the degree of enzyme deviation shown by hepatomas produced a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L8 ANSWER 34 OF 34 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1972:41990 CAPLUS Full-text
DOCUMENT NUMBER: 76:41990
ORIGINAL REFERENCE NO.: 76:6747a,6750a
TITLE: Effect of barbiturates of anaerobic glycolysis
AUTHOR(S): Kinoshita, Yoshihiro
CORPORATE SOURCE: Sapporo Med. Coll., Sapporo, Japan
SOURCE: Nippon Yakubutsugaku Zasshi (1970), 66(6), 659-68
CODEN: NIYZAM; ISSN: 0369-4461
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB In starved rats receiving single i.p. injections of 50 mg pentobarbital (I) [57-33-0]/kg or of 100 mg phenobarbital (II) [50-06-6]/kg, the blood levels of pyruvate [127-17-3] and lactate [50-21-5] were significantly decreased at the time of max. depression of motor activity. In the brain, the levels of phosphorylated metabolites of glucose [50-99-7] were slightly decreased. Anaerobic glycolysis in vitro was inhibited only at a concn. of >3mM of I and II. The activities of hexokinase, phosphofructokinase and pyruvate kinase were significantly inhibited in the presence of more than 10mM of I and II. Aldolase, glyceraldehyde 3-phosphate dehydrogenase and lactate dehydrogenase were insensitive to the barbiturates. These results suggest that barbiturates may suppress anaerobic glycolysis through inhibition of activities of enzymes which catalyze irreversible steps of glycolysis.

=> log hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	606.20	606.44

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 11:56:09 ON 07 JUL 2022

s (("emesis") or ("anti-emetic"))

```
          5348 "EMESIS"
       1731617 "ANTI"
            53 "ANTIS"
       1731649 "ANTI"
                 ("ANTI" OR "ANTIS")
          4551 "EMETIC"
           602 "EMETICS"
          4878 "EMETIC"
                 ("EMETIC" OR "EMETICS")
           901 "ANTI-EMETIC"
                 ("ANTI"(W)"EMETIC")
L1        6022 (("EMESIS") OR ("ANTI-EMETIC"))
```

```
=> s (("nausea") or ("vomiting"))

          42791 "NAUSEA"
             26 "NAUSEAS"
          42811 "NAUSEA"
                  ("NAUSEA" OR "NAUSEAS")
          42213 "VOMITING"
             16 "VOMITINGS"
          42218 "VOMITING"
                  ("VOMITING" OR "VOMITINGS")
L2        58521 (("NAUSEA") OR ("VOMITING"))

=> s ("dexamethasone")

          72200 "DEXAMETHASONE"
             20 "DEXAMETHASONES"
L3        72201 ("DEXAMETHASONE")
                  ("DEXAMETHASONE" OR "DEXAMETHASONES")

=> s L1 or L2

L4        60780 L1 OR L2

=> s L3 (L) L4

L5         1548 L3 (L) L4

=> s L3 (W) L4

L6           75 L3 (W) L4

=> display L6 1-75 ibib abs hitstr


L6   ANSWER 1 OF 75  CAPLUS  COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER:         2022:301812  CAPLUS Full-text
DOCUMENT NUMBER:          179:55917
TITLE:                    Cost-effectiveness of palonosetron and
                          dexamethasone-based triple and quadruple regimens in
                          preventing highly emetogenic chemotherapy-induced
                          nausea and vomiting
AUTHOR(S):                Halloush, Shiraz; Alhifany, Abdullah A.; Alkhatib,
                          Nimer S.; Al Bawab, Abdel Qader; AL-Qawasmeh, Batool;
                          Al Shawakri, Esra'a; Koeller, Jim
CORPORATE SOURCE:         Faculty of Pharmacy, Applied Science Private
                          University, Amman, Jordan
SOURCE:                   Current Medical Research and Opinion (2022), 38(4),
                          571-577
                          CODEN: CMROCX; ISSN: 0300-7995
DIGITAL OBJECT ID:        10.1080/03007995.2022.2033011
PUBLISHER:                Taylor & Francis Ltd.
DOCUMENT TYPE:            Journal; (online computer file)
LANGUAGE:                 English
AB   Cost-effectiveness analyses that consider all currently used antiemetics
     in the case of emetogenic chemotherapy-induced nausea and vomiting (CINV)
     have not been performed yet.  We aim to compare the cost-effectiveness of
     olanzapine (OLA), or/and neurokinin-1 receptor antagonists (NK-1-RAs), in
     combination with palonosetron (PAL) and dexamethasone (DEX) in preventing
     highly emetogenic CINV.  Two decision analytic models were constructed.
     The first model was based on overall complete response (CR); the second
     model was based on rate of absence of nausea.  Four antiemetic regimens
     PAL + DEX, NK-1-RAs + PAL + DEX, OLA + PAL + DEX, and PAL + NK-1-RA + DEX
     + OLA were compared in terms of cost, overall CR and rate of absence of
     nausea.  Base case incremental cost-effectiveness ratio (ICER) ests. were
     calcd.  The study was from the US payer perspective.  In terms of CR, the
     PAL + NK-1-RA + DEX + OLA was assocd. with the highest gains in the
     percentage of CR among all treatment regimens at base case ICERs of $4220
     vs. PAL + DEX, $4656 vs. NK-1-RA + PAL + DEX, $16,471 vs. OLA + PAL + DEX.
     In term of rate of absence of nausea, the PAL + NK-1-RA + DEX + OLA was
     assocd. with the highest rate of absence of nausea among all the treatment
     regimens at base case ICERs of $2291 vs. PAL + DEX, $1304 vs. NK-1-RA +
     PAL + DEX, $2657 vs. OLA + PAL + DEX.  From an economic perspective, our
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study revealed that whether to use overall CR or/and rate of absence of nausea as determinants in the antiemetic decision for the CINV patients, the CR-based-, and rate of absence of nausea-based cost-effectiveness analyses, showed negotiable ICER ests. for the treatment PAL + NK-1-RA + DEX + OLA over the combinations PAL + DEX, NK-1-RA + PAL + DEX, and OLA + PAL + DEX regimens.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2021:2009735 CAPLUS Full-text
TITLE: Effect of Evodia sticking Yongquan of tropisetron combined with dexamethasone on nausea and vomiting after thyroidectomy
AUTHOR(S): Zhang, Huijun; Fu, Zheng; Lu, Aiying; Liu, Ya
CORPORATE SOURCE: Anesthesiology Dept., the Second Hospital, Hebei Medical University, Shijiazhuang, 050000, Peop. Rep. China
SOURCE: Liaoning Zhongyi Zazhi (2017), 44(10), 2100-2102
CODEN: LZZAEJ; ISSN: 1000-1719
DIGITAL OBJECT ID: 10.13192/j.issn.1000-1719.2017.10.028
PUBLISHER: Liaoning Zhongyi Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: To explore the effect of Evodia sticking Yongquan of tropisetron combined with dexamethasone on nausea and vomiting after thyroidectomy. Methods: A total of 96 cases of thyroidectomy from Dec. 2014 to Dec. 2016 in our hospital were randomly divided into exptl. group and control group, 48 in each. The control group used dexamethasone tropisetron and the exptl. group used Evodia sticking Yongquan of tropisetron combined with dexamethasone in the treatment of nausea and vomiting. We compared two groups' incidence of nausea and vomiting 2, 8, 16 and 24 h after operation and compared postoperative nausea and vomiting and postoperative complications between the two groups. Results: Exptl. group's incidence of nausea and vomiting 2, 8, 16 and 24 h after operation was 18.8%, 30.2%, 23.2%, 14%, resp. and the control group's was 34.9%, 48.8%, 44.2%, 30.2%. Two groups' differences were statistically significant (P<0.05). The exptl. group's postoperative nausea and vomiting in 1 to 4 grade was 68.8% and that was 89.6% in the control group. Two groups had statistically significant difference (P<0.05). The exptl. group's postoperative dizziness and drowsiness ratio were 25%, 12.5% and those were 37.4% and 25% of the control group. Two groups' postoperative dizziness and headache ratio were statistically significant (P<0.05). Conclusion: Evodia sticking Yongquan of tropisetron combined with dexamethasone can reduce degree and times of postoperative nausea and vomiting and occurrence of complications.
IT INDEXING IN PROGRESS

L6 ANSWER 3 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2021:1853625 CAPLUS Full-text
DOCUMENT NUMBER: 178:276488
TITLE: Dexamethasone versus placebo for prevention of nausea, vomiting and pain after open total abdominal hysterectomy
AUTHOR(S): Kashanian, Maryam; Javanmanesh, Forough; Rokhtabnak, Faranak; AmirZargar, Shahla; Sheikhansari, Narges; Abdollahi, Hoda
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Akbarabadi Teaching Hospital, Iran University of Medical Sciences, Tehran, Iran
SOURCE: Journal of Obstetrics and Gynaecology (Abingdon, United Kingdom) (2022), 42(4), 687-691
CODEN: JOGYDW; ISSN: 0144-3615
DIGITAL OBJECT ID: 10.1080/01443615.2021.1931065
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Post-operative nausea and vomiting (PONV) is a disturbing issue. Dexamethasone has been suggested for the prevention of PONV. The aim of the present study was to evaluate the efficacy of dexamethasone as an

anti-emetic and analgesic following total abdominal hysterectomy. The study was performed as a double blind, placebo-controlled randomised clin. trial on 102 women undergoing an open total abdominal hysterectomy. The intervention group received 8 mg dexamethasone 1 h before surgery, and the control group received a placebo. The total no. of emesis episodes during the 24 h after surgery did not show significant difference between the two groups, however, the no. of emesis episodes in hours 2 and 4 after the surgery were less in the intervention group, but not in hours 0, 6, 12 and 24. The nausea severity in hours 0, 2, 4, 6 and 12 after the surgery, was less in the intervention group. The severity of pain was not different between the two groups. IMPACT STATEMENTWhat is already known on this subject. Post-operative nausea and vomiting (PONV) is an important and disturbing issue. It is one of the most common problems following gynaecol. surgeries including open total abdominal hysterectomy (TAH). Dexamethasone has been suggested as a prophylaxis for the prevention of PONV. What do the results of this study add. Dexamethasone 8 mg is effective for the prevention of late onset PONV (after 2 h of surgery) in the cases of open total abdominal hysterectomy. However, it has no effect on PONV immediately following surgery (hour 0) and pain. What are the implications of these findings for clin. practice and/or further research. Dexamethasone can be considered as an effective prophylaxis for PONV for the first 24 h after an open total abdominal hysterectomy, but it has limited effects on the management of early onset of PONV; between 0 and 2 h after surgery. Since the highest rates of emesis episodes and nausea severity are at this time, it is suggested to combine another rapid onset medication with dexamethasone. Also, dexamethasone, 8 mg, cannot be considered for pain relief after an open total abdominal hysterectomy. Higher amts. of dexamethasone should be evaluated for this purpose, in order to find appropriate dosages.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2021:1398482 CAPLUS Full-text

TITLE: Efficacy and safety of adding olanzapine to the standard preventive regimen for chemotherapy-induced nausea and vomiting in children: a randomized double-blind controlled trial

AUTHOR(S): Moshayedi, Mona; Salehifar, Ebrahim; Karami, Hossein; Hendouei, Narjes; Mousazadeh, Mahmoud; Haji, Somaye Alizadeh

CORPORATE SOURCE: Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran

SOURCE: Iranian Journal of Pharmaceutical Research (2021), 20(1), 318-326
CODEN: IJPRC9; ISSN: 1726-6890
URL: http://ijpr.sbmu.ac.ir/

DIGITAL OBJECT ID: 10.22037/ijpr.2019.112514.13803

PUBLISHER: Shaheed Beheshti University of Medical Sciences and Health Services, School of Pharmacy

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB This study aimed to assess the additive value of olanzapine to a combination of ondansetron and dexamethasone to prevent chemotherapy-induced nausea and vomiting (CINV) in pediatric patients. A total of 40 patients between 4 to 18 years of age were enrolled in this randomized clin. trial. Both groups received a combination of ondansetron and dexamethasone, and 0.14 mg/kg olanzapine or matched placebo were administered for olanzapine and control groups, resp. The primary end points were complete response and lack of nausea as far as three days after chemotherapy evaluated by the Common Terminol. Criteria for Adverse Effects (CTCAE) v5.0 and the Multinational Assocn. of Supportive Care in Cancer (MASCC) Anti-emesis Tool (MAT). Side effects of olanzapine were also analyzed. In patients receiving the std. regimen of ondansetron and dexamethasone, nausea was obsd. in 10.5% and 21% of patients according to MAT and CTCAE scales, resp. In the olanzapine group, 37.5% (MAT scale) and 31.3% (CTCAE scale) of patients developed nausea. Complete response was obsd. in 84% (MAT scale) and 94.7% (CTCAE scale) of patients in the placebo group receiving ondansetron and dexamethasone. In comparison, it was obsd. in 87.5% (MAT scale) and 81.25% (CTCAE scale) for patients

allocated to the olanzapine group. Neither acute nor delayed CINV was statistically different between placebo and olanzapine groups. The frequency of adverse effects was higher in the olanzapine group. Adding olanzapine to the std. regimen of CINV prophylaxis was only unhelpful in pediatric patients receiving moderately emetogenic chemotherapy but also assocd. with a higher rate of minor side effects.
IT INDEXING IN PROGRESS
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2020:2396700 CAPLUS Full-text
TITLE: Clinical observation of aprepitant triple therapy on prevention of nausea and vomiting caused by anthracycline combined cyclophosphamide chemotherapy regimen for breast cancer
AUTHOR(S): Tong, Ya-lan; Han, Tao; Song, Shu-xi; Zheng, Zhen-dong; Qu, Shu-xian; Qiu, Jia-ning; Liu, Zhao-zhe; Guo, Fang; Xie, Xiao-dong
CORPORATE SOURCE: Postgraduate School, Dalian Medical University, Dalian, 116000, Peop. Rep. China
SOURCE: Linchuang Wuzhen Wuzhi (2016), 29(4), 83-86
CODEN: LWWIA3; ISSN: 1002-3429
DIGITAL OBJECT ID: 10.3969/j.issn.1002-3429.2016.04.028
PUBLISHER: Linchuang Wuzhen Wuzhi Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective To investigate the effect of combined therapy consisting of aprepitant, tropisetron and dexamethasone in prevention of nausea and vomiting induced by breast cancer chemotherapy based on anthracycline and cyclophosphamide. Methods A total of 62 cases of breast cancer collected from Oncol. Department in General Hospital of Shenyang Military Area Command during Jan. 2014 and June 2015 were selected, and those patients all underwent chemotherapy consisting of anthracycline (epirubicin or doxorubicin) combined cyclophosphamide and they were divided into exptl. group (n = 31) and control group (n = 31) by CINV (chemotherapy-induced nausea and vomiting) regimen. The control group was given tropisetron and dexamethasone combined regimen in prevention of CINV while the exptl. group was added with aprepitant based on the drug used by the control group. The effect and adverse reaction of two groups in acute phase (0-24 h) and delay period (24-120 h) on preventing nausea and vomiting were obsd. Results The complete response rate and the control rate of acute phase had no statistical difference between the two groups (Z = -1.579, P = 0.114), however, for the delayed vomiting, the complete response rate and control rate of the exptl. group were higher than that of the control group and there was significant statistical difference (Z = -2.196, P = 0.028). Adverse reactions were mild and tolerable with no significant differences between the 2 groups (P>0.05). Conclusion The combined therapy of aprepitant is definitely effective for the delayed vomiting induced by anthracycline combined cyclophosphamide chemotherapy regimen of breast cancer, and the toxic reaction is tolerable.
IT INDEXING IN PROGRESS

L6 ANSWER 6 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2020:2302047 CAPLUS Full-text
DOCUMENT NUMBER: 175:338679
TITLE: A comparative study of metoclopramide alone and in mixture with dexamethasone for deterrence of post-operative nausea and vomiting after laparoscopic cholecystectomy
AUTHOR(S): Afzal, Muhammad Azeem; Babar, Fatima; Babar, Amna
CORPORATE SOURCE: Punjab Medical College, Faisalabad, Pak.
SOURCE: Indo American Journal of Pharmaceutical Sciences (2020), 7(8), 1001-1004
CODEN: IAJPBB; ISSN: 2349-7750
URL: http://www.iajps.com/
DIGITAL OBJECT ID: 10.5281/zenodo.4009333
PUBLISHER: Indo American Journal of Pharmaceutical Sciences
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB To compare the efficacy of i.v. administration of metoclopramide alone and in combination with dexamethasone in the prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy. Randomized, single-blind, intervention study. This study was conducted at the Surgical department of Allied Hospital Faisalabad for one-year duration from March 2019 to March 2020. After obtaining the approval of the hospital's ethics committee, the study was conducted on 100 patients who were randomly divided into two groups A and B, 50 people in each group. They all belonged to the age of 25-40. Randomization was performed using the envelope randomization method. Patients received metoclopramide 10 mg alone or metoclopramide 5 mg and dexamethasone 4 mg i.v. 30 min prior to induction of anesthesia. All patients were subjected to general anesthesia with endotracheal intubation with sodium thiopentone and succinylcholine and was maintained with isoflurane and N2O with O2 in both groups. PONV was assessed after surgery. Patients in group B who received metoclopramide in combination with dexamethasone had significantly less nausea and vomiting in the first 24 h after surgery compared to patients in group A who received only metoclopramide. In this study, a single dose of 5 mg metoclopramide and 4 mg dexamethasone produced a better antiemetic effect after laparoscopic cholecystectomy than 10 mg metoclopramide alone.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2020:2301996 CAPLUS Full-text
DOCUMENT NUMBER: 175:334951
TITLE: Efficacy of preoperative dexamethasone to decrease nausea and vomiting after laparoscopic cholecystectomy
AUTHOR(S): Tahir, Ifrah; Abid, Sana; Amjad, Sheeza
CORPORATE SOURCE: Fatima Jinnah Medical University, Lahore, Pak.
SOURCE: Indo American Journal of Pharmaceutical Sciences (2020), 7(9), 500-504
CODEN: IAJPBB; ISSN: 2349-7750
URL: http://www.iajps.com/
DIGITAL OBJECT ID: 10.5281/zenodo.4017081
PUBLISHER: Indo American Journal of Pharmaceutical Sciences
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Laparoscopic cholecystectomy (LC) is one of the most common, popular, and accepted procedures in patients with symptomatic gallstones. Although serious adverse events are rare following laparoscopic cholecystectomy, 50% to 75% of patients experience post-operative nausea or vomiting (PONV). Several randomized controlled trials have shown that a single pre-operative dose of Inj. Dexamethasone is effective in reducing postoperative nausea and vomiting and the need for antiemetics after laparoscopic cholecystectomy because it is freely available, economical, and a single dose does not have any significant side effects, so it should be used more frequently in patients undergoing cholecystectomy laparoscopy. The objective of the present study is to investigate the outcome in terms of Post-operative nausea and vomiting within 24 h in patients undergoing Laparoscopic Cholecystectomy receiving preoperative dexamethasone and those not receiving. This randomized, placebo-controlled, double-blind study will be conducted at the Surgical Unit-II of Sir Ganga Ram Hospital, Lahore for one-year duration from March 2019 to March 2020. A 100 patients; 50 in each group with 80% power of study, 5% significance level and taking percentages of vomiting and nausea in both Dexamethasone and placebo groups, i.e., 14% and 46% resp. Dexamethasone improves the surgical outcome by reducing disabling symptoms of nausea and vomiting without apparent side effects. However, there is no evidence in redn. of postoperative pain or analgesic requirements in this trial. So preoperative dexamethasone 8mg may be used as a routine in patients two hours before undergoing elective laparoscopic cholecystectomy.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2020:2162519 CAPLUS Full-text
TITLE: Clinical effect of droperidol or tropisetron combined

with dexamethasone in preventing nausea and vomiting after gynecological laparoscopy
AUTHOR(S): Wang, Wu; Wu, Duo-zhi
CORPORATE SOURCE: Department of Anesthesiology, Tunchang People's Hospital, Tunchang, 571600, Peop. Rep. China
SOURCE: Linchuang Junyi Zazhi (2016), 44(7), 752-753
CODEN: LJZIAT; ISSN: 1671-3826
DIGITAL OBJECT ID: 10.16680/j.1671-3826.2016.07.28
PUBLISHER: Linchuang Junyi Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: The article compared the effects of droperidol or tropisetron combined with dexamethasone on the prevention of postoperative nausea and vomiting (PONV) in patients undergoing gynecol. laparoscopic surgery. Methods: In the paper, 60 patients who underwent elective gynecol. laparoscopic surgery at Tunchang County People's Hospital in Hainan Province from August 2013 to June 2014 were selected as the research objects. In the article, patients were randomly divided into droperidol combined with dexamethasone group (F group) and tropisetron combined with dexamethasone group (T group), 30 cases in each group. Patients in group F were given i.v. dexamethasone 10.0 mg before induction, and droperidol 2.5 mg 30 min before the end of the operation. In addn. to dexamethasone, patients in group T were given tropisetron 4.0 mg 30 min before the end of the operation. Blindly observe the occurrence of PONV in the two groups of patients within 2, 6, and 24 h after surgery. Results: The incidence of PONV at 24 h after operation in group F was 40.0% (12/30), which was significantly lower than the 70.0% (21/30) in group T. The total no. of postoperative nausea and vomiting in group F, and the VAS score of PONV pain at 2, 6, and 24 h after surgery were lower than those in group T ($P < 0.05$). Conclusion: Droperidol combined with dexamethasone could prevent PONV better than tropisetron combined with dexamethasone.
IT INDEXING IN PROGRESS

L6 ANSWER 9 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2020:2143803 CAPLUS Full-text
DOCUMENT NUMBER: 176:208049
TITLE: Retrospective analysis of risk factors of postoperative nausea and vomiting in patients undergoing ambulatory strabismus surgery via general anaesthesia
AUTHOR(S): Li, Jinfei; Ye, Huijin; Shen, Weihua; Chen, Qianru; Lin, Yiquan; Gan, Xiaoliang
CORPORATE SOURCE: State Key Laboratory of Ophthalmology, Department of Anesthesiology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, Guangdong Province, Peop. Rep. China
SOURCE: Indian Journal of Anaesthesia (2020), 64(5), 375-382
CODEN: IJANBN; ISSN: 0019-5049
URL: http://www.ijaweb.org/
DIGITAL OBJECT ID: 10.4103/ija.ija_16_20
PUBLISHER: Medknow Publications
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background and Aims: Postoperative nausea and vomiting (PONV), one of the common complications following strabismus surgery, would delay the ambulatory discharge time. The aim of this retrospective study was to det. the risk factors of PONV in patients undergoing ambulatory strabismus surgery under general anesthesia, with the treatments of dexamethasone and 5-HT3 antagonist combination. Methods: We reviewed 721 consecutive patients (12-60 years old) undergoing ambulatory strabismus surgery under general anesthesia at an academic eye center between Dec. 2016 and Jan. 2019. Patients received prophylactic treatment of dexamethasone and 5-HT3 antagonist combination during anesthesia induction, and PONV was evaluated during the early recovery period before discharge. Results: The dexamethasone and 5-HT3 antagonist combination effectively reduced the incidence of PONV (3.05%, 22/721), and the patients who experienced PONV had statistically prolonged phase II recovery time as compared those who did not ($P = 0.006$). The sum of the extraocular muscles manipulated and the use of nalbuphine (vs flurbiprofen axetil) were the independent risk factors for PONV ($P < 0.05$). Conclusion: The sum of the extraocular muscles manipulated and the use of nalbuphine are potentially modifiable

risk factors for PONV after strabismus surgery with the treatments of dexamethasone and 5-HT3 antagonist combination.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2019:92493 CAPLUS Full-text

DOCUMENT NUMBER: 173:90631

TITLE: A comparison of palonosetron and dexamethasone for postoperative nausea and vomiting in orthopedic patients receiving patient-controlled epidural analgesia

AUTHOR(S): Kim, Byung-Gun; Kim, Hyunzu; Lim, Hyun-Kyoung; Yang, Chunwoo; Oh, Sora; Lee, Byung-Wook

CORPORATE SOURCE: Department of Anesthesiology and Pain Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, S. Korea

SOURCE: Korean Journal of Anesthesiology (2017), 70(5), 520-526
CODEN: KJAOBE; ISSN: 2005-6419

DIGITAL OBJECT ID: 10.4097/kjae.2017.70.5.520

PUBLISHER: Korean Society of Anesthesiologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Postoperative nausea and vomiting (PONV) is one of the major concerns after anesthesia and surgery, and it may be more frequent in orthopedic patients receiving patient-controlled epidural analgesia (PCEA). The purpose of this study was to compare the effect of palonosetron and dexamethasone on the prevention of PONV in patients undergoing total joint arthroplasty and receiving PCEA. Methods: Patients scheduled for total hip or knee arthroplasty under spinal anesthesia/PCEA were randomly allocated to receive either i.v. palonosetron (0.075 mg, n = 50) or dexamethasone (5 mg, n = 50). Treatments were administered i.v. to the patients 30 min before the beginning of surgery. The total incidence of PONV and incidence in each time period, severity of nausea, need for rescue anti-emetics, pain score, and adverse effects during the first 48 h postoperatively were evaluated. Results: The total incidence of PONV was lower in the palonosetron group compared with the dexamethasone group (18.4% vs. 36.7%, P = 0.042), but there were no statistically significant differences in incidence between the groups at all time points. No significant intergroup differences were obsd. in the severity of nausea, use of rescue anti-emetics, pain score, and adverse effects. Conclusions: Although there were no significant differences in the incidence of PONV between the treatment groups at all time points, i.v. palonosetron reduced the total incidence of PONV in orthopedic patients receiving PCEA compared with dexamethasone.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2018:1646059 CAPLUS Full-text

DOCUMENT NUMBER: 172:397065

TITLE: Phase III Randomized Trial of Palonosetron and Dexamethasone With or Without Aprepitant to Prevent Nausea and Vomiting Induced by Full-dose Single-day Cisplatin-based Chemotherapy in Lung Cancer

AUTHOR(S): Wu, Fang; Lin, Xiaoping; Yang, Zhanghuan; Sun, Ziyi; Zeng, Fanxu; Heng, Jianfu; Qu, Jingjing; Zeng, Liang; Yang, Nong; Zhang, Yongchang

CORPORATE SOURCE: Department of Medical Oncology, Lung Cancer and Gastrointestinal Unit, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, Peop. Rep. China

SOURCE: Clinical Lung Cancer (2018), 19(6), e913-e918
CODEN: CLCLCA; ISSN: 1525-7304

DIGITAL OBJECT ID: 10.1016/j.cllc.2018.08.006

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB This study aimed to det. the efficacy and safety of aprepitant, palonosetron, and dexamethasone to prevent chemotherapy-induced nausea and vomiting in patients with locally advanced or metastatic lung cancer receiving full-dose single-day cisplatin-based combination chemotherapy. Patients diagnosed with locally advanced or metastatic lung cancer who received full dose single-day cisplatin-based chemotherapy were randomized (1:1) to aprepitant plus palonosetron and dexamethasone, or placebo plus palonosetron and dexamethasone. The primary endpoint was complete response of nausea and vomiting in the first cycle. The secondary endpoints were the proportion of patients with nausea and vomiting who received rescue antiemetic medication, the response of cross-over patients, and safety.A total of 244 patients were randomized. There was no difference between the 2 groups regarding personal characteristics. The administration of aprepitant significantly improved the complete response for vomiting in the overall period (92.6% vs. 79.93%; P <.01), but not a nausea-free response (75.4% vs. 71.3%; P > .05) in the first cycle. The percentage of patients who received rescue antiemetic medication was decreased for the aprepitant group (14.8% vs. 37.1%; P < .001). Patients who did not use aprepitant and suffered with nausea and vomiting in cycle 1 were crossed over to the aprepitant group (N = 32), and the rate of nausea and vomiting in cycle 2 was decreased to 37.5% (P < .05) and 25% (P < .05), resp. There were no drug-related adverse effects.Aprepitant plus palonosetron and dexamethasone proved to be effective and well-tolerated in preventing chemotherapy-induced nausea and vomiting after administration of full-dose single-day cisplatin-based combination chemotherapy.
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2018:1182306 CAPLUS Full-text
TITLE: Safety of Dexamethasone for Nausea and Vomiting Prophylaxis in Children Receiving Hematopoietic Stem Cell Transplantation
AUTHOR(S): Paw Cho Sing, Edric; Schechter, Tal; Ali, Muhammad; Sung, Lillian; Dupuis, L. Lee
CORPORATE SOURCE: Department of Pharmacy, Can.
SOURCE: Journal of Pediatric Hematology/Oncology (2018), 40(5), e278-e282
CODEN: JPHOFG; ISSN: 1077-4114
DIGITAL OBJECT ID: 10.1097/mph.0000000000001186
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Many children undergoing hematopoietic stem cell transplantation (HSCT) experience chemotherapy-induced nausea and vomiting (CINV) despite receiving prophylaxis. Guideline-consistent CINV prophylaxis includes dexamethasone, but uncertainty with regard to safety potentially limits the use of dexamethasone in children. We describe immediate adverse events (AEs) attributable to dexamethasone given for CINV prophylaxis to children during HSCT conditioning. Children enrolled in a previous prospective study were retrospectively analyzed. Objective parameters related to specific AEs occurring within 5 days of dexamethasone administration were abstracted from health records and graded according to the Common Terminol. Criteria for Adverse Events version 4.03 (CTCAE v4.03). Their assocn. to dexamethasone was assessed using the Liverpool Causality Assessment Tool. Forty-six children (median age, 10.2 y) were eligible for anal. The most frequent AEs attributable to dexamethasone (Liverpool Causality Assessment Tool category of probable or definite) were hyperglycemia (63%; CTCAE v4.03 grade 3: 2%), hypertension (52%; CTCAE v4.03 grade 3: 15%), and bradycardia (46%; CTCAE v4.03 grade 3: 0%). Other AEs included dyspepsia or gastroesophageal reflux disease (24%) and alterations in mood and behavior (9%). No AE exceeded CTCAE v4.03 grade 3 in severity. In children undergoing HSCT who received dexamethasone for CINV prophylaxis, immediate AEs attributable to dexamethasone were most often of minor clin. importance and transient.

IT INDEXING IN PROGRESS
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2017:1690445 CAPLUS Full-text
DOCUMENT NUMBER: 168:197511
TITLE: Dexamethasone alone vs in combination with transcutaneous electrical acupoint stimulation or tropisetron for prevention of postoperative nausea and vomiting in gynaecological patients undergoing laparoscopic surgery
AUTHOR(S): Yang, X. Y.; Xiao, J.; Chen, Y. H.; Wang, Z. T.; Wang, H. L.; He, D. H.; Zhang, J.
CORPORATE SOURCE: Department of Anaesthesiology, Huashan Hospital, Fudan University, Shanghai, 200040, Peop. Rep. China
SOURCE: British Journal of Anaesthesia (2015), 115(6), 883-889
CODEN: BJANAD; ISSN: 0007-0912
DIGITAL OBJECT ID: 10.1093/bja/aev352
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: Postoperative nausea and vomiting (PONV) is commonly reported after surgery and anesthesia. We compared the effects of combinations of elec. acupoint stimulation or tropisetron with dexamethasone with the effects of dexamethasone alone, for inhibition of PONV in gynaecol. patients undergoing laparoscopic surgery. Methods: We randomized 157 patients undergoing elective gynaecol. laparoscopic surgery under general anesthesia into the following three groups: acupoint stimulation+dexamethasone (Group Acu, n=53), tropisetron+dexamethasone (Group Trp, n=53), and dexamethasone alone (Group Dxm, n=51). The incidence of nausea, vomiting, and need for rescue antiemetics was recorded 2, 6, 24, and 48 h after surgery. Results: We found significant differences in the incidence of PONV during 24 h after surgery between the combination therapy groups and the dexamethasone-alone group (P=0.021). In the first 24 h, 28% of patients in Group Acu, 26% of patients in Group Trp, and 50% of patients in Group Dxm experienced nausea, vomiting, or both. The incidence of 24 h PONV in Group Acu was significantly lower than that in Group Dxm (P=0.048; odds ratio 0.389; 95% CI 0.170-0.891). The incidence of 24 h PONV in Group Trp was also significantly lower than that in Group Dxm (P=0.042; odds ratio 0.359; 95% CI 0.157-0.819). There was no significant difference between Group Acu and Group Trp (P=0.857). The need for antiemetic rescue medication was similar in the three groups. All groups expressed similar patient satisfaction. ConclusionsCombined with dexamethasone, elec. acupoint stimulation or tropisetron is more effective in PONV prophylaxis than dexamethasone alone in gynaecol. patients undergoing laparoscopic surgery.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2016:751501 CAPLUS Full-text
DOCUMENT NUMBER: 166:14963
TITLE: Comparison of dexamethasone or intravenous fluids or combination of both on postoperative nausea, vomiting and pain in pediatric strabismus surgery
AUTHOR(S): Sayed, Jehan Ahmed; Riad, Mohamed Amir F.; Ali, Mohamed Omar M.
CORPORATE SOURCE: Department of Anesthesia and Intensive Care, Assuit university, Assuit, Egypt
SOURCE: Journal of Clinical Anesthesia (2016), 34, 136-142
CODEN: JCLBE7; ISSN: 0952-8180
DIGITAL OBJECT ID: 10.1016/j.jclinane.2016.03.049
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Strabismus surgery is perhaps a pediatric surgical procedure that has the strongest evidence of postoperative nausea and vomiting (PONV) risk. This randomized controlled blind study was designed to evaluate the efficacy of combined therapy of dexamethasone and intraoperative superhydration vs their monotherapy on the incidence and severity of PONV and on pain intensity after pediatric strabismus surgery. A total of 120 children aged 6 to 12 years undergoing strabismus surgery were randomized to equally 3 groups to receive 0.15 mg/kg dexamethasone (dexamethasone group) or intraoperative superhydration of lactated Ringer's soln. in a dose of 30 mL/kg per fasting time (superhydration group), or a combination of dexamethasone and intraoperative fluid in the same strategy (combination therapy group). The incidence and severity of PONV and pain using visual analog scale score, and need for supplemental antiemetic and analgesic therapy and their consumptions were assessed and compared in the 3 studied groups for 24 h postoperatively. The incidence of PONV and postoperative vomiting was significantly lower (P> .001) in the combination therapy group (5% and 5% resp.) compared with the dexamethasone group (35% and 30%) and superhydration group (32.5% and 35%). There was no significant difference among patients in the superhydration group and dexamethasone group in the cumulative incidences of PONV in the whole 24 h postoperatively. Postoperative aggregated visual analog scale pain score and total acetaminophen consumption showed a significant redn. (P> .05) in the combination therapy group together with significant prolongation of time to the first analgesic request compared with both the superhydration group and the dexamethasone group. Combined therapy of 0.15 mg/kg dexamethasone 1 min before induction and intraoperative fluid superhydration is an effective and safe way to reduce PONV and pain better than monotherapy of dexamethasone, or intraoperative superhydration sep. for pediatric strabismus surgery.

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2015:1652623 CAPLUS Full-text

DOCUMENT NUMBER: 165:137330

TITLE: Palonosetron in combination with 1-day versus 3-day dexamethasone for prevention of nausea and vomiting following paclitaxel and carboplatin in patients with gynecologic cancers: A randomized, multicenter, phase-II trial

AUTHOR(S): Matsuura, Motoki; Satohisa, Seiro; Teramoto, Mizue; Tanaka, Ryoichi; Iwasaki, Masahiro; Nishikawa, Akira; Mizunuma, Masahiro; Tanaka, Satoshi; Hayakawa, Osamu; Saito, Tsuyoshi

CORPORATE SOURCE: Department of Gynecology and Obstetrics, Sapporo Medical University, Sapporo, Japan

SOURCE: Journal of Obstetrics and Gynaecology Research (2015), 41(10), 1607-1613
CODEN: JOGRFD; ISSN: 1447-0756

DIGITAL OBJECT ID: 10.1111/jog.12748

PUBLISHER: Wiley-Blackwell

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Aim : Chemotherapy-induced nausea and vomiting (CINV) can affect a patient's quality of life, leading to poor compliance with further treatments. Previous studies have provided minimal data about carboplatin-based regimens. Female sex is a known risk factor for CINV. The purpose of this study was to evaluate palonosetron plus single-dose dexamethasone (DEX) for preventing CINV caused by carboplatin plus paclitaxel combination therapy (TC regimen) in patients with gynecol. cancers. Material and Methods : Patients were recruited for this phase-II, multicenter, randomized trial from 12 hospitals in Hokkaido, Japan. Eligible patients were women with uterine cervical, endometrial or ovarian cancer scheduled to receive conventional TC regimen or dose-dense TC regimen; 116 patients were randomly assigned to receive palonosetron in combination with 1-day DEX or 3-day DEX. Results : During the overall period, complete response (CR) was obsd. in 67.9% (95% confidence interval, 53.7-80.1) of patients in the 3-day DEX arm, and 60.7% (95% confidence interval, 46.8-73.5) of patients in the 1-day DEX arm; CR was

significantly lower in the 1-day DEX arm if motion sickness was already present (P = 0.0370). In the severe hyperemesis gravidarum cohort, CR in the 1-day DEX arm tended to be lower than in the 3-day DEX arm. Conclusion : Combination therapy of palonosetron and 1-day DEX was effective for subjects undergoing a TC regimen for gynecol. cancers. However, the possibility of reduced efficacy of 1-day only DEX therapy in women undergoing a TC regimen could not be refuted and requires further investigation.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2015:1380714 CAPLUS Full-text

DOCUMENT NUMBER: 163:641168

TITLE: Postoperative hyperglycemia after 4- vs. 8-10-mg dexamethasone for postoperative nausea and vomiting prophylaxis in patients with type II diabetes mellitus: a retrospective database analysis

AUTHOR(S): Low, Ying; White, William D.; Habib, Ashraf S.

CORPORATE SOURCE: Department of Anesthesiology, Duke University Medical Center, Durham, NC, 27710, USA

SOURCE: Journal of Clinical Anesthesia (2015), 27(7), 589-594 CODEN: JCLBE7; ISSN: 0952-8180

DIGITAL OBJECT ID: 10.1016/j.jclinane.2015.07.003

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB The study objective is to compare change in postoperative blood glucose from preoperative values in patients with type II diabetes mellitus receiving 4- or 8-10-mg dexamethasone for postoperative nausea and vomiting prophylaxis. This is a retrospective database study. The setting is at an academic university medical center. There are 1037 adult patients, American Society of Anesthesiologists phys. status I-IV, with type II diabetes mellitus, undergoing elective surgery between Jan. 1, 2006, and March 31, 2012, and who were hospitalized for at least 24 h. The interventions are dexamethasone 4 or 8-10 mg for postoperative nausea and vomiting prophylaxis. Age, sex, American Society of Anesthesiologists class, height, wt., body mass index, surgery date, type and duration of surgery, Hb A1c (HbA1c) within 180 days of surgery, type of anesthesia, preoperative blood glucose in the preoperative holding area, max. blood glucose in the postanesthesia care unit (PACU) and first 24 h postoperatively, and insulin requirements intraoperatively and in PACU. In unadjusted anal., the 8-10-mg dose was assocd. with greater (mean ± SD) increase in blood glucose compared with the 4-mg dose in PACU (58 ± 50 vs. 43 ± 45 mg/dL, P <.0001) and over 24 h (101 ± 71 vs. 67 ± 65 mg/dL, P <.0001). In the multivariable model, predictors of blood glucose increase in PACU included dexamethasone dose (P <.0001), preoperative serum glucose (P <.0001), duration of surgery (P <.0001), and total dose of insulin (P <.0001). Over 24 h, the significant predictors of glucose increase included dexamethasone dose (P <.0001), preoperative blood glucose level (P <.0001), duration of surgery (P <.0001), year of surgery (P =.04), and neurosurgical procedures (P =.02). This model ests. the increase in postoperative glucose to be 25 mg/dL higher over 24 h with dexamethasone 8-10 mg than with 4 mg (95% confidence limits, 18-32 mg/dL). Dexamethasone 8-10 mg is assocd. with a significantly greater perioperative increase in blood glucose compared with a 4-mg dose.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2014:1922650 CAPLUS Full-text

DOCUMENT NUMBER: 162:560404

TITLE: Combined use of multiday palonosetron with aprepitant and low-dose dexamethasone in prevention of nausea and emesis among patients with multiple myeloma and lymphoma undergoing autologous hematopoietic stem cell

transplant: a pilot study
AUTHOR(S): Deauna-Limayo, Delva; Aljitawi, Omar S.; Ganguly, Siddhartha; Abhyankar, Sunil; Wick, Jo A.; McGuirk, Joseph P.
CORPORATE SOURCE: Hematology/Oncology, UC San Diego Nevada Cancer Institute, Las Vegas, NV, USA
SOURCE: Journal of Oncology Pharmacy Practice (2014), 20(4), 263-269
CODEN: JOPPFI; ISSN: 1078-1552
DIGITAL OBJECT ID: 10.1177/1078155213502103
PUBLISHER: Sage Publications Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: The current std. for prevention of chemotherapy-induced nausea/vomiting in autologous stem cell transplant only achieves 4-20% emetic control. Objectives: To assess emetic responses to multiday palonosetron, aprepitant, and low-dose dexamethasone among patients with myeloma and lymphoma undergoing autologous hematopoietic stem cell transplant. Methods: Oral aprepitant 125/80/80 mg was administered with i.v. dexamethasone 4mg and palonosetron 0.25 mg on days -3, -2, -1 for multiple myeloma and days -7 through -3 for lymphoma. Palonosetron was repeated day +3 in both groups. Results: A total of 20 patients were enrolled and 18 analyzed. None experienced emetic failure with complete control achieved in 78, 33, and 17% in the acute, delayed, and extended phases, resp. Nausea occurred in 78% although not significant in 61%, with median Nausea Visual Score of 4.5. Quality of life correlated with emetic and nausea control. Eight patients developed grade 2-3 nonhematol. toxicities with only one event attributed to the study medications. Conclusions: This triplet regimen was feasible with acceptable safety profile in the autologous hematopoietic stem cell transplant setting. Emetic control was best achieved in the acute phase. Lesser degree of emetic and nausea control in the delayed and extended phases impacted quality of life. Our results warrant further evaluation in a larger autologous hematopoietic stem cell transplant population.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2014:1886744 CAPLUS Full-text
DOCUMENT NUMBER: 162:569895
TITLE: Comparison of Metoclopramide and Dexamethasone with alone for prevention of post-operative nausea vomiting
AUTHOR(S): Tiwari, Madhu; Tiwari, Pawan; Garg, Nidhi; Chhabra, Balbir; Garg, Krishan Lal
CORPORATE SOURCE: Department of Anaesthesia, Faculty of Medicine and Health Sciences, SGT University, Haryana, India
SOURCE: Journal of Evolution of Medical and Dental Sciences (2014), 3(26), 7344-7348
CODEN: JEMDBT; ISSN: 2278-4748
DIGITAL OBJECT ID: 10.14260/jemds/2014/2900
PUBLISHER: Akshantala Enterprises
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. OBJECTIVE: To study the antiemetic efficacy of combination of Metoclopramide and Dexamethasone as compared to Dexamethasone alone in prevention of post-operative nausea and vomiting in patients undergoing elective abdominal surgical procedures. SETTING AND DURATION OF STUDY: It is a prospective, randomized and blind study done in the department of Anesthesiol., SGT University of Health Sciences from June 2010 to Nov. 2011. PATIENTS AND METHODS: 100 adult ASA I and II patients undergoing elective surgical procedures were divided into groups A and B. Patients were randomized into 2 groups, Group A (n=50) were given Dexamethasone 8mg I/V (2ml), Group B (n=50) were given a combination of Metoclopramide 10 mg and Dexamethasone 8 mg, 30 min before end of surgery. All patients were obsd. for 24 h in the ward for nausea and vomiting (PONV) postoperatively. RESULTS: Less than two episodes were seen in 59 (59%) cases in which 36% (18/50) were in group A and 82% (41/50) in group B. Two episodes of vomiting were obsd. in 29(29%) and more than two episodes of vomiting was obsd. in 12(12%) cases. Less than two episodes of vomiting was

significantly high in group B than group A (82% vs. 36%). CONCLUSION: There was significant redn. in post-operative nausea and vomiting (PONV) when Dexamethasone and Metoclopramide was used per operatively.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2014:1885665 CAPLUS Full-text
DOCUMENT NUMBER: 163:345467
TITLE: The impact of prophylactic dexamethasone on nausea and vomiting after thyroidectomy: a systematic review and meta-analysis
AUTHOR(S): Zou, Zhenhong; Jiang, Yuming; Xiao, Mingjia; Zhou, Ruiyao
CORPORATE SOURCE: Department of General Surgery, Southern Medical University, Guangzhou City, Guangdong, Peop. Rep. China
SOURCE: PLoS One (2014), 9(10), e109582/1-e109582/11, 11 pp.
CODEN: POLNCL; ISSN: 1932-6203
DIGITAL OBJECT ID: 10.1371/journal.pone.0109582
PUBLISHER: Public Library of Science
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: We carried out a systematic review and meta-anal. to evaluate the impact of prophylactic dexamethasone on post-operative nausea and vomiting (PONV), post-operative pain, and complications in patients undergoing thyroidectomy. Methods: We searched Pubmed, Embase, and Cochrane Library databases for randomized controlled trials (RCTs) that evaluated the prophylactic effect of dexamethasone vs. placebo with or without other antiemetics for PONV in patients undergoing thyroidectomy. Meta-analyses were performed using RevMan 5.0 software. Results: Thirteen RCTs that considered high quality evidence including 2,180 patients were analyzed. The meta-anal. demonstrated a significant decrease in the incidence of PONV (RR 0.52, 95% CI 0.43 to 0.63, P < 0.00001), the need for rescue anti-emetics (RR 0.42, 95% CI 0.30 to 0.57, P < 0.00001), post-operative pain scores (WMD -1.17, 95% CI -1.91 to -0.44, P = 0.002), and the need for rescue analgesics (RR 0.65, 95% CI 0.50-0.83, P = 0.0008) in patients receiving dexamethasone compared to placebo, with or without concomitant antiemetics. Dexamethasone 8-10 mg had a significantly greater effect for reducing the incidence of PONV than dexamethasone 1.25-5 mg. Dexamethasone was as effective as other anti-emetics for reducing PONV (RR 1.25, 95% CI 0.86-1.81, P = 0.24). A significantly higher level of blood glucose during the immediate post-operative period in patients receiving dexamethasone compared to controls was the only adverse event. Conclusions: Prophylactic dexamethasone 8-10 mg administered i.v. before induction of anesthesia should be recommended as a safe and effective strategy for reducing the incidence of PONV, the need for rescue anti-emetics, post-operative pain, and the need for rescue analgesia in thyroidectomy patients, except those that are pregnant, have diabetes mellitus, hyperglycemia, or contraindications for dexamethasone. More high quality trials are warranted to define the benefits and risks of prophylactic dexamethasone in potential patients with a high risk for PONV.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2014:1012567 CAPLUS Full-text
DOCUMENT NUMBER: 161:209623
TITLE: Study of dexamethasone in preventing postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy
AUTHOR(S): Zhou, Liang; Han, Zhi-cheng; Dong, Ying-jie
CORPORATE SOURCE: Hospital of Liang Zhuang Mining Group, Xintai, Shandong Province, 271219, Peop. Rep. China
SOURCE: Taishan Yixueyuan Xuebao (2014), 35(2), 110-113
CODEN: TYXUEE; ISSN: 1004-7115
DIGITAL OBJECT ID: 10.3969/j.issn.1004-7115.2014.02.011
PUBLISHER: Taishan Yixueyuan Xuebao Bianjibu
DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The efficacy of i.v. of different dosages of dexamethasone in preventing postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy (LC) was investigated. Two hundred cases of ASA phys. status I and II patients, aged from 18 to 65 years old, were randomly divided into five groups (n=40 each). Patients received dexamethasone 0.05 mg·kg-1 (D0.05 group), 0.1 mg·kg-1 (D0.1 group), 0.2 mg·kg-1 (D0.2 group), ondansetron 4 mg (0 group) and saline (S group) before the induction of general anesthesia. All patients received a standardized anesthetic and surgical treatment. The episodes of nausea and vomiting and antiemetic requirements were recorded during 0-24 h resp. after operation. Groups D0.1 and D0.2 were significantly different from group S during 0-24 h after operation in the incidences of postoperative nausea and vomiting (PONV) (resp. P<0.01) and the patients requiring rescue antiemetics (P<0.05, resp.). The PONV and the proportions of patients requiring rescue anti emetics between groups D0.1 and D0.2 were not significantly different (P>0.05). The efficacy of groups D0.05 for preventing PONV was poor. Groups D0.05 and S were not significantly different (P>0.05). Group D0.1 was significantly different from group D0.05 during 0-24 h after operation in the incidences of PONV (P<0.01) and the proportions of patients requiring rescue anti emetics (P<0.05). Group D0.1 was significantly different from group 0 during 0-24 h after operation in the incidences of PONV (P<0.05). Dexamethasone 0.1 mg·kg-1 was the same effective as dexamethasone 0.2 mg·kg-1, and was more effective than saline control for preventing PONV in patients undergoing LC. Dexamethasone 0.05 mg·kg-1 was in effective for this purpose. Dexamethasone 0.1 mg·kg-1 is suggested to be the min. ED in this patient population.

L6 ANSWER 21 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2013:1898439 CAPLUS Full-text

DOCUMENT NUMBER: 161:354358

TITLE: Effect of dexamethasone on emesis after morphine administration in an animal model

AUTHOR(S): Marjani, M.; Mirfakhrai, J.

CORPORATE SOURCE: Department of Clinical Sciences, Faculty of Veterinary Medicine, Karaj Branch, Islamic Azad University, Karaj, Iran

SOURCE: Journal of Fasa University of Medical Sciences (2013), 3(2), 163-168
CODEN: JFUMAY; ISSN: 2228-5105
URL: http://journal.fums.ac.ir

PUBLISHER: Fasa University of Medical Sciences

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: Persian

AB Morphine is commonly used to relieve moderate to severe pain, but some side effects include vomiting. The objective of this study was to evaluate the anti-emetic properties of dexamethasone in animal models receiving morphine. In a clin. study fourteen cross breed dogs that were 2 and 4 years old were assigned to two equals groups. The treatment group received dexamethasone (1 mg/kg intra muscularly), 60 min prior to morphine administration. The control group received 2 cc of saline i.m. (IM), 60 min prior to morphine administration. After 60 min all dogs received morphine (1 mg/kg i.m.). After morphine was administered all dogs were obsd. for 1 h to allow assessment of frequency of emesis and time until the onset of the first emetic episode and then they were compared accordingly. The Mean ± SD for the first emetic episode in the treatment group was 266 ± 49. The same no. was 197.6 ± 31.84 in the control group. There was no statistically significant deference for the time of the first emetic episode between treatment and control group (P = 0.23). There was no statistically significant deference for the no. of emetic episodes between the treatment and control group (P = 0.16). There was no statistically significant deference for the wt. of the dogs between the treatment and control groups (P = 0.95). In the current study, the administration of dexamethasone 1 h before administering morphine was not able to significantly affect the frequency of emetic episodes or the time period before the occurrence of the first emetic episode.

L6 ANSWER 22 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2013:1716650 CAPLUS Full-text
DOCUMENT NUMBER: 160:451382
TITLE: Evaluation of the relation between patient characteristics and the state of chemotherapy-induced nausea and vomiting in patients with gynecologic cancer receiving paclitaxel and carboplatin
AUTHOR(S): Furukawa, Naoto; Akasaka, Juria; Shigemitsu, Aiko; Sasaki, Yoshikazu; Nagai, Akira; Kawaguchi, Ryuji; Kobayashi, Hiroshi
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara, 634-8522, Japan
SOURCE: Archives of Gynecology and Obstetrics (2014), 289(4), 859-864
CODEN: AGOBEJ; ISSN: 0932-0067
DIGITAL OBJECT ID: 10.1007/s00404-013-3058-7
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Purpose: An antiemetic regimen for patients taking paclitaxel and carboplatin (TC) includes dexamethasone (20 mg) to protect against hypersensitivity. Chemotherapy-induced nausea and vomiting (CINV), however, is difficult to adequately control in patients receiving TC. In the present study, we retrospectively investigated risk factors for CINV in patients receiving TC with this antiemetic regimen based on a questionnaire. Methods: Eligible patients were diagnosed with gynecol. cancer and receiving paclitaxel (175 mg/m2) i.v. for 3 h and carboplatin (area under the curve 5 mg/mL per min) on day 1 every 3 wk in our institution, and treated with granisetron (3 mg) and dexamethasone (20 mg) for antiemesis. Data of nausea and vomiting assessed by Common Terminol. Criteria for Adverse Events version4.0 were collected from the medical records. Patients were asked to complete a questionnaire including items such as age and hyperemesis. Logistic regression anal. was used to evaluate univariate and independent multivariate assocns. with items on nausea of grade 2 or greater and vomiting of grade 1 or greater. Results: On univariate logistic anal., no item was significantly assocd. with nausea of grade 2 or greater. Hypertension and hyperemesis gravidarum and adjuvant chemotherapy were significantly assocd. with delayed vomiting of grade 1 or greater. Multivariate anal. was performed with delayed vomiting of grade 1 or greater as an endpoint, and the resulting independent items were hypertension and hyperemesis gravidarum. Conclusions: The present study showed that the risk factor for delayed vomiting of grade 1 or higher was a history of hyperemesis gravidarum in patients receiving conventional TC with dexamethasone (20 mg) and granisetron. Therefore, in patients with this risk factor, criteria of major organizations should be followed first.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:1595670 CAPLUS Full-text
DOCUMENT NUMBER: 159:600211
TITLE: Efficacy of pantoprazole combined with granisetron in prevention of nausea and vomiting induced by cisplatin-based chemotherapy
AUTHOR(S): Ma, Chun-xi; Peng, Guo-lin; Deng, Lan
CORPORATE SOURCE: Department of Oncology, The 184th Hospital of the Chinese People's Liberation Army, Yingtan, 335000, Peop. Rep. China
SOURCE: Nanchang Daxue Xuebao, Yixueban (2012), 52(12), 70-72, 75
CODEN: NDXYBE
PUBLISHER: Nanchang Daxue Xuebao Yixueban Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: To explore the clin. curative effect and adverse reactions of pantoprazole combined with granisetron and dexamethasone in the prevention of nausea and vomiting induced by cisplatin-based chemotherapy. Methods: A total of 108 cancer patients undergoing chemotherapy were randomly

divided into group A and group B, with 54 patients in each group. All patients received two courses of cisplatin-based chemotherapy (21 days per course). Cisplatin 60-75 mg · m-2 dild. in 500 mL of physiol. saline was administered by i.v. infusion on day 1. For the prevention of nausea and vomiting, patients in group A were i.v. infused with pantoprazole 40 mg in 100 mL of physiol. saline, granisetron 3 mg in 10 mL of physiol. saline and dexamethasone 5 mg in 100 mL physiol. saline 30 min before chemotherapy once per day within the first 3 days during the first treatment course, followed by cimetidine 800 mg in 100 mL of physiol. saline 30 min before chemotherapy once per day within the first 3 days during the second treatment course. Patients in group B were i.v. infused with cimetidine 800 mg in 100 mL of physiol. saline, granisetron 3 mg in 10 mL of physiol. saline and dexamethasone 5 mg in 100 mL of physiol. saline 30 min before chemotherapy once per day within the first 3 days during the first treatment course, followed by pantoprazole 40 mg in 100 mL of physiol. saline 30 min before chemotherapy once per day within the first 3 days during the second treatment course. Clin. curative effects and adverse reactions (headache, dizziness, fatigue, stomachache, diarrhea, dry mouth and insomnia) were obsd. in both groups. Results: The total effective rate in group A was significantly higher than that in group B ($P < 0.05$). No obvious differences in adverse reactions were found between the two groups ($P > 0.05$). Conclusion: Pantoprazole combined with granisetron and dexamethasone is effective for the prevention of nausea and vomiting induced by cisplatin-based chemotherapy.

L6 ANSWER 24 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:1519750 CAPLUS Full-text
DOCUMENT NUMBER: 160:659138
TITLE: Dexamethasone reduces emesis after major gastrointestinal surgery (DREAMS)
AUTHOR(S): Hamilton, Emma; Ravikumar, Reena; Bartlett, David; Hepburn, Elizabeth; Hwang, Mei-Ju; Mirza, Nazzia; Bahia, Sandeep S.; Wilkey, Anthony; Bodenham Chilton, Helen; Handley, Kelly; Magill, Laura; Morton, Dion
CORPORATE SOURCE: The West Midlands Research Collaborative, West Midlands Deanery/West Midlands Research Collaborative, Birmingham, UK
SOURCE: Trials (2013), 14, 249, 8 pp.
CODEN: TRIACW; ISSN: 1745-6215
DIGITAL OBJECT ID: 10.1186/1745-6215-14-249
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: Postoperative nausea and vomiting is one of the most common complications affecting patients after surgery and causes significant morbidity and increased length of hospital stay. It is accepted that patients undergoing surgery on the bowel are at a higher risk. In the current era of minimally invasive colorectal surgery combined with enhanced recovery, reducing the incidence and severity of postoperative nausea and vomiting is particularly important. Dexamethasone is widely, but not universally used. It is known to improve appetite and gastric emptying, thus reduce vomiting. However, this benefit is not established in patients undergoing bowel surgery, and dexamethasone has possible side effects such as increased risk of wound infection and anastomotic leak that could adversely affect recovery. Design: DREAMS is a phase III, double-blind, multicenter, randomized controlled trial with the primary objective of detg. if preoperative dexamethasone reduces postoperative nausea and vomiting in patients undergoing elective gastrointestinal resections. DREAMS aims to randomize 1,350 patients over 2.5 years. Patients undergoing laparoscopic or open colorectal resections for malignant or benign pathol. are randomized between 8 mg i.v. dexamethasone and control (no dexamethasone). All patients are given one addnl. antiemetic at the time of induction, prior to randomization. Both the patient and their surgeon are blinded as to the treatment arm. Secondary objectives of the DREAMS trial are to det. whether there are other measurable benefits during recovery from surgery with the use of dexamethasone, including quicker return to oral diet and reduced length of stay. Health-related quality of life, fatigue and risks of infections will be investigated.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:945669 CAPLUS Full-text
DOCUMENT NUMBER: 160:303206
TITLE: Is a Dexamethasone-Sparing Strategy Capable of Preventing Acute and Delayed Emesis Caused by Combined Doxorubicin and Paclitaxel for Breast Cancer? Analysis of a Phase II Trial
AUTHOR(S): Damian, Silvia; Celio, Luigi; De Benedictis, Elena; Mariani, Paola; Agustoni, Francesco; Ricchini, Francesca; De Braud, Filippo
CORPORATE SOURCE: Medical Oncology Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
SOURCE: Oncology (2013), 84(6), 371-377
CODEN: ONCOBS; ISSN: 0030-2414
DIGITAL OBJECT ID: 10.1159/000348538
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: The effectiveness of palonosetron without delayed dexamethasone dosing against emesis was investigated in patients scheduled to receive the corticosteroid-contg. combination of doxorubicin and paclitaxel (AT) for 3 cycles. Methods: Chemo-naive women with breast cancer receiving doxorubicin (60 mg/m2) and paclitaxel (200 mg/m2) were eligible. Patients received palonosetron 0.25 mg i.v. before chemotherapy, however, all patients also received a premedication consisting of prednisone (25 mg orally the evening before therapy) and hydrocortisone (250 mg i.v. just before paclitaxel). The primary end point was complete control (CC; no vomiting, no rescue anti-emetics, and no more than mild nausea) during the overall phase (days 1-5) following cycle 1. Results: Seventy-six patients were enrolled and evaluable (median age 50 years). Fifty-six patients (74%; 95% CI 62-83%) achieved overall CC. Acute (day 1) and delayed (days 2-5) CC rates were 78 and 74%, resp. No vomiting rates for the acute, delayed and overall phases were 85, 85 and 83%, resp. An exploratory anal. showed only a small decrease in the probability of achieving CC between cycle 1 (74%) and cycle 3 (66%). Conclusion: The dexamethasone-sparing strategy prevented emesis in more than 70% of breast cancer patients receiving their initial cycle of AT chemotherapy.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:708201 CAPLUS Full-text
DOCUMENT NUMBER: 159:240779
TITLE: Single-dose palonosetron and dose-reduced regimen of dexamthasone in preventing neausea and vomiting by anthracycline-including chemotherapy in patients with early breast cancer
AUTHOR(S): Pacetti, Umberto; Veltri, Enzo; Fattoruso, Silvia Ileana Sara; Cardillo, Francesca D'Assisi; Evangelista, Salvatore; Cognetti, Francesco; Fabi, Alessandra
CORPORATE SOURCE: Operative Unit of Oncology, A. Fiorini Hospital, Terracina, Italy
SOURCE: Anticancer Research (2013), 33(4), 1721-1724
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASFORMULTNS 2013:708201
AB Aim: To evaluate the efficacy of redn. of dexamethasone with a single-dose of palonosetron in preventing acute and delayed nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC) for early breast cancer. Patients and methods: Chemotherapy-naive patients with breast cancer were given HEC in an adjuvant or neoadjuvant setting. Palonosetron and dexamethasone 4 mg i.v. were given on day 1 and another two administrations of dexamethasone 4 mg i.m. were given on days 2 and 3. The end-point was complete response (CR) and complete control (CC) during

the acute and delayed phases. Results: Twenty-six patients were obsd. Complete response was achieved in 19 out of 26 patients (72.4%); the same result was shown in 72.4% out of 76 courses given. Conclusion: This alternative schedule suggests efficacy for the control of acute and delayed emesis in moderately emetogenic chemotherapy. Further investigations are required to confirm these results.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 27 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2013:522322 CAPLUS Full-text

DOCUMENT NUMBER: 160:17848

TITLE: Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial

AUTHOR(S): Cardoso, Monica M. S.; Leite, Alexandre O.; Santos, Elisa A.; Gozzani, Judymara L.; Mathias, Ligia A. S. T.

CORPORATE SOURCE: Faculdade de Ciencias Medicas da Santa Casa de Sao Paulo, Sao Paulo, Brazil

SOURCE: European Journal of Anaesthesiology (2013), 30(3), 102-105
CODEN: EJANEG; ISSN: 0265-0215

DIGITAL OBJECT ID: 10.1097/EJA.0b013e328356676b

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Context: Spinal morphine is a common form of postoperative analgesia after cesarean section, but it is assocd. with postoperative nausea and vomiting. Objective: To evaluate the hypothesis that dexamethasone reduces nausea and vomiting in patients undergoing cesarean section under spinal anesthesia with morphine. Design: Interventional, randomized, double-blinded, placebo-controlled study to evaluate a preoperative single dose of dexamethasone. Setting: Patients from a tertiary hospital in the city of Sao Paulo, Sao Paulo, Brazil obsd. from 1 Jan. through 30 June 2008. Patients or other participants: Seventy full-term pregnant patients (American Society of Anesthesiologists 1 or 2) were studied. Patients were randomly allocated into two groups detd. by a computerized table. Exclusion criteria were contraindication to regional anesthesia, allergy to dexamethasone, opioids or local anesthetics, hypertension or diabetes originated during pregnancy and use of any antiemetic drug received before surgery. Spinal anesthesia consisted of hyperbaric bupivacaine and morphine. Intervention: Patients received either dexamethasone 10 mg in 100 mL of isotonic saline, i.v. or 100 mL of isotonic saline (placebo) prior to surgery. Main outcome: Incidence of postoperative nausea and vomiting in the first 24 h were rated and recorded. Pain scores at rest and on movement were evaluated using a visual analog scale. Results: During the first 24 h, nausea occurred in 12/35 (34.4%) patients receiving dexamethasone and in 32/35 (91.4%) receiving placebo ($P < 0.001$). During the same time period, vomiting occurred in 12/35 (34.4%) patients receiving dexamethasone and in 29/35 (82.9%) receiving placebo ($P < 0.001$). Pain at rest and pain on movement was lower in patients who received dexamethasone at some time points during the study period. Conclusion: Dexamethasone reduced the cumulative incidence of nausea and vomiting after cesarean section under spinal anesthesia with morphine and lowered pain scores on the first postoperative day.

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2013:124175 CAPLUS Full-text

DOCUMENT NUMBER: 158:644990

TITLE: Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy

AUTHOR(S): Gao, H. F.; Liang, Y.; Zhou, N. N.; Zhang, D. S.; Wu, H. Y.
CORPORATE SOURCE: State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, Peop. Rep. China
SOURCE: Internal Medicine Journal (2013), 43(1), 73-76
CODEN: IMJNAK; ISSN: 1444-0903
DIGITAL OBJECT ID: 10.1111/j.1445-5994.2011.02637.x
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background : Chemotherapy-induced nausea and vomiting remain among the most feared adverse effects for cancer patients. Aim : The aim of this study was to evaluate the efficacy and safety of a combination of aprepitant, palonosetron and dexamethasone as antiemetic prophylaxis in patients receiving multiple-day cisplatin-based chemotherapy. Methods : Forty-one solid cancer patients received aprepitant, palonosetron and dexamethasone during a 3-day cisplatin-based chemotherapy. Primary end-point was complete response in the overall phase (day 1 until 5 days after the end of chemotherapy). Results : Aprepitant in combination with palonosetron and dexamethasone was safe, with hiccups (31.7%), fatigue (17.1%), headache (14.6%) and constipation (12.2%) the most common treatment-related adverse events, mostly mild. Complete response was seen in 58.5% of patients in the overall phase. In 23 patients receiving aprepitant in combination with palonosetron and dexamethasone more than one cycle (range: 2-5 cycles), the cumulative emetic protection rate after five cycles was 0.82. Conclusion : This study shows aprepitant in combination with palonosetron and dexamethasone is safe and effectively controls chemotherapy-induced nausea and vomiting in patients undergoing 3-day cisplatin-based chemotherapy, moreover, the efficacy is maintained during multiple cycles.
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 29 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2013:50234 CAPLUS Full-text
DOCUMENT NUMBER: 158:614099
TITLE: Prevention of Nausea and Vomiting Associated with Stem Cell Transplant: Results of a Prospective, Randomized Trial of Aprepitant Used with Highly Emetogenic Preparative Regimens
AUTHOR(S): Stiff, Patrick J.; Fox-Geiman, Mary P.; Kiley, Karen; Rychlik, Karen; Parthasarathy, Mala; Fletcher-Gonzalez, Donna; Porter, Nancy; Go, Aileen; Smith, Scott E.; Rodriguez, Tulio E.
CORPORATE SOURCE: Bone Marrow Transplant Program, Departments of Pharmacy, Nursing, and Medicine, Loyola University Medical Center, Maywood, IL, USA
SOURCE: Biology of Blood and Marrow Transplantation (2013), 19(1), 49-55.e1
CODEN: BBMTF6; ISSN: 1083-8791
DIGITAL OBJECT ID: 10.1016/j.bbmt.2012.07.019
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Uncontrolled delayed nausea and vomiting remains a problem after high-dose preparative regimens used for autologous and allogeneic hematopoietic stem cell transplants. Recently, aprepitant was approved for highly and moderately emetogenic chemotherapy, and, in particular, is effective for decreasing delayed emesis. To evaluate its safety and efficacy in the transplantation setting, we performed a randomized, placebo-controlled, phase 3 trial of aprepitant in combination with ondansetron and dexamethasone in patients treated with ablative preparative regimens. Patients were randomized to receive oral aprepitant or placebo daily with oral ondansetron and dexamethasone during and for 3 days after the completion of the preparative regimen in this prospective randomized, double-blind study. The primary objective was complete response (CR) rate, defined as no emesis with no or mild nausea. Other endpoints included no. of emetic episodes, nausea severity assessed using a 100-mm

visual analog scale (VAS), the need for rescue antiemetics, and transplantation outcome, including regimen-related toxicity. One hundred eighty-one patients were randomized and 179 patients were eligible for anal. Overall, CR rates were 81.9% for the aprepitant and 65.8% for the placebo arms (P < .001). Percentages of patients with no emesis all days were 73.3% for aprepitant and 22.5% placebo (P < .001). Mean VAS scores were 16.6 mm aprepitant and 16.9 mm placebo (NS), and there were no differences in the amt. of rescue antiemetics used, regimen related toxicity, engraftment, or transplantation outcome. Aprepitant in combination with dexamethasone and ondansetron significantly decreased emesis and significant nausea, whereas not increasing RRT or affecting short-term survival but had no significant impact on the use of PRN antiemetics, or overall VAS nausea scores.

OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 30 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2012:1887498 CAPLUS Full-text

DOCUMENT NUMBER: 159:393086

TITLE: Dexamethasone to Prevent Postoperative Nausea and Vomiting: An Updated Meta-Analysis of Randomized Controlled Trials

AUTHOR(S): De Oliveira, Gildasio S., Jr.; Castro-Alves, Lucas J. Santana; Ahmad, Shireen; Kendall, Mark C.; McCarthy, Robert J.

CORPORATE SOURCE: Department of Anesthesiology, Northwestern University, Chicago, IL, USA

SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2013), 116(1), 58-74
CODEN: AACRAT; ISSN: 0003-2999

DIGITAL OBJECT ID: 10.1213/ANE.0b013e31826f0a0a

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Background: Dexamethasone has an established role in decreasing postoperative nausea and vomiting (PONV); however, the optimal dexamethasone dose for reducing PONV when it is used as a single or combination prophylactic strategy has not been clearly defined. In this study, we evaluated the use of 4 mg to 5 mg and 8 mg to 10 mg IV doses of dexamethasone to prevent PONV when used as a single drug or as part of a combination preventive therapy. Methods: A wide search was performed to identify randomized clin. trials that evaluated systemic dexamethasone as a prophylactic drug to reduce postoperative nausea and/or vomiting. The effects of dexamethasone dose were evaluated by pooling studies into 2 groups: 4 mg to 5 mg and 8 mg to 10 mg. The first group represents the suggested dexamethasone dose to prevent PONV by the Society for Ambulatory Anesthesia (SAMBA) guidelines, and the second group represents twice the dose range recommended by the guidelines. The SAMBA guidelines were developed in response to studies, which have been performed to examine different dosages of dexamethasone. Results: Sixty randomized clin. trials with 6696 subjects were included. The 4-mg to 5-mg dose dexamethasone group experienced reduced 24-h PONV compared with control, odds ratio (OR, 0.31; 95% confidence interval [CI], 0.23-0.41), and no. needed to treat (NNT, 3.7; 95% CI, 3.0-4.7). When used together with a second antiemetic, the 4-mg to 5-mg dexamethasone group also experienced reduced 24-h PONV compared with control (OR, 0.50; 95% CI, 0.35-0.72; NNT, 6.6; 95% CI, 4.3-12.8). The 8-mg to 10-mg dose dexamethasone group experienced decreased 24-h PONV compared with control (OR, 0.26; 95% CI, 0.20-0.32; NNT, 3.8; 95% CI, 3.0-4.3). Asym. funnel plots were obsd. in the 8-mg to 10-mg dose anal., suggesting the possibility of publication bias. When used together with a second antiemetic, the 8-mg to 10-mg dose group also experienced reduced incidence of 24-h PONV (OR, 0.35; 95% CI, 0.22-0.53; NNT, 6.2; 95% CI, 4.5-10). In studies that provided a direct comparison between groups, there was no clin. advantage of the 8-mg to 10-mg dexamethasone dose compared with the 4-mg to 5-mg dose on the incidence of postoperative nausea and/or vomiting. Conclusions: Our results showed that a 4-mg to 5-mg dose of dexamethasone seems to have similar clin. effects in the redn. of PONV as the 8-mg to 10-mg dose when dexamethasone was used as a single drug or as a combination therapy.

These findings support the current recommendation of the SAMBA guidelines for PONV, which favors the 4-mg to 5-mg dose regimen of systemic dexamethasone.

OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS RECORD (67 CITINGS)

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2012:1727308 CAPLUS Full-text

DOCUMENT NUMBER: 159:271436

TITLE: Dexamethasone for Antiemesis in Laparoscopic Gynecologic Surgery: A Systematic Review and Meta-Analysis

AUTHOR(S): Pham, Alice; Liu, Grace

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, Toronto, ON, Can.

SOURCE: Obstetrics & Gynecology (Hagerstown, MD, United States) (2012), 120(6), 1451-1458
CODEN: OBGNAS; ISSN: 0029-7844

DIGITAL OBJECT ID: 10.1097/AOG.0b013e31827590f3

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Objective: To est. the beneficial and harmful effects of dexamethasone for prevention of postoperative nausea and vomiting in women undergoing laparoscopic gynecol. surgery. Data sources: We searched the following bibliog. databases: MEDLINE (from 1946 to Jan. 2012), Embase (from 1980 to 2012 wk 3), the Cochrane Central Register of Controlled Trials (from inception to Jan. 2012), and ISI Web of Knowledge (from 1950 to Jan. 2012). We also screened trial registries, ref. lists of retrieved studies, and other sources of unpublished literature. Methods of study selection: Two reviewers screened in duplicate and independently searched results for inclusion. We included randomized controlled trials (RCTs) comparing dexamethasone with a placebo in patients undergoing laparoscopic gynecol. surgery. TABULATION, INTEGRATION, AND Results: Two reviewers completed data extn. and assessed trials for bias in duplicate and independently. We used the Grading of Recommendations Assessment, Development, and Evaluation methodol. to assess the quality of evidence across studies at the outcome level. A total of 13 RCTs with 1,695 patients met inclusion criteria. Data were pooled based on the random-effects model. The use of prophylactic dexamethasone significantly decreases the incidence of postoperative nausea (relative risk [RR] 0.56, 95% confidence interval [CI] 0.45-0.71), postoperative vomiting (RR 0.35, 95% CI 0.25-0.48), the need for rescue antiemetics (RR 0.39, 95% CI 0.29-0.52), and time to meet discharge criteria (mean 28.5 min, 95% CI 24.6-32.4). The estd. no. needed to treat to prevent nausea in one patient was eight (95% CI 5-13), whereas that for vomiting was five (95% CI 4-6). There was no obsd. increase in adverse events. The quality of the evidence ranged from very low to moderate. Conclusion: This systematic review provides evidence that dexamethasone decreases the incidence of postoperative nausea and vomiting after laparoscopic gynecol. surgery, with no obsd. increase in side effects.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 32 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2012:1525687 CAPLUS Full-text

DOCUMENT NUMBER: 159:159149

TITLE: A randomized double-blind placebo-controlled cross-over trial of the impact on quality of life of continuing dexamethasone beyond 24 h following adjuvant chemotherapy for breast cancer

AUTHOR(S): Vardy, J.; Pond, G.; Dodd, A.; Warr, D.; Seruga, B.; Clemons, M.; Bordeleau, L.; Goodwin, P.; Tannock, I. F.

CORPORATE SOURCE: Princess Margaret Hospital, University of Toronto,

Toronto, ON, Can.
SOURCE: Breast Cancer Research and Treatment (2012), 136(1), 143-151
CODEN: BCTRD6; ISSN: 0167-6806
DIGITAL OBJECT ID: 10.1007/s10549-012-2205-3
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Uncertainty remains about the optimal anti-emetic regimen for control of delayed nausea and vomiting after adjuvant chemotherapy for breast cancer. Many patients receive dexamethasone but complain of insomnia, anxiety/agitation, and indigestion. The aim was to det. if patients receiving chemotherapy for breast cancer prefer treatment with dexamethasone or placebo for prophylaxis against delayed nausea and vomiting, and to compare quality of life (QOL) between the two treatments. In this randomized, double-blind, cross-over trial, we compared oral dexamethasone (4 mg twice daily for 2 days) vs. placebo for chemotherapy-naive patients with breast cancer. All patients received i.v. granisetron and dexamethasone pre-chemotherapy and oral granisetron on day 2. Primary endpoints were: (i) patient preference; (ii) difference between cycles in change of QOL from days 1 to 8. Median age of the 94 women was 51 years (range 27-76): 79 received fluorouracil/epirubicin/cyclophosphamide and 15 received doxorubicin/cyclophosphamide. Thirteen withdrew pre-cycle 2 with no differences between arms. Of 80 patients stating a preference, 31 preferred placebo (39 %, 95 % CI: 28-50 %) and 37 (46 %, 95 % CI: 35-58 %) preferred dexamethasone; 12 had no preference. There were no differences in intensity of vomiting, nausea, or time to onset of vomiting. There was greater decrease in global QOL (p = 0.06) when patients received dexamethasone. No other symptom/QOL domains differed significantly. In conclusion, no significant difference was found in patient preference, QOL, or symptoms regardless of whether dexamethasone or placebo was used after adjuvant chemotherapy.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2012:686952 CAPLUS Full-text
DOCUMENT NUMBER: 157:595582
TITLE: Qualitative comparison of Metoclopramide, Ondansetron and Granisetron alone and in combination with Dexamethasone in the Prevention of Postoperative Nausea and Vomiting in Day Care Laparoscopic Gynaecological Surgery under General Anaesthesia
AUTHOR(S): Daria, Usha; Kumar, Vinod
CORPORATE SOURCE: Department of Anaesthesia, Jhalawar Medical College, Jhalawar, 326001, India
SOURCE: Asian Journal of Pharmaceutical and Clinical Research (2012), 5(2), 165-167
CODEN: AJPCBB; ISSN: 0974-2441
URL: http://www.ajpcr.com/Vol5Issue2/923.pdf
PUBLISHER: Asian Journal of Pharmaceutical and Clinical Research
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Aim: To compare qual. Metoclopramide, Ondansetron and Granisetron alone and in combination with Dexamethasone in the Prevention of Postoperative Nausea and Vomiting in Day Care Laparoscopic Gynaecol. Surgery under General Anesthesia. Method: 180 adult female patients of ASA Grade I and II, BMI <30, aged 18 to 55 years undergoing laparoscopic gynaecol. surgery under general anesthesia included in the study. Patients with history of motion sickness and past history of PONV were excluded from the study. The study was carried out in six groups consisting of randomly selected 30 patients in each. Before induction of general anesthesia, the antiemetic drugs under study given i.v. i.e. Metoclopramide (10 mg), Ondansetron (4 mg) and Granisetron (3 mg) were given alone in group A, B and C resp. while in group D, E and F these drugs were combined with Dexamethasone (8 mg) resp. The study drugs were given as i.v. injections. Result: The study found that Metoclopramide is very poor because of higher incidence of side effects and only 36.7% success rate in the prevention of PONV.

The success rate in the prevention of PONV is poor in Ondansetron & Granisetron (nearly two-third, 63.3% & 66.7% resp.). The success rate found good (nearly three-fourth, 73.3%) in combination of Metoclopramide with Dexamethasone and very good in combination of Ondansetron & Granisetron with Dexamethasone (90% in both).

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 34 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2012:589959 CAPLUS Full-text

DOCUMENT NUMBER: 157:427578

TITLE: Palonosetron plus 1-day dexamethasone for the prevention of nausea and vomiting due to moderately emetogenic chemotherapy: effect of established risk factors on treatment outcome in a phase III trial

AUTHOR(S): Celio, Luigi; Denaro, Angela; Agustoni, Francesco; Bajetta, Emilio

CORPORATE SOURCE: Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

SOURCE: Journal of Supportive Oncology (2012), 10(2), 65-71
CODEN: JSOOBY; ISSN: 1544-6794

DIGITAL OBJECT ID: 10.1016/j.suponc.2011.06.007

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: The non-inferiority of palonosetron plus 1-day vs. 3-day dexamethasone in preventing chemotherapy-induced nausea and vomiting (CINV) due to moderately emetogenic chemotherapy (MEC) has been previously demonstrated. Objective: The objectives of this prespecified post hoc anal. were to demonstrate the non-inferiority hypothesis in an adjusted model for known risk factors (age, gender, alc. consumption, and type of MEC [anthracycline plus cydophosphamide (AC)- based vs. other MEC]) for CINV and to explore the impact on antiemetic outcome of these risk factors. Methods: Chemonaive patients (n = 324) with solid tumors were randomized to receive palonosetron 0.25 mg IV plus dexamethasone 8 mg IV on day 1 of chemotherapy or the same regimen followed by oral dexamethasone 8 mg on days 2 and 3. The primary end point was complete response (CR, no emesis and no rescue antiemetics) during the 5-day study period. A modified intention-to-treat approach was used for multivariable anal. Results: Non-inferiority of the 1-day regimen was confirmed even after adjusting for risk factors (risk difference -4.4%, 95% CI -14.1 % to 5.4%; P = .381). Only age less than 50 years (P = .044) independently predicted a poor outcome of antiemetic treatment. However, most of the younger patients were women (1-day regimen 81.8%, 3-day regimen 88.4%) who underwent AC-based chemotherapy (1-day regimen 61.1%, 3-day regimen 71.0%). There were no significant between-treatment differences in the CR rate according to risk factors. Conclusion: This anal. confirmed that the 1-day regimen provides a valid treatment option for prevention of CINV in delayed, non-AC-based MEC.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 35 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2012:470210 CAPLUS Full-text

DOCUMENT NUMBER: 157:704320

TITLE: Clinical study on palonosetron for preventing nausea and vomiting induced by highly-nauseant chemotherapy

AUTHOR(S): Huang, Haijun; Xu, Hua; Chen, Fengjuan

CORPORATE SOURCE: Zhejiang Province Traditional Chinese Medicine Hospital, Hangzhou, 310018, Peop. Rep. China

SOURCE: Shiyong Yixue Zazhi (2011), 27(18), 3390-3391
CODEN: SYZAFM; ISSN: 1006-5725

DIGITAL OBJECT ID: 10.3969/j.issn.1006-5725.2011.18.054

PUBLISHER: Shiyong Yixue Zazhi Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The objective of this paper was to prevent nausea and vomiting induced by high-dose cisplatin with palonosetron combined with dexamethasone and granisetron combined with dexamethasone resp., and to observe the therapeutic effect and safety of palonosetron combined with dexamethasone. 56 Cases with non-small cell lung carcinoma (NSCLC) after high-dose cisplatin chemotherapy were randomly and averagely divided into treatment group and control group. The cases in treatment group were given 0.25 mg palonosetron and 12 mg dexamethasone by i.v. injection 30 min before chemotherapy, while those in control group were given 3 mg granisetron and 12 mg dexamethasone by i.v. injection. The complete therapeutic rates for preventing acute vomiting in treatment group and control group were 82.1% and 78.6% resp. The nausea improvement rates in treatment group and control group were 64.3% and 60.7% resp., and there was no significant difference (P>0.05). The complete therapeutic rates for preventing delayed nausea in treatment group and control group were 60.7% and 39.3% resp., and there was significant difference (P<0.05). The therapeutic effect for preventing nausea and vomiting induced by high-dose cisplatin between palonosetron combined with dexamethasone and granisetron combined with dexamethasone was equiv., while palonosetron had better therapeutic effect for preventing delayed nausea, lighter side effect and better patient compliance compared with granisetron. Palonosetron combined with dexamethasone could be used for preventing nausea and vomiting induced by highly-nauseant chemotherapy.

L6 ANSWER 36 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2012:14350 CAPLUS Full-text
DOCUMENT NUMBER: 157:122116
TITLE: Single dose palonosetron and dexamethasone in preventing nausea and vomiting induced by high emetogenic ABVD regimen in Hodgkin Lymphoma patients
AUTHOR(S): Rigacci, Luigi; Landi, Carla; Caruso, Jean Pierre; Puccini, Benedetta; Alterini, Renato; Carrai, Valentina; Perrone, Tania; Bosi, Alberto
CORPORATE SOURCE: Haematology Department, Azienda Ospedaliero Universitaria Careggi, Florence, 50139, Italy
SOURCE: Leukemia Research (2012), 36(2), 182-185
CODEN: LEREDD; ISSN: 0145-2126
DIGITAL OBJECT ID: 10.1016/j.leukres.2011.06.025
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB To evaluate the efficacy of a new agent, palonosetron, in Hodgkin Lymphoma patients treated with ABVD regimen. Complete response during the overall phase of the first ABVD cycle, was the primary endpoint. Secondary end points were: emesis-free patients and use of rescue medication during the acute and overall phases. From Jan. 2008 to Feb. 2009 36 patients were enrolled. The primary endpoint (CR 0-120 h) was achieved by 55.6% patients. In conclusion our study demonstrated that a single dose of palonosetron plus a single dose of dexamethasone was effective in preventing CINV in patients treated with ABVD regimen.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 37 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2012:1855 CAPLUS Full-text
DOCUMENT NUMBER: 156:132703
TITLE: Patch with antiemetic agent
INVENTOR(S): Ye, Jincui; Yu, Wenying; Xu, Lihua; Chen, Guoshen; Zheng, Gaoli
PATENT ASSIGNEE(S): Zhejiang Academy of Medical Sciences, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 17pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

CN 102293761	A	20111228	CN 2010-10206421	20100622
CN 102293761	B	20140108		

PRIORITY APPLN. INFO.: CN 2010-10206421 20100622

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 102293761	A	Alive	20201121
CN 102293761	B	Alive	20201120

AB Application(for antiemetic purpose) of the invention should be covered in the abstr. The title patch consists of backing cloth layer, pressure sensitive adhesive layer and antisticking layer. The pressure sensitive adhesive layer contains antiemetic agent 0.2-4%, penetration enhancer 10-45%, gummy polymer 40-75%, stabilizing agent 0.5-15% and pH regulator 0.2-20%. The antiemetic agent is ramosetron or its salt, the content of which is 0.1-1 mg/cm2. The gummy polymer is prepd. with lipophilic polymer and hydrophilic polymer in the ratio of 1-3.5:1. The lipophilic polymer is lipophilic pressure sensitive adhesive of polyacrylic ester, polyisobutylene or silicon rubber. The hydrophilic polymer is hydrophilic pressure sensitive adhesive of polyacrylic ester, carbomer or the like. The salt of ramosetron is its org. salt or inorg. salt. The penetration enhancer is laurocapram or the like. The pH regulator is tromethamine, triethanolamine or so on. The stabilizing agent is butylated hydroxytoluene, vitamin E or the like.

L6 ANSWER 38 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2011:1337823 CAPLUS Full-text

DOCUMENT NUMBER: 156:47295

TITLE: Efficacy of intravenous dexamethasone for the prevention of vomiting associated with intrathecal chemotherapy and ketamine sedation in children: a randomized, double-blinded, crossover, placebo-controlled trial

AUTHOR(S): Traivaree, Chanchai; Torcharus, Kitti; Lumkul, Rachata; Komoltri, Chulalak; Charuluxananan, Somrat

CORPORATE SOURCE: Division of Haematology/Oncology, Department of Pediatrics, Phramongkutklao College of Medicine, Bangkok, 10400, Thailand

SOURCE: Asian Biomedicine (2011), 5(4), 441-448
CODEN: ABSICN; ISSN: 1905-7415

DIGITAL OBJECT ID: 10.5372/1905-7415.0504.058

PUBLISHER: Chulalongkorn University, Faculty of Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Chemotherapy-induced nausea and vomiting remains a significant problem for children with leukemia. There is limited evidence to support using prophylactic antiemetic prior to the administration of intrathecal chemotherapy. Objective: Det. whether vomiting and nausea assocd. with i.v. ketamine and intrathecal chemotherapy may be reduced by the addn. of prophylactic dexamethasone in children. Method: A randomized, double-blinded, crossover, placebo-controlled trial was completed in 33 children receiving intrathecal chemotherapy with methotrexate and ketamine sedation at Pharmongkutklao Hospital. Patients were randomly assigned in a double-blinded fashion to receive one of two interventions during the first period, either an infusion of normal saline or i.v. dexamethasone at 0.25 mg/kg/dose. Each patient acted as his or her own control, and each patient was studied at two time-points. Results: Period effect, sequence effect, and carry over effect were not demonstrated. The abs. risk redn. of vomiting was significantly greater after infusion of dexamethasone than after placebo at 33.3 % (p = 0.02). The no. needed to treat was three to prevent one episode of vomiting. Fifteen patients in the treatment group reported nausea vs. 26 patients in the placebo group (p = 0.007). In the group of patients treated with dexamethasone, five required antiemetic vs. 16 of those receiving placebo (p = 0.02). There was no complication from dexamethasone. Conclusion: I.v. dexamethasone reduced vomiting assocd. with intrathecal chemotherapy and ketamine sedation, without significant side-effects. It may be recommended a reasonable option before intrathecal chemotherapy.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 39 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2011:1190049 CAPLUS Full-text
DOCUMENT NUMBER: 156:468891
TITLE: Single-dose palonosetron and dexamethasone in preventing nausea and vomiting induced by moderately emetogenic chemotherapy in breast and colorectal cancer patients
AUTHOR(S): Brugnatelli, Silvia; Gattoni, Elisabetta; Grasso, Donatella; Rossetti, Franca; Perrone, Tania; Danova, Marco
CORPORATE SOURCE: Medical Oncology, Fondazione Policlinico San Matteo, Pavia, Italy
SOURCE: Tumori (2011), 97(3), 362-366
CODEN: TUMOAB; ISSN: 0300-8916
DIGITAL OBJECT ID: 10.1177/030089161109700318
PUBLISHER: Il Pensiero Scientifico Editore
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aims and background: Palonosetron, a unique second-generation 5-HT3 receptor antagonist, has been demonstrated to control emesis related to chemotherapy-induced nausea and vomiting (CINV). The aim of this study was to evaluate the efficacy and tolerability of palonosetron followed by a single dose of dexamethasone in patients with breast cancer (BC) or colorectal cancer (CRC) receiving moderate emetogenic chemotherapy (MEC). Methods and study design: Chemotherapy-naive BC and CRC patients were given MEC as adjuvant or first-line treatment. Palonosetron (0.25 mg IV) and dexamethasone (8 mg IV) were administered before chemotherapy on day 1. The primary end-point was complete response (CR; no vomiting and no use of rescue medication) during the overall study period (days 1-5). The antiemetic response was evaluated during the acute (day 1) and delayed (days 2-5) phases. Results: Sixty-eight patients were enrolled (median age 61 years, 56 females; BC = 40, CRC = 28). CR was obsd. in 46 of 68 patients (67.6%), while CR during the acute and delayed phases was 75.0% in each cancer group. The antiemetic regimen was well tolerated. Conclusions: A single administration of palonosetron and dexamethasone on day 1 in BC and CRC patients adequately controls CINV during the entire period of emetic risk.
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 40 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2011:1046277 CAPLUS Full-text
DOCUMENT NUMBER: 155:321139
TITLE: Method for preventing post-operative nausea and vomiting in children after otolaryngological surgery
INVENTOR(S): Ivlev, E. V.; Grigor'ev, E. V.; Zhdanov, R. V.; Trofimova, O. A.; Churlyaev, Yu. A.
PATENT ASSIGNEE(S): GOU Dop. Prof. Obrazovaniya "Novokuznetskii Gos. Inst. Usoversh. Vrachei Fed. Agentstva po Zdravookhr. i Sotsial'nomu Razvitiyu", Russia
SOURCE: Russ., 7pp.
CODEN: RUXXE7
DOCUMENT TYPE: Patent
LANGUAGE: Russian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
RU 2426541	C1	20110820	RU 2010-118805	20100511

PRIORITY APPLN. INFO.: RU 2010-118805 20100511
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
RU 2426541	C1	Dead	20201121

AB The invention relates to medicine, and can be used for prevention of post-operation nausea and vomiting after otolaryngol. (ENT) surgery in children. The method involves premedication, pre-operative i.v.

administration of dexamethasone 0.2 mg/kg (8 mg max.) followed by propofol 2-3 mg/kg i.v., fentanyl 4-5 mcg/kg i.v. and nitrous oxide - oxygen mixt. N2O+O2 with ratio 2:1 for anesthesia induction. Propofol 2.5-3.5 mg/kg/h i.v., fentanyl 3-4 mcg/kg/h in micro-jet manner in basis-anesthesia. In the period immediately after operation metoclopramide is administered in dose 0.2 mg/kg i.v. not more than 10 mg. After extubation oxygenation with oxygen through facial mask in dose 3-4 l/min is carried out for 3-5 min. The proposed method makes it possible to prevent post-operation nausea and vomiting in children in ENT surgery.

L6 ANSWER 41 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2011:1006257 CAPLUS Full-text
DOCUMENT NUMBER: 156:551950
TITLE: Curative effect of ondansetron, droperidol, and dexamethasone in preventing nausea and vomiting of PCEA
AUTHOR(S): Li, Gang; Ma, Yongxin; Fan, Yumeng
CORPORATE SOURCE: Anesthesiology Department, Central Hospital of Lingyuan, Lingyuan, 122500, Peop. Rep. China
SOURCE: Liaoning Yixueyuan Xuebao (2011), 32(2), 154-155
CODEN: LYXIAM; ISSN: 1674-0424
PUBLISHER: Liaoning Yixueyuan Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: TO observe the effect of ondansetron, droperidol, and dexamethasone in preventing nausea and vomiting of PCEA. Method: 120 patients received PCEA, and randomized into four groups: group A receiving morphine, group B receiving morphine + droperidol, group C i.v. receiving ondansetron, droperidol, dexamethasone and morphine, and group D receiving morphine + droperidol, and ondansetron + dexamethasone i.v. Nausea and vomiting were obsd. 24 h after surgery. Result: Groups B, C and D had reduced severity than control group A ($P < 0.05$ or $P < 0.01$). Conclusion: The ondansetron, droperidol, and dexamethasone is effective in preventing nausea and vomiting of PCEA.

L6 ANSWER 42 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2011:376838 CAPLUS Full-text
DOCUMENT NUMBER: 155:423139
TITLE: A Comparison of the Combination of Aprepitant and Dexamethasone Versus the Combination of Ondansetron and Dexamethasone for the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Craniotomy
AUTHOR(S): Habib, Ashraf S.; Keifer, John C.; Borel, Cecil O.; White, William D.; Gan, Tong J.
CORPORATE SOURCE: Duke University Medical Center, Durham, NC, USA
SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2011), 112(4), 813-818
CODEN: AACRAT; ISSN: 0003-2999
DIGITAL OBJECT ID: 10.1213/ANE.0b013e3181ff47e2
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 h. In addn. to causing patient discomfort, the phys. act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 h postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia. Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 h before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 min of the end of surgery. All patients received dexamethasone

10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 h after surgery. Statistical anal. was performed using Wilcoxon's ranked sum test and χ test. $P < 0.05$ was considered statistically significant. 104 Patients completed the study. The cumulative incidence of vomiting at 48 h was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 h (6% vs. 21%, $P = 0.0419$) and 24 h (14% vs. 36%, $P = 0.0124$). From 0 to 48 h, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%), nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV. The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 43 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2010:1007192 CAPLUS Full-text

DOCUMENT NUMBER: 154:301595

TITLE: A survey on the effect of multi-dose administration of dexamethasone on postoperative nausea and vomiting following spinal surgery

AUTHOR(S): Gayatri, P.; Koshy, Thomas; Sinha, Prabhat K.; Rao, B. Ravi Mohan

CORPORATE SOURCE: Department of Anaesthesia, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Kerala, 695011, India

SOURCE: Journal of Anaesthesiology, Clinical Pharmacology (2010), 26(2), 247-249
CODEN: JAPHFW; ISSN: 0970-9185

PUBLISHER: Research Society of Anaesthesiology Clinical Pharmacology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Dexamethasone is a known antiemetic. Patients with spinal pathol. receive dexamethasone as part of surgical treatment. This audit was conducted to det. the effect of multi-dose dexamethasone administration on Post Operative Nausea and Vomiting (PONV) in patients undergoing spinal surgery. Patients and Material: We included 80 adult patients undergoing elective spinal surgery. Patients who received dexamethasone 4mg at 8 hourly intervals in the perioperative period were categorized as Group-1 (n=43; 26 males). Patients who had not received any dexamethasone as Group-2 (n=36; 24 males). They were followed up for 24 h in the postoperative period for the occurrence of PONV. Results: The overall incidence of PONV was 34.9% (15/43) and 52.8% (19/36) in group-1 and group-2 resp. The incidence of nausea and vomiting was 23.3% (10/43) and 13.9% (6/43) in group-1 and 27.8% (10/36) and 38.9% (14/36) in group-2 resp. The redn. in the incidence of vomiting after multi dose dexamethasone was significant (p=0.01) whereas it was not statistically significant for nausea (0.79) and overall PONV (0.119). Conclusions: The multi-dose dexamethasone group had 18% lower incidence of vomiting following spine surgery.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 44 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2010:32170 CAPLUS Full-text

DOCUMENT NUMBER: 153:28783

TITLE: Phase 2 trial results with the novel neurokinin-1 receptor antagonist casopitant in combination with ondansetron and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer

patients receiving moderately emetogenic chemotherapy
AUTHOR(S): Arpornwirat, Wichit; Albert, Istvan; Hansen, Vincent L.; Levin, Jeremey; Bandekar, Rajesh R.; Grunberg, Steven M.
CORPORATE SOURCE: Department of Medicine, National Cancer Institute, Bangkok, Thailand
SOURCE: Cancer (Hoboken, NJ, United States) (2009), 115(24), 5807-5816
CODEN: CANCAR; ISSN: 0008-543X
DIGITAL OBJECT ID: 10.1002/cncr.24630
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BACKGROUND: This randomized, double-blind, dose-ranging, placebo-controlled, phase 2 trial evaluated the neurokinin-1 receptor antagonist casopitant mesylate in combination with ondansetron/dexamethasone (ond/dex) for the prevention of chemotherapy-induced nausea and vomiting (CINV) related to moderately emetogenic chemotherapy (MEC). METHODS: Chemotherapy-naive patients who were receiving MEC (N = 723) were randomized to receive either oral placebo or casopitant at doses of 50 mg, 100 mg, or 150 mg daily (on Days 1-3) plus ondansetron (on Days 1-3) and dexamethasone (Day 1). Two exploratory arms evaluated single-dose casopitant (150 mg) plus ond/dex and a 3-day casopitant regimen with once-daily ondansetron and dexamethasone. Primary endpoints were rates of complete response (CR) (no vomiting, retching, rescue therapy, or premature discontinuation) and significant nausea (SN) (≥25 mm on a visual analog scale) over the first 120 h after Cycle 1 of MEC. Secondary endpoints included acute and delayed CR and SN rates, rates of nausea, vomiting, and safety. RESULTS: All casopitant doses that were tested significantly increased the proportion of patients with CR: The CR rates were 80.8% with casopitant 50 mg, 78.5% with casopitant 100 mg, and 84.2% with casopitant 150 mg compared with 69.4% in the control group (P = .0127); casopitant 150 mg was identified as the minimally ED. In exploratory analyses, single-dose casopitant demonstrated a 79.2% CR rate, and once-daily ondansetron plus casopitant produced an 83.5% CR rate. Vomiting rates in the first 5 days after MEC were reduced with casopitant-contg. regimens (from 23% to 10%-16%). Rates of SN did not differ among treatment arms (range, 28%-29%). Casopitant appeared to be well tolerated with no notable differences in overall adverse event frequency. CONCLUSIONS: Casopitant plus ond/dex was more effective than ond/dex alone for the prevention of CINV.
OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 45 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2008:1071645 CAPLUS Full-text
DOCUMENT NUMBER: 149:370188
TITLE: Does the application of dexamethasone to prevent postoperative nausea and vomiting increase the incidence of postoperative wound infections?
AUTHOR(S): Holdorf, Stefanie
CORPORATE SOURCE: Germany
SOURCE: (2008) No pp. Avail.: Metadata on Internet Documents, Order No. 384007
From: Metadata Internet Doc. [Ger. Diss.] 2008, (D0904-3), No pp. given
URL: http://www.meind.de/search.py?recid=384007
DOCUMENT TYPE: Dissertation
LANGUAGE: German
AB Unavailable

L6 ANSWER 46 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2008:782819 CAPLUS Full-text
DOCUMENT NUMBER: 149:192277
TITLE: The effect of dexamethasone on nausea, vomiting and pain in parturients undergoing cesarean delivery
AUTHOR(S): Jaafarpour, M.; Khani, A.; Dyrekvandmoghadam, A.;

Khajavikhan, J.; Saadipour, Kh
CORPORATE SOURCE: Nursing & Midwifery Faculty, Ilam University Of Medical Science, Ilam, Iran
SOURCE: Journal of Clinical and Diagnostic Research (2008), 2(3), 854-858
CODEN: JCDRAB; ISSN: 0973-709X
URL: http://www.jcdr.net/articles/PDF/260/240_E(C)_Ed(&)_F(P)_Pf_p1.pdf
PUBLISHER: Journal of Clinical and Diagnostic Research
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background and Aim: Nausea, retching, vomiting and pain are common in parturients undergoing cesarean delivery which is performed under regional anesthesia. The purpose of the present study was to evaluate the prophylactic use of dexamethasone for reducing emetic symptoms (nausea, retching, and vomiting) during cesarean section and analgesic requirements after cesarean surgery. Material and Method: This is a quasi-exptl. study. In a randomized, double-blind trial, 80 parturients received IV placebo (saline) or dexamethasone 8 mg, immediately after clamping of the umbilical cord. Intraoperative, post delivery emetic episodes, severity of pain after surgery, and analgesic requirements were performed by an investigator. The patients experiencing nausea evaluated its severity on a linear numeric scale ranging from 0 (no nausea) to 10 (severe nausea). To det. severity of pain, we used the VAS scale. Results: The results of this study showed that the rate of emetic symptoms (nausea, retching, and vomiting) in an intraoperative, post delivery period, was lower in patients who received 8 mg dexamethasone than in the placebo group ($p < 0.001$). Requests for total requirements of opioids to relieve intolerable pain, were less in patients in the dexamethasone group, as compared with the placebo group ($P<0.001$). In addn., patients in group dexamethasone had significantly lower pain after cesarean than in the placebo group ($p<0.05$, $p<0.001$). Discussion and Conclusion: In the parturients undergoing cesarean delivery performed under spinal anesthesia in this study, prophylactic use of 8 mg dexamethasone was found to be effective for reducing emetic symptoms (nausea, retching, and vomiting) and analgesic requirements after cesarean section, and is recommended for routine use.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 47 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2008:305791 CAPLUS Full-text
DOCUMENT NUMBER: 148:276480
TITLE: Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. [Erratum to document cited in CA147:439992]
AUTHOR(S): Riad, W.; Altaf, R.; Abdulla, A.; Oudan, H.
CORPORATE SOURCE: Department of Anaesthesia, King Khaled Eyes Specialist Hospital, Riyadh, Saudi Arabia
SOURCE: European Journal of Anaesthesiology (2008), 25(1), 88
CODEN: EJANEG; ISSN: 0265-0215
DIGITAL OBJECT ID: 10.1017/S0265021507003055
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On page 699, there is an error in the transposition of data columns two and three in Table 1. The correct version of Table 1 has been reprinted.

L6 ANSWER 48 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2007:1346433 CAPLUS Full-text
DOCUMENT NUMBER: 148:439936
TITLE: Recent advances, trends and economic considerations in the risk assessment, prevention and treatment of postoperative nausea and vomiting
AUTHOR(S): Kranke, Peter; Schuster, Frank; Eberhart, Leopold H.
CORPORATE SOURCE: Department of Anaesthesiology, University Hospitals of Wuerzburg, Wuerzburg, D-97080, Germany

SOURCE: Expert Opinion on Pharmacotherapy (2007), 8(18), 3217-3235
CODEN: EOPHF7; ISSN: 1465-6566
DIGITAL OBJECT ID: 10.1517/14656566.8.18.3217
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. During the last two decades there have been considerable achievements regarding the management of postoperative nausea and vomiting (PONV). Due to the importance of these symptoms in the aim to streamline clin. processes and to improve patient satisfaction, the debate on the best strategies and also research that focuses on PONV continues. This review summarizes the recent developments with respect to the management of PONV. Following a brief review on what is already known on the risk assessment, prevention and treatment of PONV, newer trends in the pharmacol. prevention (dexamethasone, neurokinin-1 antagonists, multimodal prevention) will be discussed as well as new insights regarding the value of algorithms for the prevention of PONV. Further, pharmacogenetically based algorithms (according to the metabolizer status) as well as new treatment strategies (dexamethasone, multimodal treatment) will be covered. No drug so far can achieve a redn. of PONV of more than one third. Furthermore, all clin. studies consistently demonstrated that a combination treatment has a simple additive effect without any relevant interaction between different drugs or classes of drugs. The relative redn. of ~ 30% can also be expected from dexamethasone and it is likely that the substances presently in development and in an early clin. use (e.g., neurokinin-1 antagonists) will not represent the new panacea. However, they will probably replenish the existing antiemetic portfolio to better cope with high risk patients. Stratified prevention using pharmacogenetic knowledge is still in the early stages. Algorithms need to be customized to the local settings in order to prove efficient. Treatment remains a most important pillar and there is evidence that the principles of combining antiemetics to prolong effects and improve protection can be similarly applied to treatment. Recent developments in the area of PONV are more related to implementing the already existing evidence than based on the introduction of new mols. New mols. replenish the pharmacol. antiemetic portfolio, which is needed due to the limited efficacy of any single agent available so far. The new neurokinin-1 receptor antagonist, aprepitant, and the long lasting 5-HT3 receptor antagonist palonosetron are the latest developments in this context. Treatment is most important and can also be regarded as a secondary prevention. Due to limited efficacy of single treatment interventions, combination therapy may gain more widespread use in the future.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 49 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2007:1011895 CAPLUS Full-text
DOCUMENT NUMBER: 147:439992
TITLE: Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children
AUTHOR(S): Riad, W.; Altaf, R.; Abdulla, A.; Oudan, H.
CORPORATE SOURCE: Department of Anaesthesia, King Khaled Eyes Specialist Hospital, Riyadh, Saudi Arabia
SOURCE: European Journal of Anaesthesiology (2007), 24(8), 697-701
CODEN: EJANEG; ISSN: 0265-0215
DIGITAL OBJECT ID: 10.1017/S0265021507000166
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Postoperative nausea and vomiting is a common complication following strabismus surgery. This randomized and double-blind study was designed to evaluate the efficacy of midazolam alone or in combination with dexamethasone in reducing the incidence of postoperative nausea and vomiting in children undergoing strabismus repair. One hundred ASA I children, aged 4-12 yr, scheduled to undergo elective strabismus surgery,

were enrolled. No premedication was given. Anesthesia was induced with sevoflurane, nitrous oxide and oxygen. After induction, fentanyl 2 μg kg-1 and cisatracurium 0.1 mg kg-1 were administered and an endotracheal tube was inserted. After induction of anesthesia and before start of surgery, patients were randomly allocated into one of four groups of 25 children each to receive placebo, midazolam 50 μg kg-1, dexamethasone 0.5 mg kg-1 or a combination of midazolam 50 μg kg-1 and dexamethasone 0.5 mg kg-1. Episodes of nausea, and retching and vomiting were recorded during the first 24 h after surgery. The incidence of postoperative nausea was 48%, 32%, 12%, and 0% with placebo, dexamethasone, midazolam and the midazolam-dexamethasone combination, resp. The incidence of vomiting was 52% and 32% with placebo and dexamethasone, resp.; no child vomited with midazolam alone, or with the midazolam-dexamethasone combination. Prophylactic midazolam with or without dexamethasone reduces the incidence of PONV in children undergoing strabismus repair.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 50 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2007:939847 CAPLUS Full-text

DOCUMENT NUMBER: 148:862

TITLE: Comparison of prophylactic effect of granisetron, droperidol, dexamethasone and droperidol plus dexamethasone on postoperative nausea and vomiting after laparoscopic cholecystectomy

AUTHOR(S): Li, Jun; Duan, Si-yuan; ShangGuan, Yun-fang; Yao, Ying

CORPORATE SOURCE: Department of Anaesthesiology, Shanghai TCM-Intergranted Hospital, Shanghai, 200082, Peop. Rep. China

SOURCE: Linchuang Mazuixue Zazhi (2007), 23(5), 369-370
CODEN: LMZIAG; ISSN: 1004-5805

PUBLISHER: Linchuang Mazuixue Zazhi Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB Objective: To compare the prophylactic effect of granisetron, droperidol and dexamethasone on postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy (LC). Methods: One hundred and sixty ASA I or II patients scheduled for LC were randomly divided into four groups with 40 cases each. The patients in group A received a single pre-anesthesia i.v. does of dexamethasone 10 mg, and in group B droperidol 2.5 mg, in group C droperidol 2.5 mg plus dexamethasone 10 mg, and in group D granisetron 3 mg. The incidence of PONV was obsd. in the 24 h. Results: The PONV incidences of group A, B, C and D are 78%, 63%, 25% and 28%. Both group C and group D significantly decreased the total incidences of PONV ($P < 0.01$) in the 24 h. But there was no marked difference between group C and D. Conclusion: Dexamethasone or droperidol alone did not significantly reduce the incidence of PONV after LC. Granisetron and the combination of droperidol and dexamethasone have obvious effects for this purpose. But the value-capability ratio of droperidol plus dexamethasone is better than granisetron.

L6 ANSWER 51 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2007:448934 CAPLUS Full-text

DOCUMENT NUMBER: 147:227403

TITLE: There Is No Dose-Escalation Response to Dexamethasone (0.0625-1.0 mg/kg) in Pediatric Tonsillectomy or Adenotonsillectomy Patients for Preventing Vomiting, Reducing Pain, Shortening Time to First Liquid Intake, or the Incidence of Voice Change

AUTHOR(S): Kim, Michelle S.; Cote, Charles J.; Cristoloveanu, Carmen; Roth, Andrew G.; Vornov, Polina; Jennings, Melissa A.; Maddalozzo, John P.; Sullivan, Cristine

CORPORATE SOURCE: Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2007), 104(5), 1052-1058
CODEN: AACRAT; ISSN: 0003-2999

DIGITAL OBJECT ID: 10.1213/01.ane.0000263276.52287.3b

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tonsillectomy is assocd. with postoperative nausea and vomiting (PONV) if no prophylaxis is administered. Previous studies have shown that a single dose of dexamethasone decreases the incidence of PONV. The most ED of dexamethasone to affect clin. outcome is yet to be defined. One-hundred-twenty-five children were enrolled in a double-blind, prospective, randomized, dose-escalating study of dexamethasone: 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg, max. dose 24 mg. Nonparametric ANOVA was used to analyze the incidence of vomiting by treatment group for 0 to ≤5 h, >5 to 24 h. The Cox Proportional Likelihood Ratio Test was used to compare the time of first vomit and time to first pain medication across treatment groups. There was no difference in the incidence of vomiting for the five escalating doses of dexamethasone in the time period. There were no differences in secondary outcomes (analgesic requirements, time to first liq., and change in voice) across treatment groups. The authors conclude that the lowest dose of dexamethasone (0.0625 mg/kg) was as effective as the highest dose of dexamethasone (1.0 mg/kg) for preventing PONV or reducing the incidence of other secondary outcomes following tonsillectomy or adenotonsillectomy. There is no justification for the use of high-dose dexamethasone for the prevention of PONV in this cohort of children.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 52 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2007:40795 CAPLUS Full-text
DOCUMENT NUMBER: 146:176797
TITLE: Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT3 antagonists and dexamethasone
AUTHOR(S): Oechsle, Karin; Mueller, Martin R.; Hartmann, Joerg T.; Kanz, Lothar; Bokemeyer, Carsten
CORPORATE SOURCE: Medizinsche Klinik und Poliklinik II, Abteilung fuer Haematologie / Onkologie / Immunologie / Rheumatologie / Pulmonologie, Universitaetsklinik Tuebingen, Tuebingen, Germany
SOURCE: Onkologie (2006), 29(12), 557-561
CODEN: ONKOD2; ISSN: 0378-584X
DIGITAL OBJECT ID: 10.1159/000096689
PUBLISHER: S. Karger GmbH
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Despite prophylaxis with 5-HT3 antagonists and dexamethasone, nausea/emesis are common chemotherapy-induced toxicities. The aim of this trial was to evaluate the efficacy of adding the NK1 antagonist aprepitant in patients refractory to std. prophylaxis. Patients with significant nausea/vomiting despite prophylaxis with 5-HT3 antagonists and dexamethasone were eligible. Aprepitant was added to the same antiemetic regimen used during previous cycles. 34 Patients received 92 cycles of chemotherapy with aprepitant which was applied orally at 125 mg on day 1 and 80 mg on days 2 and 3. All patients were refractory to std. antiemetic prophylaxis during cisplatin-based (n = 12) or other chemotherapy (n = 22). With the addn. of aprepitant, all patients reported subjective improvement. The no. of patients with nausea for >4 days decreased from 24 (71%) to 4 (12%) ($p < 0.001$), and the no. of those with emesis for >2 days decreased from 26 (77%) to 0 (0%) ($p < 0.001$). In 12 patients receiving aprepitant for >2 cycles (3-8) the efficacy was maintained. No toxicity possibly related to aprepitant was obsd. Aprepitant demonstrated significant activity in patients with nausea/vomiting refractory to prophylaxis with 5-HT3 antagonists and dexamethasone.
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 53 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2006:1210598 CAPLUS Full-text
DOCUMENT NUMBER: 146:93155
TITLE: Infusion of palonosetron plus dexamethasone for the prevention of chemotherapy-induced nausea and vomiting
AUTHOR(S): Hajdenberg, Julio; Grote, Thomas; Yee, Lorrin; Arevalo-Araujo, Roberto; Latimer, Laurie A.
CORPORATE SOURCE: M. D. Anderson Cancer Center, Orlando, FL, USA
SOURCE: Journal of Supportive Oncology (2006), 4(9), 467-471
CODEN: JSOOBY; ISSN: 1544-6794
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Serotonin (5-HT3) receptor antagonists are the foundation of std. antiemetic care for cancer patients receiving emetogenic chemotherapy. To enhance the efficacy of these supportive care agents, dexamethasone is routinely admixed with the 5-HT3 receptor antagonist, which is administered by i.v. infusion before chemotherapy begins. This phase II study evaluated the safety and efficacy of i.v. palonosetron admixed with dexamethasone to prevent chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy. Cancer patients received palonosetron 0.25 mg plus dexamethasone 8 mg admixed in 50 mL of infusion soln. before receiving at least one qualifying chemotherapeutic agent (cyclophosphamide ≤ 1,500 mg/m2, doxorubicin ≥ 20 mg/m2, carboplatin, or oxaliplatin). Patients used diaries to record nausea and emesis experienced and rescue medications used. Of 32 participants, 27 (84%) had a complete response (no emesis and no rescue medication) during the acute (0-24 h) interval posttherapy, 19 (59%) had a complete response during the delayed (> 24-120 h) posttherapeutic interval, and 19 (59%) had a complete response during the overall (0-120 h) posttreatment interval. A total of 23 patients (72%) had no emetic episodes, 16 (50%) had no nausea, and 21 (66%) used no rescue medication throughout the overall 5-day interval. The combination was well tolerated. Palonosetron plus dexamethasone given as a pretreatment infusion is effective and safe in preventing acute and delayed CINV in patients receiving moderately emetogenic chemotherapy.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 54 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2006:1018931 CAPLUS Full-text
DOCUMENT NUMBER: 146:75032
TITLE: Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomized double blind multicentre trial
AUTHOR(S): Wallenborn, Jan; Gelbrich, Goetz; Bulst, Detlef; Behrends, Katrin; Wallenborn, Hasso; Rohrbach, Andrea; Krause, Uwe; Kuehnast, Thomas; Wiegel, Martin; Olthoff, Derk
CORPORATE SOURCE: Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, D-04103, Germany
SOURCE: BMJ [British Medical Journal] (2006), 333(7563), 324-327
CODEN: BMJBFE; ISSN: 0959-8146
DIGITAL OBJECT ID: 10.1136/bmj.38903.419549.80
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objectives: To det. whether 10 mg, 25 mg, or 50 mg metoclopramide combined with 8 mg dexamethasone, given intraoperatively, is more effective in preventing postoperative nausea and vomiting than 8 mg dexamethasone alone, and to assess benefit in relation to adverse drug reactions. Design: Four-armed, parallel group, double blind, randomized controlled clin. trial. Setting: Four clinics of a university hospital and four district hospitals in Germany. Participants: 3140 patients who received balanced or regional anesthesia during surgery. Main outcome measures: Postoperative nausea and vomiting within 24 h of surgery (primary end point); occurrence of adverse reactions. Results: Cumulative incidences

(95% confidence intervals) of postoperative nausea and vomiting were 23.1% (20.2% to 26.0%), 20.6% (17.8% to 23.4%), 17.2% (14.6% to 19.8%), and 14.5% (12.0% to 17.0%) for 0 mg, 10 mg, 25 mg, and 50 mg metoclopramide. In the secondary anal., 25 mg and 50 mg metoclopramide were equally effective at preventing early nausea (0-12 h), but only 50 mg reduced late nausea and vomiting (> 12 h). The most frequent adverse drug reactions were hypotension and tachycardia, with cumulative incidences of 8.8% (6.8% to 10.8%), 11.2% (9.0% to 13.4%), 12.9% (10.5% to 15.3%), and 17.9% (15.2% to 20.6%) for 0 mg, 10 mg, 25 mg, and 50 mg metoclopramide. Conclusion: The addn. of 50 mg metoclopramide to 8 mg dexamethasone (given intraoperatively) is an effective, safe, and cheap way to prevent postoperative nausea and vomiting. A reduced dose of 25 mg metoclopramide intraoperatively, with addnl. postoperative prophylaxis in high risk patients, may be equally effective and cause fewer adverse drug reactions.

OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 55 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2006:357609 CAPLUS Full-text

DOCUMENT NUMBER: 145:284672

TITLE: Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy

AUTHOR(S): Feo, C. V.; Sortini, D.; Ragazzi, R.; De Palma, M.; Liboni, A.

CORPORATE SOURCE: Sections of General Surgery, Department of Surgery, Anaesthesiology and Radiology, University of Ferrara, Ferrara, Italy

SOURCE: British Journal of Surgery (2006), 93(3), 295-299
CODEN: BJSUAM; ISSN: 0007-1323

DIGITAL OBJECT ID: 10.1002/bjs.5252

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Preoperative dexamethasone may reduce disabling symptoms such as pain, nausea and vomiting after laparoscopic cholecystectomy. Methods: This was a randomized, double-blind, placebo-controlled trial. Between Mar. and Dec. 2004, 101 patients undergoing laparoscopic cholecystectomy were randomized to receive 8 mg dexamethasone (n = 49) or placebo (n = 52) i.v. before surgery. Six patients were excluded from the study. All patients received a standardized anesthetic, surgical and multimodal analgesic treatment. The primary endpoints were: first, postoperative nausea, vomiting and pain; second, postoperative analgesic and antiemetic requirements. The pain scores (visual analog and verbal response scales), the episodes of nausea (verbal response scale) and vomiting were recorded at 1, 3, 6 and 24 h, resp., after the operation. Analgesic and antiemetic requirements were also recorded. Results: No apparent drug side-effects were noted. Seven patients (14 per cent) in the treatment group reported nausea and vomiting compared with 24 (46 per cent) in the control group (P = 0.001). In the group of patients treated with dexamethasone, five (10 per cent) required antiemetics vs. 23 (44 per cent) of those receiving placebo (P < 0.001). No difference in postoperative pain scores and analgesic requirements was detected between groups. Conclusion: Preoperative dexamethasone reduces postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy, with no side-effects, and may be recommended for routine use.

OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 56 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2006:315959 CAPLUS Full-text

DOCUMENT NUMBER: 145:137951

TITLE: Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy

AUTHOR(S): Vardy, J.; Chiew, K. S.; Galica, J.; Pond, G. R.;

Tannock, I. F.
CORPORATE SOURCE: Department of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, Toronto, ON, M5G2M9, Can.
SOURCE: British Journal of Cancer (2006), 94(7), 1011-1015
CODEN: BJCAAI; ISSN: 0007-0920
DIGITAL OBJECT ID: 10.1038/sj.bjc.6603048
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of dexamethasone to reduce delayed emesis following highly emetogenic chemotherapy is proven, but there is less evidence of benefit after mild-moderately emetogenic regimens. Here, we develop and evaluate a Dexamethasone Symptom Questionnaire (DSQ) to assess the side effects of dexamethasone in the week after patients receive moderately emetogenic chemotherapy. The DSQ was first optimized with the aid of a focus group. Sixty patients receiving oral dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy for cancer completed and then evaluated the DSQ. Patients reported that the DSQ was clearly worded and addressed items important to them. Patients receiving dexamethasone reported moderate-severe problems with insomnia (45%), indigestion/epigastric discomfort (27%), agitation (27%), increased appetite (19%), wt. gain (16%) and acne (15%) in the week following chemotherapy. The side effects of dexamethasone may outweigh its benefits when used with moderately emetogenic chemotherapy. A randomized, double-blind crossover trial is underway to det. the effect of dexamethasone on nausea and vomiting, and the impact of side effects of dexamethasone and of nausea and vomiting on quality of life.
OS.CITING REF COUNT: 69 THERE ARE 69 CAPLUS RECORDS THAT CITE THIS RECORD (69 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 57 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2005:1181658 CAPLUS Full-text
DOCUMENT NUMBER: 144:184374
TITLE: Effects of granisetron with droperidol or dexamethasone on prevention of postoperative nausea and vomiting after general anesthesia for cesarean section
AUTHOR(S): Kocamanoglu, I. S.; Baris, S.; Karakaya, D.; Sener, B.; Tur, A.; Cetinkaya, M.
CORPORATE SOURCE: Department of Anesthesiology, Ondokuz Mayis University, Samsun, Turk.
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology (2005), 27(7), 489-493
CODEN: MFEPDX; ISSN: 0379-0355
DIGITAL OBJECT ID: 10.1358/mf.2005.27.7.920930
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This prospective, placebo-controlled, double-blinded, and randomized study was undertaken to compare the efficacy of granisetron, droperidol, and combinations of granisetron with droperidol or dexamethasone on postoperative nausea and vomiting in patients undergoing general anesthesia for cesarean section. Patients (n = 150) who were scheduled for cesarean section under general anesthesia were randomly assigned to one of the five groups: physiol. saline 5 mL in Group A, granisetron 40 μg/kg + dexamethasone 8 mg in Group B, granisetron 40 μg/kg + droperidol 1.25 mg in Group C, droperidol 1.25 mg in Group D, and granisetron 40 μg/kg in Group E were administered i.v. after clamping of the fetal umbilical cord. Postoperative nausea and vomiting was obsd. for 0-24 h after the anesthesia. Cesarean sections were all performed under general anesthesia. Postoperative nausea and vomiting was more common in placebo group (56.7%) than the others during the 0-24 h after the anesthesia ($p < 0.05$). All granisetron groups were more effective than placebo and droperidol groups during the postoperative 3-24 h ($p < 0.01$). Although this trial lacks statistical power, granisetron alone and combinations with droperidol or dexamethasone were effective similarly. All treatment groups, except droperidol during the postoperative 3-24 h, were effective for prevention of postoperative nausea and vomiting during

the postoperative 0-24 h.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 58 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2005:436809 CAPLUS Full-text
DOCUMENT NUMBER: 143:186935
TITLE: Prophylactic Dexamethasone for Postoperative Nausea and Vomiting in Pediatric Strabismus Surgery: A Dose Ranging and Safety Evaluation Study
AUTHOR(S): Madan, Rashmi; Bhatia, Anuj; Chakithandy, Sajith; Subramaniam, Rajeshwari; Rammohan, Gurram; Deshpande, Shrinivas; Singh, Manorama; Kaul, H. L.
CORPORATE SOURCE: Department of Anaesthesiology and Intensive Care, All India Institute of Medical Sciences, New Delhi, India
SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2005), 100(6), 1622-1626
CODEN: AACRAT; ISSN: 0003-2999
DIGITAL OBJECT ID: 10.1213/01.ANE.0000150977.14607.E1
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this double-blind, randomized, placebo-controlled study, we evaluated the efficacy and safety of different doses of prophylactic i.v. dexamethasone for postoperative nausea and vomiting (PONV) in 168 children (aged 2-15 yr) scheduled for strabismus surgery. Patients received i.v. dexamethasone 0.25 mg/kg (D 0.25), 0.5 mg/kg (D 0.5), 1.0 mg/kg (D 1), or saline (S) immediately after induction of general anesthesia. Patients were discharged 24 h after surgery. Nausea and vomiting were assessed at 0-2, 2-6, and 6-24 h after surgery. Blood glucose was measured preoperatively and at 4 h after study drug administration. Wound healing and infection were assessed after 1 wk. More patients in group S had vomiting at 0-2, 2-6, and 6-24 h and required larger doses of rescue antiemetics compared with the dexamethasone groups. Fewer patients in the dexamethasone groups (6, 3, and 6 in D 0.25, D 0.5, and D 1, resp.) had severe PONV compared with group S. No significant increase in postoperative blood glucose levels was obsd. and wound healing was satisfactory in all four groups. The results suggest that dexamethasone 0.25 mg/kg is more effective than saline and equally effective compared with larger doses for preventing PONV for pediatric strabismus surgery.
OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 59 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2005:239389 CAPLUS Full-text
DOCUMENT NUMBER: 142:475798
TITLE: Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications
AUTHOR(S): Geling, Olga; Eichler, Hans-Georg
CORPORATE SOURCE: Department of Public Health Sciences and Epidemiology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA
SOURCE: Journal of Clinical Oncology (2005), 23(6), 1289-1294
CODEN: JCONDN; ISSN: 0732-183X
DIGITAL OBJECT ID: 10.1200/JCO.2005.04.022
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose 5-Hydroxytryptamine-3 receptor antagonists (5-HT3 antagonists) are effective for preventing acute chemotherapy-induced emesis but the benefits of continuing administration of these agents beyond 24 h after chemotherapy (delayed emesis) remain unclear. The purpose of this study was to provide ests. of clin. efficacy and drug acquisition cost assocd. with administering 5-HT3 antagonists beyond 24 h, as monotherapy or as

added to dexamethasone. Methods This anal. is based on the Cancer Care Ontario Practice Guidelines Initiative meta-anal. of the efficacy of 5-HT3 antagonists. Results from the clin. trials covered in that meta-anal. were reanalyzed to provide ests. of abs. risk redns. (ARR) and nos. needed to treat (NNT) for 5-HT3 antagonists, as monotherapy or as adjunct treatment. Nos. of 5-HT3 antagonist unit doses per successfully treated patient were also calcd. Results Five studies (comprising 1,716 assessable patients) compared a 5-HT3 antagonist with placebo; five studies (2,240 patients) compared a combination of a 5-HT3 antagonist and dexamethasone with dexamethasone monotherapy. ARR for monotherapy was only 8.2% (95% CI, 3.0% to 13.4%). On av., 74 5-HT3 antagonist doses must be administered to 12 patients (NNT, 12.2; 95% CI, 7.5 to 33.4) not receiving dexamethasone to protect one patient from delayed emesis. In those patients receiving dexamethasone as std. antiemetic treatment in the delayed phase, the addn. of a 5-HT3 antagonist did not significantly improve control of delayed emesis as compared with dexamethasone monotherapy (ARR, 2.6%; 95% CI, -0.6% to 5.8%). Conclusion Neither clin. evidence nor considerations of cost effectiveness justify using 5-HT3 antagonists beyond 24 h after chemotherapy for prevention of delayed emesis.

OS.CITING REF COUNT: 115 THERE ARE 115 CAPLUS RECORDS THAT CITE THIS RECORD (115 CITINGS)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 60 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2003:625721 CAPLUS Full-text

DOCUMENT NUMBER: 139:240225

TITLE: Vomiting after strabismus surgery in children: Propofol versus propofol and dexamethasone

AUTHOR(S): Ismail, Olfat M.; Said, Mostafa A.; El Din, Mohamed N. Serag

CORPORATE SOURCE: Anaesthesia Department, Faculty of Medicine, Mansoura University, Egypt

SOURCE: Egyptian Journal of Anaesthesia (2003), 19(3), 305-310
CODEN: EJAGAP; ISSN: 1683-1810

PUBLISHER: Central Society of Egyptian Anaesthesiologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present study was conducted to evaluate and compare the effect of propofol vs. dexamethasone/propofol for the prevention of postoperative emesis in children undergoing strabismus surgery. Sixty children, ASA I or II were randomly allocated to three equal groups. In the thiopentone group, each patient received 10 mL normal saline after induction of anesthesia with thiopentone. In the propofol group, each patient received 10 mL normal saline after induction of anesthesia with propofol. In the dexamethasone/propofol group, each patient received 0.15 mg/kg dexamethasone dild. to 10 mL saline after induction of anesthesia with propofol. Then, anesthesia was managed in a standardized manner in all groups. At the conclusion of the procedure, 0.04 mg/kg neostigmine, and 0.02 mg/kg atropine were given to antagonize the residual effect of blockade. Std. monitoring of patients was used throughout anesthesia and extended during their stay in the PACU. Pain intensity was assessed by an observational scoring system. Vomiting was assessed immediately after operation and graded as none, mild (1-3), moderate (4-6), severe (7 or more) episodes, recording its time of occurrence. All groups were similar with respect to demog. data, duration of anesthesia, and no. of muscles operated. All groups showed significant decrease in pain score in 2nd hour compared to 1st hour ($P < 0.01$). There was no difference in the postanaesthetic recovery score between the groups. However, the scores at time of discharge from PACU were higher than that recorded at time of admission ($P < 0.05$). Incidence of vomiting in propofol group and dexamethasone/propofol group was significantly decreased compared to thiopentone group ($P = 0.001$). We concluded that the use of propofol as an induction agent is the same as the combination of propofol and dexamethasone in reducing postoperative vomiting and the use of dexamethasone has no effect on decreasing intensity of pain after strabismus surgery.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 61 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2003:137116 CAPLUS Full-text
DOCUMENT NUMBER: 138:297361
TITLE: Comparison of granisetron and granisetron plus dexamethasone for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy
AUTHOR(S): Biswas, B. N.; Rudra, A.
CORPORATE SOURCE: Department of Anesthesiology, Calcutta National Medical College and Hospital, Calcutta, India
SOURCE: Acta Anaesthesiologica Scandinavica (2003), 47(1), 79-83
CODEN: AANEAB; ISSN: 0001-5172
DIGITAL OBJECT ID: 10.1034/j.1399-6576.2003.470114.x
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Laparoscopic cholecystectomies are assocd. with an appreciably high rate of postoperative nausea and vomiting (PONV). This study was designed to compare the effectiveness of granisetron plus dexamethasone with granisetron alone for the prevention of postoperative nausea and vomiting in patients after laparoscopic cholecystectomy. In a randomized, double-blind study, 120 patients of both sexes received granisetron 40 μg kg-1 alone or granisetron 40 μg kg-1 plus dexamethasone 8 mg (n=60 of each) i.v. immediately before induction of anesthesia. Perioperative anesthetic care was standardized in all patients. Patients were then obsd. for 24 h after administration of the study drug. A complete response (defined as no PONV and no need for another rescue antiemetic) was achieved in 83% of the patients given granisetron and in 95% of the patients given granisetron plus dexamethasone ($P < 0.05$). The overall cumulative incidences (0 - 24h) of PONV were 11 (18.3%) in the granisetron and three (5%) in the combination group. No difference in adverse events were obsd. in any of the groups. The combination (granisetron plus dexamethasone) further increases the chance of complete response than granisetron alone. Therefore, the combination might be considered clin. relevant in a high risk setting.
OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 62 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 2002:905015 CAPLUS Full-text
DOCUMENT NUMBER: 139:62757
TITLE: Treatment of nausea and emesis during cancer chemotherapy: discrepancies between antiemetic effect and well-being
AUTHOR(S): Boerjeson, Sussanne; Hursti, Timo J.; Tishelman, Carol; Peterson, Curt; Steineck, Gunnar
CORPORATE SOURCE: Division of Nursing Science, Faculty of Health Sciences, Linkoeping University, Linkoeping, Swed.
SOURCE: Journal of Pain and Symptom Management (2002), 24(3), 345-358
CODEN: JPSMEU; ISSN: 0885-3924
DIGITAL OBJECT ID: 10.1016/S0885-3924(02)00543-2
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to describe the relationship between antiemetic effect and well-being in patients receiving four different antiemetic treatment strategies, representing developments in the field during the past 15 yr. A total of 162 women with ovarian cancer receiving cisplatin-based chemotherapy and participating in two comparative antiemetic trials were enrolled and studied for up to four cycles. In study I, a combined antiemetic strategy including a nursing intervention program (increased access to support and increased information) and antiemetics based on high-dose metoclopramide and dexamethasone was compared with the std. antiemetic treatment during the 1980s. In study II, ondansetron plus dexamethasone/placebo was evaluated. The assessment methods used were similar for all patients. Questionnaires were used to assess frequency, intensity, and duration of nausea, emesis, anxiety,

pain, and well-being at baseline, and for acute (24 h after chemotherapy) and delayed (up to 2 wk after chemotherapy) symptoms. The mean intensity of acute nausea during the first cycle was higher in the groups in study I, as compared to the groups in study II The group receiving a nursing intervention reported better well-being than the other groups. Duration of nausea was an important predictor of well-being, even when nausea intensity was controlled. Apart from nausea intensity, nausea duration and nursing interventions may be important determinants for well-being during chemotherapy.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 63 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2002:485662 CAPLUS Full-text

DOCUMENT NUMBER: 137:88217

TITLE: Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. A randomized controlled trial

AUTHOR(S): Van Belle, Simon; Lichinitser, Michael R.; Navari, Rudolph M.; Garin, August M.; Decramer, Marc L. A.; Riviere, Alain; Thant, Myo; Brestan, Elmer; Bui, Binh; Eldridge, Krista; De Smet, Marina; Michiels, Nicole; Reinhardt, Rick R.; Carides, Alexandra D.; Evans, Judith K.; Gertz, Barry J.

CORPORATE SOURCE: Oncologisch Centrum, Universitair Ziekenhuis, Ghent, Belg.

SOURCE: Cancer (New York, NY, United States) (2002), 94(11), 3032-3041
CODEN: CANCAR; ISSN: 0008-543X

DIGITAL OBJECT ID: 10.1002/cncr.10516

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent studies have suggested that antiemetic therapy with a triple combination of the neurokinin-1 receptor antagonist MK-869, a serotonin (5-HT3) antagonist, and dexamethasone provides enhanced control of cisplatin-induced emesis compared with std. therapy regimens. The authors compared the antiemetic activity of a dual combination of MK-869 and dexamethasone with that of a std. dual combination of ondansetron and dexamethasone to characterize further the efficacy and tolerability profile of MK-869. This was a multicenter, double-blind, randomized, active agent-controlled study of 177 cisplatin-naive patients with malignant disease. On day 1, MK-869 was given i.v. as its water-sol. prodrug, L-758,298. Patients were randomized to one of three groups as follows. Group I received L-758,298 100 mg i.v., then dexamethasone 20 mg i.v., and cisplatin ≥ 70 mg/m2 on day 1 followed by 300 mg MK-869 (tablet) orally on days 2-5; Group II received L-758,298 100 mg i.v., then dexamethasone 20 mg i.v., and cisplatin ≥ 70 mg/m2 on day 1 followed by placebo on days 2-5; and Group III received ondansetron 32 mg i.v., then dexamethasone 20 mg i.v., and cisplatin ≥ 70 mg/m2 on day 1 followed by placebo on days 2-5. Emesis was recorded over days 1-5 in a diary. Nausea was assessed every 24 h by visual analog scale. Addnl. medication was available for emesis or nausea at any time. The primary efficacy parameters of interest were the proportion of patients without emesis and the proportion without emesis or rescue therapy on day 1 (acute phase) and on days 2-5 (delayed phase). No serious adverse events were attributed to L-758,298 or MK-869. On day 1, the proportions of patients with no emesis and no use of rescue medication were 44 % of patients in Group I, 36 % of patients in Group II, 40 % of patients in Groups I and II combined, and 83 % of patients in Group III ($P < 0.001$ for Group III vs. the combined Groups I and II). The proportions of patients with no emesis and no use of rescue medication on days 2-5 were 59 % of patients in Group I, 46 % of patients in Group II, and 38 % of patients in Group III ($P < 0.05$ for Group I vs. Group III). The proportions of patients who were without emesis on day 1 were 49 % of patients in Group I, 47 % of patients in Group II, and 84 % of patients in Group III ($P < 0.01$ for Group I or II vs. Group III). On days 2-5, however, the proportions of patients who were without emesis on days 2-5 were 65 % of patients in Group I, 61 % of patients in Group II, and 41 % of patients in Group III ($P < 0.05$ for Group I or II vs. Group III). Nausea scores in the acute phase were lower for Group III than for Group I, Group II, or

Groups I and II combined (P < 0.05), although there was no significant difference among groups either for the delayed phase or overall for days 1-5. Although the L-758,298 and dexamethasone combination reduced acute (day 1) emesis compared with historic rates, dual therapy with ondansetron and dexamethasone was superior in controlling acute emesis. Continued dosing with MK-869 may enhance control of other measures of delayed emesis, such as the use of rescue medication, although confirmation is required before a definitive conclusion may be drawn. MK-869 given as dual therapy with dexamethasone was superior to ondansetron with dexamethasone for the control of delayed emesis (days 2-5) and control of the need for rescue medication on Days 2-5.

OS.CITING REF COUNT: 81 THERE ARE 81 CAPLUS RECORDS THAT CITE THIS RECORD (81 CITINGS)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 64 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2002:171306 CAPLUS Full-text

DOCUMENT NUMBER: 136:396129

TITLE: Low-dose dexamethasone reduces nausea and vomiting after epidural morphine: a comparison of metoclopramide with saline

AUTHOR(S): Tzeng, Jann-Inn; Hsing, Chung-Hsi; Chu, Chin-Chen; Chen, Ying-Hui; Wang, Jhi-Joung

CORPORATE SOURCE: Department of Anesthesiology, Municipal Women's and Children's General Hospital, Kaohsiung, Taiwan

SOURCE: Journal of Clinical Anesthesia (2002), 14(1), 19-23
CODEN: JCLBE7; ISSN: 0952-8180

DIGITAL OBJECT ID: 10.1016/S0952-8180(01)00345-2

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to compare the efficacy of a low dose of dexamethasone (5 mg) with metoclopramide 10 mg and saline in preventing nausea and vomiting after epidural morphine in post-hysterectomy analgesia. This was a randomized, placebo-controlled study. The study setting was innpatient surgery at Municipal Women's and Children's General Hospital. There were 120 ASA phys. status I and II women receiving epidural morphine for post-hysterectomy analgesia. All patients received epidural morphine 3 mg for postoperative analgesia. The dexamethasone group received dexamethasone 5 mg, the metoclopramide group received metoclopramide 10 mg, and the saline group received saline. The occurrence of nausea and vomiting appeared more frequently during 6 to 24 h following the administration of epidural morphine. The total frequency of nausea and vomiting in the dexamethasone group was significantly lower than that of the metoclopramide and saline groups during this period, with reporting frequencies of 21%, 49%, and 53%, resp. (each). However, the difference between metoclopramide and saline did not reach statistical significance. Dexamethasone 5 mg was more effective than metoclopramide or saline in the prevention of nausea and vomiting assocd. with epidural morphine for postoperative analgesia.

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 65 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 2000:383447 CAPLUS Full-text

DOCUMENT NUMBER: 133:541

TITLE: Dexamethasone for the prophylaxis of radiation-induced emesis: a National Cancer Institute of Canada Clinical Trials Group Phase III study

AUTHOR(S): Kirkbride, P.; Bezjak, A.; Pater, J.; Zee, B.; Palmer, M. J.; Wong, R.; Cross, P.; Gulavita, S.; Blood, P.; Sun, A.; Dundas, G.; Ganguly, P. K.; Lim, J.; Chowdhury, A. D.; Kumar, S. E.; Dar, A. R.

CORPORATE SOURCE: National Cancer Institute of Canada Clinical Trials Group, Kingston, ON, Can.

SOURCE: Journal of Clinical Oncology (2000), 18(9), 1960-1966
CODEN: JCONDN; ISSN: 0732-183X

DIGITAL OBJECT ID: 10.1200/JCO.2000.18.9.1960
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to investigate the efficacy of dexamethasone as a prophylactic antiemetic for patients receiving fractionated radiotherapy to the upper abdomen in a randomized controlled trial. One hundred fifty-four patients planned to receive fractionated radiotherapy to fields involving the upper abdomen (min. total dose, 20 Gy; min. no. of fractions, five) were randomized to receive prophylactic dexamethasone (2 mg orally three times a day [tid], starting in the morning of first treatment and continuing until after their fifth treatment) or placebo. The primary end point of the study was the proportion of patients free from emesis during the study period. Secondary end points included a quality-of-life assessment using the core questionnaire of the European Organization for Research and Treatment of Cancer and side effects of dexamethasone therapy in this population of patients. Fifty-four (70%) out of 75 patients receiving dexamethasone had complete protection vs. 37 (49%) out of 75 patients on placebo (P = .025). Most emetic episodes occurred during the initial phase of treatment. Although there was no difference in global quality of life between the two sets of patients, patients receiving dexamethasone had less nausea and vomiting and less loss of appetite but more insomnia. Dexamethasone 2 mg tid seems to be an effective prophylactic antiemetic in this situation. Side effects were acceptable, but there seemed to be no overall effect on global quality of life.
OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 66 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1999:750417 CAPLUS Full-text
DOCUMENT NUMBER: 131:331942
TITLE: Double-blind comparative study of droperidol, and granisetron plus dexamethasone as prophylactic anti-emetic therapy in patients undergoing abdominal, gynaecological, breast or otolaryngological surgery
AUTHOR(S): Janknegt, R.; Pinckaers, J. W. M.; Rohof, M. H. C.; Ausems, M. E. M.; Arbouw, M. E. L.; Van der Velden, R. W.; Brouwers, J. R. B. J.
CORPORATE SOURCE: Maasland Ziekenhuis, Sittard, 6130 MB, Neth.
SOURCE: Anaesthesia (1999), 54(11), 1059-1068
CODEN: ANASAB; ISSN: 0003-2409
DIGITAL OBJECT ID: 10.1046/j.1365-2044.1999.01075.x
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this double-blind study the clin. efficacy of a single pre-operative i.v. dose of droperidol 1.25 mg (137 patients), granisetron 1 mg (130 patients) and granisetron 1 mg plus dexamethasone 5 mg (130 patients) was investigated for the prevention of postoperative nausea and vomiting after gynecol. surgery, breast surgery, abdominal surgery and ear, nose and throat surgery. The incidence of nausea in the first 24 h postoperatively was 52% in the droperidol group, 48% in the granistron group and 34% with the combination, resp. Both granisetron and granisetron/dexamethasone performed better than droperidol in their effects on vomiting or combined nausea and vomiting (incidence in the first 24 h 22%, 18% and 42%, resp.). The no. of emetic episodes during the 5-day study period was significantly higher in the droperidol group (198) than in the granisetron (73) or combination group (78).
OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 67 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1999:514257 CAPLUS Full-text
DOCUMENT NUMBER: 131:266678
TITLE: A double-blind randomized study comparing i.m.

granisetron with i.m. granisetron plus dexamethasone in the prevention of delayed emesis induced by cisplatin
CORPORATE SOURCE: The Italian Multicenter Study Group, SmithKline Beecham, Milan, 20021, Italy
SOURCE: Anti-Cancer Drugs (1999), 10(5), 465-470
CODEN: ANTDEV; ISSN: 0959-4973
DIGITAL OBJECT ID: 10.1097/00001813-199906000-00006
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Granisetron has been shown to exert a beneficial therapeutic effect in the prophylaxis and treatment of acute nausea and vomiting due to chemotherapy. However, limited data regarding its efficacy in the prevention and treatment of delayed emesis are available. A total of 532 patients entered this multicenter double-blind study, aimed at comparing the efficacy and safety of i.m. granisetron with that of i.m. granisetron plus dexamethasone. Complete response and total control were evaluated for 3 days following the first 24 h after cisplatin administration in two groups of patients: 262 treated with granisetron 3 mg i.m. daily (plus placebo), and 265 with granisetron at the same dose plus dexamethasone 8 and 4 mg twice daily. The rate of complete response was 58.0% in the granisetron group and 78.9% in the granisetron plus dexamethasone group over days 1-3 ($p<0.01$). Similarly, over the same period total control was 44.7% with granisetron alone and 65.3% with granisetron plus dexamethasone ($p<0.01$). Local and systemic tolerability of the i.m. therapy with granisetron were satisfactory. In conclusion, granisetron plus dexamethasone showed good protection against delayed emesis due to emetogenic chemotherapy.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 68 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1998:741937 CAPLUS Full-text
DOCUMENT NUMBER: 130:133778
TITLE: Low-dose oral granisetron (1 mg) plus intravenous dexamethasone: efficacy in gynecologic cancer patients receiving carboplatin-based chemotherapy
AUTHOR(S): Markman, Maurie; Kennedy, Alexander; Webster, Kenneth; Kulp, Barbara; Peterson, Gertrude; Belinson, Jerome
CORPORATE SOURCE: The Cleveland Clinic Taussig Cancer Center, Department of, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: Gynecologic Oncology (1998), 71(1), 113-115
CODEN: GYNOA3; ISSN: 0090-8258
DIGITAL OBJECT ID: 10.1006/gyno.1998.5168
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Patients with gynecol. malignancies being treated with either single-agent carboplatin or a carboplatin-paclitaxel regimen received a single 1-mg oral dose of granisetron plus i.v. dexamethasone (20 mg) as prophylaxis for emesis, prior to chemotherapy. Of the 32 patients participating in this phase 2 trial, only 2 (6%) experienced any degree of nausea or vomiting within the 1st 24 h after chemotherapy. Both of these individuals had carcinomatosis and were experiencing emesis prior to chemotherapy. One patient developed mild delayed nausea >24 h after treatment. No major or minor toxic effects of the antiemetic regimen were obsd. Thus, a 1-mg dose of oral granisetron plus i.v. dexamethasone (20 mg) is a safe, effective, and relatively inexpensive prophylactic antiemetic regimen for patients receiving single-agent carboplatin or combination carboplatin-paclitaxel chemotherapy. (c) 1998 Academic Press.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 69 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1998:559972 CAPLUS Full-text
DOCUMENT NUMBER: 129:310507
ORIGINAL REFERENCE NO.: 129:63201a,63204a
TITLE: Comparative crossover trial of two intravenous doses of granisetron (1 mg vs 3 mg) + dexamethasone in the prevention of acute cis-platinum-induced emesis
AUTHOR(S): Martoni, A.; Piana, E.; Strocchi, E.; Angelelli, B.; Guaraldi, M.; Zamagni, C.; Camaggi, C. M.; Pannuti, F.
CORPORATE SOURCE: Division of Medical Oncology, S. Orsola-Malpighi Hospital, Bologna, 40138, Italy
SOURCE: Anticancer Research (1998), 18(4B), 2799-2803
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the 5-HT3 receptor antagonist granisetron (GRA, 1 or 3 mg) combined with dexamethasone (DEX, 20 mg) in the prevention of acute cisplatin (CP)-induced emesis were studied in 198 consecutive chemotherapy-naive cancer patients suffering mainly from lung and bladder cancer. The cytotoxic treatment included different multi-drug regimens contg. CP (median dose 60 mg/m2, range 50-70) administered on day 1 and repeated every 21-28 days (the other drugs in the antitumor regimens were epirubicin, cyclophosphamide, methotrexate, or vinorelbine). Of the 192 evaluable patients, complete protection from acute emesis after the first two CP therapy cycles was obsd. with 1 and 3 mg GRA + DEX as follows: nausea 70 and 74%, vomiting 90 and 94%, nausea and vomiting 67 and 74%, resp. No carry-over effect was obsd. on the complete protection from emesis. The crossover anal. comprising 156 patients confirmed that there were no differences between the 2 antiemetic treatments; 27% patients preferred GRA 1 + DEX, 31% preferred GRA 3 +DEX, and 42% expressed no preference. No difference was obsd. for GRA treatment tolerability, the only reported side-effect was mild headache and constipation. Thus, the 1 and 3 mg i.v. GRA doses are comparably effective when combined with 20 mg DEX in the prevention of acute CP-induced emesis in humans.
OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 70 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1998:465725 CAPLUS Full-text
DOCUMENT NUMBER: 129:225888
ORIGINAL REFERENCE NO.: 129:45785a,45788a
TITLE: The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy
AUTHOR(S): Pappas, Ana Lucia S.; Sukhani, Radha; Hotaling, Andrew J.; Mikat-Stevens, Marianna; Javorski, Joseph J.; Donzelli, Joseph; Shenoy, Kalavathi
CORPORATE SOURCE: Department of Anesthesiology, Loyola University Medical Center, Maywood, IL, 60153, USA
SOURCE: Anesthesia & Analgesia (Baltimore) (1998), 87(1), 57-61
CODEN: AACRAT; ISSN: 0003-2999
DIGITAL OBJECT ID: 10.1213/00000539-199807000-00013
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this prospective, randomized, double-blind, placebo-controlled study, we examd. the effect of preoperative dexamethasone on postoperative nausea and vomiting (PONV) and 24-h recovery in children undergoing tonsillectomy. One hundred thirty children, 2-12 yr of age, ASA phys. status I or II, completed the study. All children received oral midazolam 0.5-0.6 mg/kg preoperatively. Anesthesia was induced with halothane and nitrous oxide in 60% oxygen and maintained with nitrous oxide and isoflurane. Intubation was facilitated by mivacurium 0.2 mg/kg. Each child received fentanyl 1 μg/kg IV before initiation of surgery, as well as dexamethasone 1 mg/kg (maximal dose 25 mg) (steroid group) or an equal vol. of saline (control group). Intraoperative fluids were standardized to 25-30 mL/kg lactated Ringer's soln. All tonsillectomies were performed under the supervision of one attending surgeon using an

electrodissection technique. Postoperatively, fentanyl and acetaminophen with codeine elixir were administered as needed for pain. Rescue antiemetics were administered when a child experienced two episodes of retching and/or vomiting. Before home discharge, the incidence of PONV, need for rescue antiemetics, quality of oral intake, and analgesic requirements did not differ between groups. However, during the 24 h after discharge, more patients in the control group experienced PONV (62% vs. 24% in the steroid group) and complained of poor oral intake. Addnl., more children in the control group (8% vs. 0% in the steroid group) returned to the hospital for the management of PONV and/or poor oral intake. The preoperative administration of dexamethasone significantly decreased the incidence of PONV over the 24 h after home discharge in these children. In this double blind, placebo-controlled study, we examd. the efficacy of a single large dose (1 mg/kg; maximal dose 25 mg) of preoperative dexamethasone on posttonsillectomy postoperative nausea and vomiting (PONV) in children 2-12 yr of age undergoing tonsillectomy. Compared with placebo, dexamethasone significantly decreased the incidence of PONV in the 24 h after discharge, improved oral intake, decreased the frequency of parental phone calls, and resulted in no hospital returns for the management of PONV and/or poor oral intake.

OS.CITING REF COUNT: 49 THERE ARE 49 CAPLUS RECORDS THAT CITE THIS RECORD (49 CITINGS)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 71 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1998:456793 CAPLUS Full-text

DOCUMENT NUMBER: 129:211664

ORIGINAL REFERENCE NO.: 129:42835a,42838a

TITLE: Nausea and vomiting after dexamethasone versus droperidol following outpatient laparoscopy with a propofol-based general anesthetic

AUTHOR(S): Rothenberg, D. M.; Mccarthy, R. J.; Peng, C. C.; Normoyle, D. A.

CORPORATE SOURCE: Department of Anesthesiology, Rush Medical College at Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA

SOURCE: Acta Anaesthesiologica Scandinavica (1998), 42(6), 637-642
CODEN: AANEAB; ISSN: 0001-5172

DIGITAL OBJECT ID: 10.1111/j.1399-6576.1998.tb05294.x

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This randomized, double-blinded study compared the incidence and severity of postoperative nausea and vomiting (PONV) after dexamethasone vs. droperidol following gynecol. laparoscopy, a group at high risk for developing PONV. Patients who underwent a propofol-based general anesthesia received either dexamethasone (0.17 mg/kg i.v.), or droperidol (0.02 mg/kg i.v.), just prior to abdominal incision. Nausea, retching, vomiting, degree of sedation, and discharge times were assessed in the Post Anesthesia Care Unit (PACU), and the Ambulatory Care Unit (ACU). Following hospital discharge (24 h), the patients were contacted to assess any further complications. PONV in the PACU (14.6% vs. 14.9%) and ACU (8.3% vs. 14.9%) was as common after dexamethasone as after droperidol. PONV following hospital discharge was, however, less common after dexamethasone than after droperidol (4.2% vs. 17.0%). Postoperatively, no complications of therapy were detected. It is concluded that PONV is similar with dexamethasone and droperidol, but dexamethasone may have a longer duration of action in patients undergoing gynecol. laparoscopy.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 72 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1997:576601 CAPLUS Full-text

DOCUMENT NUMBER: 127:239128

ORIGINAL REFERENCE NO.: 127:46553a,46556a

TITLE: Anti-emetic compositions containing dexamethasone,

metoclopramide and an antihistamine or an anticholinergic agent
INVENTOR(S): Naeger, David M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5661142	A	19970826	US 1996-634083	19960417

PRIORITY APPLN. INFO.: US 1996-634083 19960417
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 5661142	A	Dead	20201106

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 1997:576601
AB An anti-emetic compn. comprises dexamethasone (DEX), metoclopramide (MTC) and an antihistamine or an anticholinergic agent. In a particular embodiment, a compn. contg. DEX:MTC:diphenhydramine in a relative wt. ratio of about 1:1:2.5, resp., is found to be effective in providing relief from the discomfort caused by symptoms of both vomiting and nausea in all patients receiving the compn. Alternatively, an effective compn. may contain DEX:MTC:scopolamine in a relative wt. ratio of about 1:1:0.025, resp. Other effective compns. and methods of their use are also disclosed.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 73 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN
ACCESSION NUMBER: 1997:560590 CAPLUS Full-text
DOCUMENT NUMBER: 127:200212
ORIGINAL REFERENCE NO.: 127:38699a,38702a
TITLE: Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy
AUTHOR(S): Lofters, Wycliffe S.; Pater, Joseph L.; Zee, Benny; Dempsey, Ellen; Walde, David; Moquin, Jean-Pierre; Wilson, Kenneth; Hoskins, Paul; Guevin, Raymond M.; Verma, Shailendra; Navari, Rudolph; Krook, James E.; Hainsworth, John; Palmer, Michael; Chin, Christine
CORPORATE SOURCE: Kingston Regional Cancer Centre, Kingston, ON, K7L 3N6, Can.
SOURCE: Journal of Clinical Oncology (1997), 15(8), 2966-2973
CODEN: JCONDN; ISSN: 0732-183X
DIGITAL OBJECT ID: 10.1200/JCO.1997.15.8.2966
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our aim was to compare the efficacy of dolasetron and ondansetron in controlling nausea and vomiting in the first 24 h; to evaluate the efficacy when dexamethasone is added to either drug in the first 24 h; and to extend these comparisons over 7 days in patients receiving moderately emetogenic chemotherapy. This was a multicenter, double-blind, randomized study with six parallel arms that used a 2 × 2 factorial design in chemotherapy-naive patients. In arm 1, dolasetron (2.4 mg/kg) was given i.v. (IV) prechemotherapy, followed 24 h later by oral dolasetron (200 mg once daily) for 6 days. Arms 2 and 3 consisted of dolasetron and dexamethasone 8 mg IV, followed 24 h later by oral dexamethasone (8 mg once daily) in one arm, and oral dexamethasone and dolasetron in the other, also for 6 days. In arms 4, 5, and 6, ondansetron (32 mg IV or 8 mg orally twice daily) was administered in a similar manner to arms 1, 2, and 3 before and 24 h after chemotherapy. Mean nausea severity (MNS) was assessed on a visual analog scale (VAS) in a daily diary. Of 703 patients

enrolled, 696 were eligible. There were 343 dolasetron- and 353 ondansetron-treated patients; 57% of dolasetron-treated patients had complete protection in the first 24 h vs. 67% of patients who received ondansetron (P = .013). MNS was also more pronounced on the dolasetron arm (P = .051). Sixty-seven percent of patients who received added dexamethasone in the first 24 h had complete protection, compared with 55% without dexamethasone (P < .001). MNS was significantly reduced with the addn. of dexamethasone (P < .001). At 7 days, dolasetron and ondansetron had equiv. complete protection rates (36% and 39%, resp.). With the addn. of dexamethasone, 48% of patients compared with 28% had complete protection (P < .001). MNS was significantly improved with added dexamethasone (P < .001). At the doses used, dolasetron was significantly less effective than ondansetron at controlling nausea and vomiting in the first 24 h in patients receiving moderately emetogenic chemotherapy, but there was no demonstrable difference between both drugs over 7 days. The addn. of dexamethasone significantly improved the efficacy of both drugs in the first 24 h and over 7 days.

OS.CITING REF COUNT: 50 THERE ARE 50 CAPLUS RECORDS THAT CITE THIS RECORD (50 CITINGS)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 74 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1995:866032 CAPLUS Full-text

DOCUMENT NUMBER: 123:306320

ORIGINAL REFERENCE NO.: 123:54611a,54614a

TITLE: Prevention of delayed emesis with metoclopramide and dexamethasone in patients receiving moderately emetogenic cytotoxic treatment

AUTHOR(S): Chiara, Silvana; Campora, Elisabetta; Simoni, Carlotta; Confalonieri, Maurizio; Psilogenis, Mary; Rosso, Riccardo

CORPORATE SOURCE: Instituto Nazionale per la Ricerca sul Cancro, Genoa, 16132, Italy

SOURCE: Anticancer Research (1995), 15(4), 1597-9
CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Forty-three untreated cancer patients receiving moderately emetogenic polychemotherapy entered a phase II trial in order to evaluate the effectiveness of the combination of metoclopramide (40 mg every 6 h) and dexamethasone (8 mg every 12 h) in the prevention of delayed emesis (days 2-3). For the control of acute emesis all patients received on day 1 ondansetron 8 mg for 3 times. Results of antiemetic treatment were as follows: complete/ major protection from acute emesis (day 1) was obsd. in 72%/88% of patients. Worst day anal. of delayed emesis (days 2 and 3) showed that complete/major protection was obtained in 93%/95% of cases, resp. Delayed nausea was not as well controlled: complete/major protection was obsd. in 44%/79% of patients. Extrapyramidal reactions occurred in 3 patients and moderate epigastric pain was reported by 3 patients. Since control of acute emesis could be one of the most important factors influencing delayed emesis, the absence of acute symptoms in 72% of our patients may be partially responsible for the excellent control of delayed emesis. The combination of metoclopramide and dexamethasone is a feasible and effective treatment for delayed emesis in outpatients receiving moderately emetogenic chemotherapy.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L6 ANSWER 75 OF 75 CAPLUS COPYRIGHT 2022 ACS on STN

ACCESSION NUMBER: 1988:52121 CAPLUS Full-text

DOCUMENT NUMBER: 108:52121

ORIGINAL REFERENCE NO.: 108:8641a,8644a

TITLE: Evaluation of domperidone as a modifier of gamma-radiation-induced emesis

AUTHOR(S): Cordts, Robert E.; Yochmowitz, Michael G.; Hardy, Kenneth A.

CORPORATE SOURCE: Radiat. Sci. Div., USAF Sch. Aerosp. Med., Brooks Air Force Base, TX, 78235-5301, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (1987), 13(9), 1333-7
CODEN: IOBPD3; ISSN: 0360-3016
DIGITAL OBJECT ID: 10.1016/0360-3016(87)90225-2
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The D2 antidopaminergic drug domperidone was evaluated, singly and in combination with synthetic adrenocorticoid and an H2 antihistamine, for its ability to reduce the acute emetic effects of 60Co whole-body γ-irradn. Random-source adult male dogs were fasted 12 h, fed a std. meal, injected 44 min later, and irradiated 47 min after that. Four groups of dogs were irradiated after drug injections as follows: saline (control), domperidone (Dom), cimetidine + thiethylperazine (Cim+Thi), and dexamethasone + domperidone + cimetidine (Dex+Dom+Cim). Drug quantities given the dogs represented 10 mg Dom, 10 mg Thi, 20 mg Dex, and 300 mg Cim for an av. human. Subjects were exposed on an up-down schedule to det. the radiation necessary to produce vomiting in 50% of each group. Emesis onset and offset times and no. of episodes were recorded. The Dom group had more emetic episodes than any other. The Dex+Dom+Cim combination significantly raised the emetic threshold while maintaining episodes at a low incidence.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	736.40	736.64

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 16:30:53 ON 11 JUL 2022

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:30 AM
L2	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L3	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L4	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT,	OR	ON	ON	2022/07/07 11:31 AM

			JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L5	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L6	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L7	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:57 PM
L8	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:58 PM
L9	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2022/07/07 01:01 PM

			JPO; DERWENT)				
L10	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:02 AM
L11	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L12	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L15	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:05 AM
L16	12	L5 AND L15	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:05 AM
L17	18	L5 AND L15	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L18	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L19	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK,	OR	ON	ON	2022/07/08 10:06 AM

			TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L20	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L21	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L22	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L23	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L24	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L25	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH,	OR	ON	ON	2022/07/08 10:06 AM

		("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L26	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L27	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L28	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L29	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L30	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L31	156	(("zankel") near2 ("todd")).in.	(US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/11 02:01 PM
L32	116351	(("anemia") OR ("hemolytic anemia"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 09:49 AM
L33	8	L32 SAME L30	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20

							09:49 AM
L34	0	"2019104134"	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 10:16 AM
L35	19	"2019104134"	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/01/20 10:16 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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                  Claims Data in Derwent World Patents Index(R)
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                  Georgia Increases Comprehensiveness of INPADOC
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                  Claims and Assignee Searching Enhancements
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FULL ESTIMATED COST                                 0.28            0.28

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COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
                                                   ENTRY          SESSION
FULL ESTIMATED COST                                 0.56            0.56

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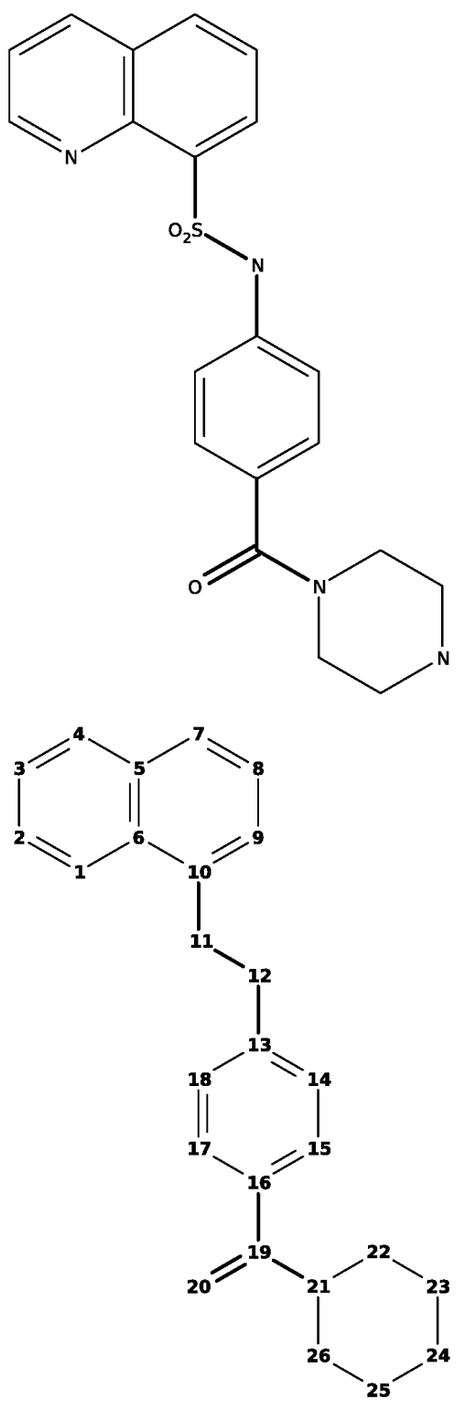
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Uploading structure file: 16900610-STN-NONFINAL-V1
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Node Attributes
Ring Nodes : 1 2 3 4 5 6 7 8 9 10 13 14 15 16 17 18 21 22 23 24 25 26
Chain Nodes : 12 19 20
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 5-7 6-1 7-8 8-9 9-10 10-6 13-14 14-15 15-16 16-17 17-18 18-13 21-22 22-23 23-24 24-25 25-26 26-21
Chain Bonds : 10-11 11-12 12-13 16-19 19-20 19-21
Exact Bonds : 10-11 16-19
Normalized Bonds : 1-2 2-3 3-4 4-5 5-6 5-7 6-1 7-8 8-9 9-10 10-6 13-14 14-15 15-16 16-17 17-18 18-13
Exact/Normalized Bonds : 11-12 12-13 19-20 19-21 21-22 22-23 23-24 24-25 25-26 26-21

Markush Attributes
Match Level (ATOM) : 1 2 3 4 5 6 7 8 9 10 13 14 15 16 17 18 21
22 23 24 25 26
Match Level (CLASS) : 11 12 19 20
Element Count Level (LIMITED) : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 1
5 16 17 18 19 20 21 22 23 24 25 26

L1 STRUCTURE UPLOADED

=> s L1 sss ful

FULL SEARCH INITIATED 10:13:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2059 TO ITERATE

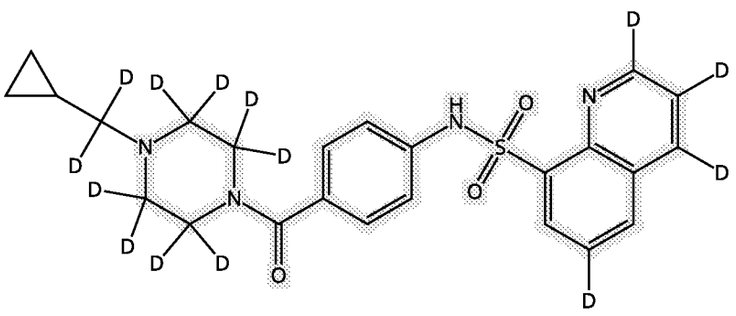
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SEARCH TIME: 00.00.01

L2 1180 SEA SSS FUL L1

=> d scan

L2 1180 ANSWERS REGISTRY COPYRIGHT 2023 ACS on STN
IN INDEX NAME NOT YET ASSIGNED
MF C24 H12 D14 N4 O3 S



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	715.14	715.70

FILE 'CAPLUS' ENTERED AT 10:13:46 ON 20 JAN 2023
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FILE COVERS 1907 - 20 Jan 2023 VOL 181 ISS 7
FILE LAST UPDATED: 19 Jan 2023 (20230119/ED)

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

Tags for Claimed substances now available in selected patents.
See NEWS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s L2

L3          37 L2

=> s (("microcrystalline cellulose") or ("MCC"))

          20536 "MICROCRYSTALLINE"
             92 "MICROCRYSTALLINES"
          20619 "MICROCRYSTALLINE"
                  ("MICROCRYSTALLINE" OR "MICROCRYSTALLINES")
         804371 "CELLULOSE"
           6601 "CELLULOSES"
         805159 "CELLULOSE"
                  ("CELLULOSE" OR "CELLULOSES")
           3395 "MICROCRYSTALLINE CELLULOSE"
                  ("MICROCRYSTALLINE"(W)"CELLULOSE")
          11404 "MCC"
            708 "MCCS"
          11690 "MCC"
                  ("MCC" OR "MCCS")
L4        13881 (("MICROCRYSTALLINE CELLULOSE") OR ("MCC"))

=> s (("croscarmellose") or ("croscarmellose sodium"))

          10418 "CROSCARMELLOSE"
          10418 "CROSCARMELLOSE"
        3122939 "SODIUM"
             75 "SODIUMS"
        3122958 "SODIUM"
                  ("SODIUM" OR "SODIUMS")
           9160 "CROSCARMELLOSE SODIUM"
                  ("CROSCARMELLOSE"(W)"SODIUM")
L5        10418 (("CROSCARMELLOSE") OR ("CROSCARMELLOSE SODIUM"))

=> s ("sodium stearyl fumarate"))

UNMATCHED RIGHT PARENTHESIS 'FUMARATE"))'

The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s ("sodium stearyl fumarate")

        3122939 "SODIUM"
             75 "SODIUMS"
        3122958 "SODIUM"
                  ("SODIUM" OR "SODIUMS")
          37561 "STEARYL"
              1 "STEARYLS"
          37561 "STEARYL"
                  ("STEARYL" OR "STEARYLS")
          42946 "FUMARATE"
           1491 "FUMARATES"
          43424 "FUMARATE"
```

```
                ("FUMARATE" OR "FUMARATES")
L6        3639 ("SODIUM STEARYL FUMARATE")
                ("SODIUM"(W)"STEARYL"(W)"FUMARATE")

=> s L4 or L5 or L6

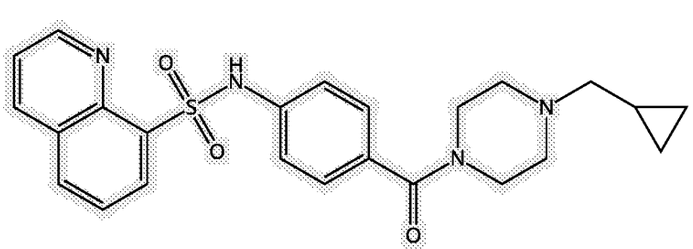
L7       26335 L4 OR L5 OR L6

=> s L3 and L7

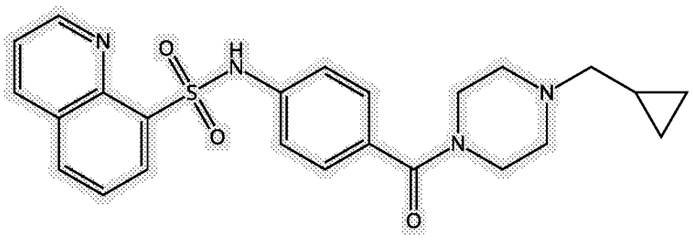
L8           3 L3 AND L7

=> display L8 1-3 ibib abs hitstr

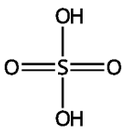

L8   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER:        2022:840098  CAPLUS Full-text
DOCUMENT NUMBER:         178:195253
TITLE:                   Pharmaceutical formulation
INVENTOR(S):             Leung, Cheuk-Yui; Simone, Eric; Yin, Ophelia Qiping
PATENT ASSIGNEE(S):      Agios Pharmaceuticals, Inc., USA
SOURCE:                  PCT Int. Appl., 63pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ---------------------    --------
     WO 2022067039        A1   20220331    WO 2021-US51957          20210924
PRIORITY APPLN. INFO.:                    US 2020-63083834     P   20200925
                                          US 2020-63107196     P   20201029
                                          US 2021-61238483     P   20210830
PATENT STATUS PATENT INFORMATION:
     PATENT NO.          KIND  STATUS          STATUS DATE
     ---------------     ----  -------------   -----------
     WO 2022067039        A1   Alive           20220407
AB   Disclosed is a pharmaceutical mini-tablet comprising mitapivat or a
     pharmaceutically acceptable salt thereof, and in a particular embodiment
     comprising a mitapivat sulfate salt, and one or more inactive ingredients
     selected from a filler, disintegrant, lubricant, binder, and diluent.
IT   1260075-17-9D, Mitapivat, pharmaceutically acceptable salt
     2151847-10-6, Mitapivat sulfate
     RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (pharmaceutical formulation)
RN   1260075-17-9  CAPLUS
CN   8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-
     piperazinyl]carbonyl]phenyl]-  (CA INDEX NAME)
```




```
RN   2151847-10-6  CAPLUS
CN   8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-
     piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3)  (CA INDEX NAME)
     CM   1
     CRN  1260075-17-9
     CMF  C24 H26 N4 O3 S
```



CM 2
CRN 7664-93-9
CMF H2 O4 S



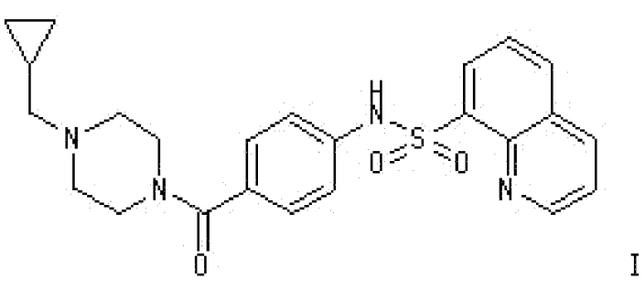
L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 2020:2428580 CAPLUS Full-text
DOCUMENT NUMBER: 174:90709
TITLE: Crystalline salt forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide
INVENTOR(S): Grove, Lisa M.
PATENT ASSIGNEE(S): Agios Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 108pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2020237047	A1	20201126	WO 2020-US33992		20200521
CA 3145138	A1	20201126	CA 2020-3145138		20200521
AU 2020280045	A1	20211223	AU 2020-280045		20200521
CN 114026071	A	20220208	CN 2020-80045139		20200521
EP 3972957	A1	20220330	EP 2020-731357		20200521
JP 2022533227	T	20220721	JP 2021-569059		20200521
PRIORITY APPLN. INFO.:			US 2019-62851344	P	20190522
			WO 2020-US33992	W	20200521

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2020237047	A1	Alive	20201203
CA 3145138	A1	Alive	20220217
AU 2020280045	A1	Alive	20220113
CN 114026071	A	Alive	20220217

GI



I

AB Provided herein are various cryst. salt forms of compd. represented by the following structural formula (I); also provided are pharmaceutical compns. comprising the cryst. salt forms, methods for their manuf., and uses thereof for treating conditions assocd. with pyruvate kinase such as e.g., pyruvate kinase deficiency.

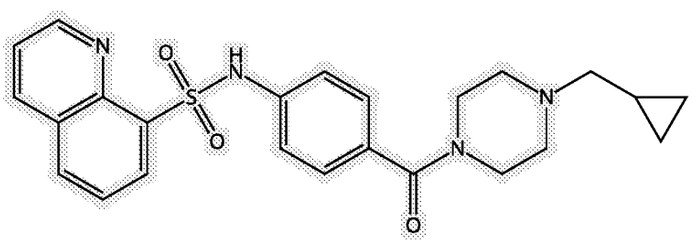
IT 2559738-66-6 2559738-67-7 2559738-68-8
2559738-69-9 2559738-70-2 2559738-71-3
2559738-72-4 2559738-73-5 2559738-74-6
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cryst. salt forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide)

RN 2559738-66-6 CAPLUS

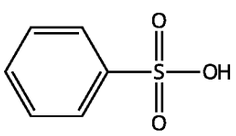
CN 8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, compd. with benzenesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 1260075-17-9
CMF C24 H26 N4 O3 S



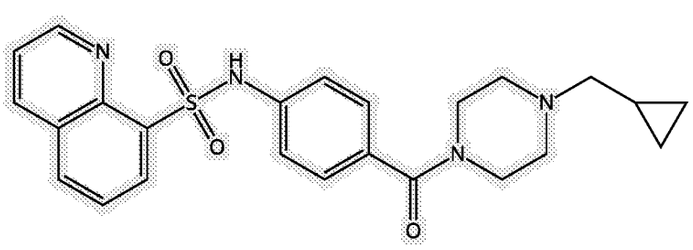
CM 2
CRN 98-11-3
CMF C6 H6 O3 S



RN 2559738-67-7 CAPLUS

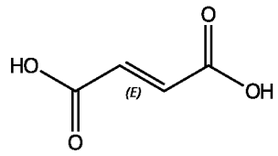
CN INDEX NAME NOT YET ASSIGNED

CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



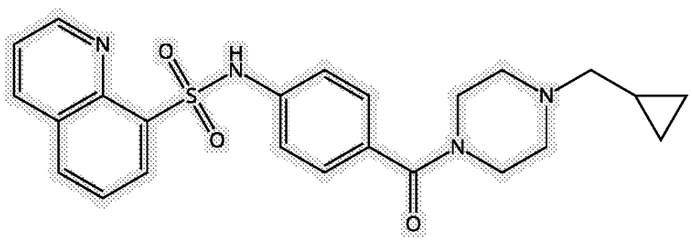
CM 2

CRN 110-17-8
CMF C4 H4 O4

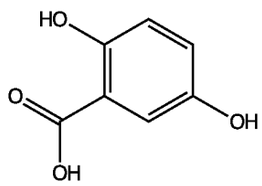


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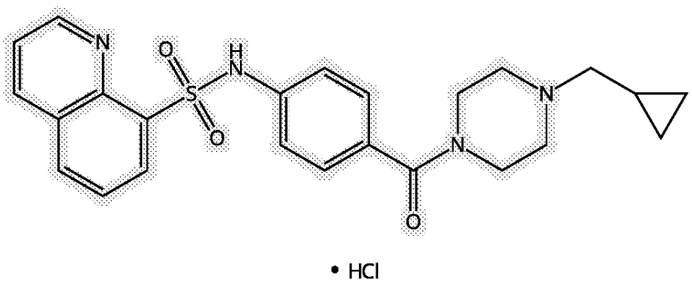
RN 2559738-68-8 CAPLUS
CN Benzoic acid, 2,5-dihydroxy-, compd. with N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-8-quinolinesulfonamide (1:1) (CA INDEX NAME)
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



CM 2
CRN 490-79-9
CMF C7 H6 O4

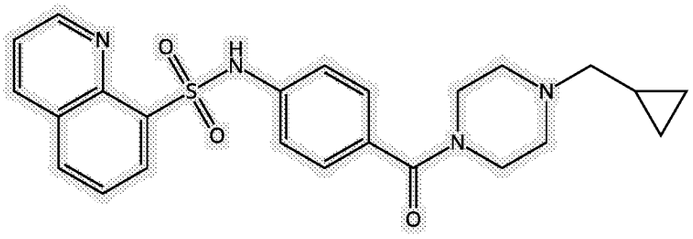


RN 2559738-69-9 CAPLUS
CN 8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, hydrochloride (1:1) (CA INDEX NAME)

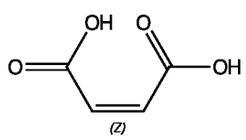


RN 2559738-70-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

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CRN 1260075-17-9
CMF C24 H26 N4 O3 S

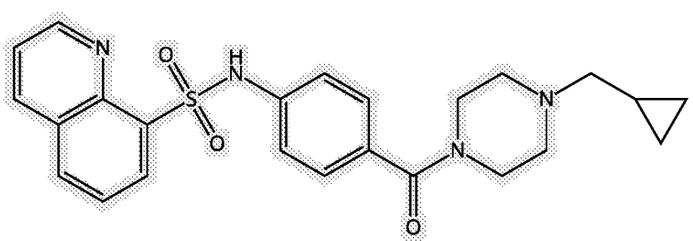


CM 2
CRN 110-16-7
CMF C4 H4 O4

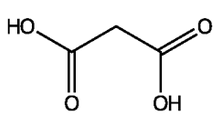


Double bond geometry shown

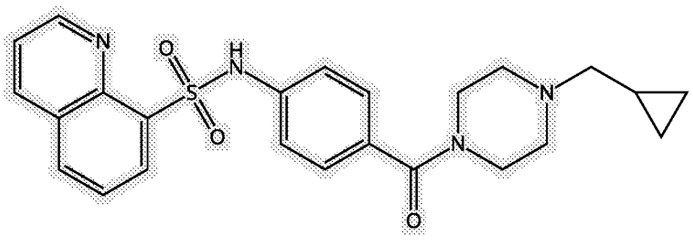
RN 2559738-71-3 CAPLUS
CN Propanedioic acid, compd. with N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-8-quinolinesulfonamide (1:1) (CA INDEX NAME)
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



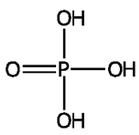
CM 2
CRN 141-82-2
CMF C3 H4 O4



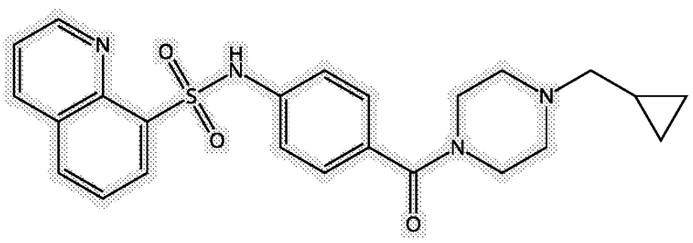
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CN INDEX NAME NOT YET ASSIGNED
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



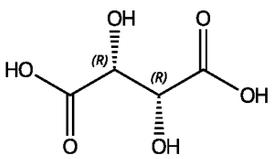
CM 2
CRN 7664-38-2
CMF H3 O4 P



RN 2559738-73-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S

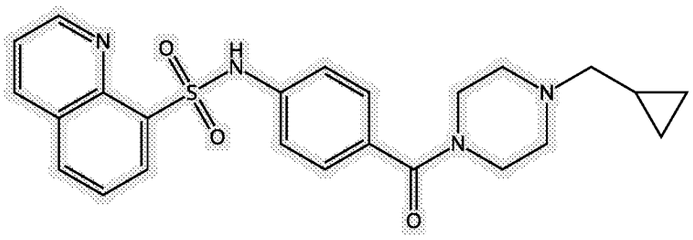


CM 2
CRN 87-69-4
CMF C4 H6 O6

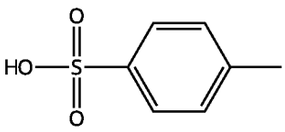


Absolute stereochemistry shown

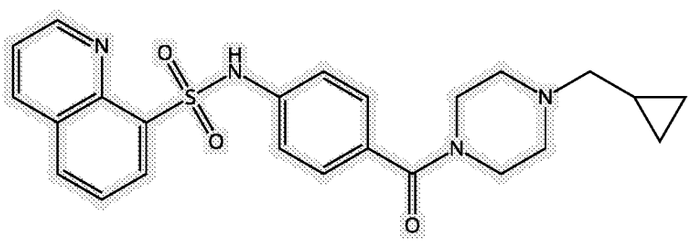
RN 2559738-74-6 CAPLUS
CN 8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, compd. with 4-methylbenzenesulfonate (1:1) (CA INDEX NAME)
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



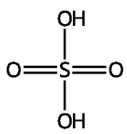
CM 2
CRN 104-15-4
CMF C7 H8 O3 S



IT 2329710-91-8
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(cryst. salt forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide)
RN 2329710-91-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



CM 2
CRN 7664-93-9
CMF H2 O4 S



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 2019:1058787 CAPLUS Full-text
DOCUMENT NUMBER: 171:49776
TITLE: Preparation of amorphous and crystalline forms of

N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide useful for treatment of pyruvate kinase associated disorders

INVENTOR(S): Sizemore, Jacob P.; Guo, Liting; Mirmehrabi, Mahmoud; Su, Yeqing

PATENT ASSIGNEE(S): Agios Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 122pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2019104134	A1	20190531	WO 2018-US62197	20181121
CA 3081945	A1	20190531	CA 2018-3081945	20181121
AU 2018373122	A1	20200521	AU 2018-373122	20181121
IL 274488	A	20200630	IL 2018-274488	20181121
CN 111372920	A	20200703	CN 2018-80075099	20181121
KR 2020090787	A	20200729	KR 2020-7015018	20181121
EP 3713919	A1	20200930	EP 2018-821779	20181121
BR 112020010185	A2	20210112	BR 2020-112020010185	20181121
JP 2021504338	T	20210215	JP 2020-528129	20181121
IN 202017020829	A	20200814	IN 2020-17020829	20200518
US 20200277279	A1	20200903	US 2020-16765456	20200519
US 11254652	B2	20220222		
US 20220220093	A1	20220714	US 2022-17575898	20220114

PRIORITY APPLN. INFO.:

US 2017-62589822	P	20171122
US 2018-62691709	P	20180629
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US 2020-16765456	A1	20200519

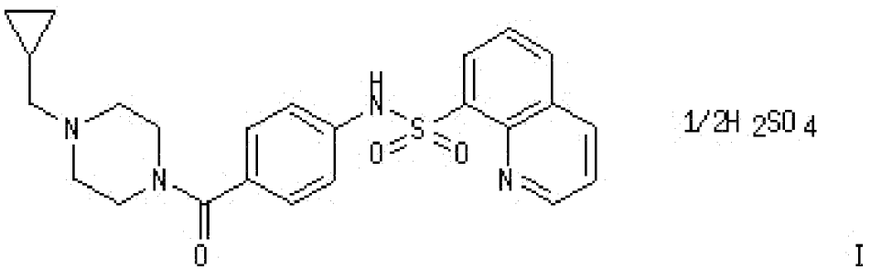
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2019104134	A1	Dead	20220721
CA 3081945	A1	Alive	20201120
AU 2018373122	A1	Alive	20201120
IL 274488	A	Alive	20220721
CN 111372920	A	Alive	20201121
KR 2020090787	A	Alive	20201121
EP 3713919	A1	Alive	20201202
BR 112020010185	A2	Alive	20210218
US 20200277279	A1	Alive	20201121
US 11254652	B2	Alive	20220303
US 20220220093	A1	Alive	20220721

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 171:49776; CASFORMULTNS 2019:1058787

GI



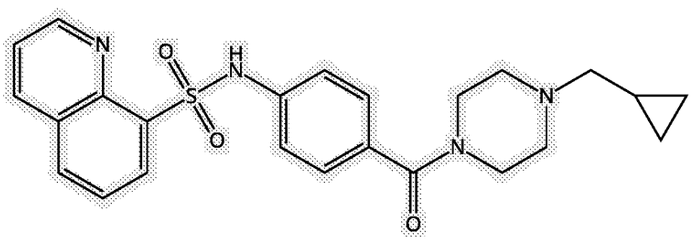
I

AB Provided herein are amorphous and cryst. hemisulfate salt forms of the compd. of formula I. Also provided are pharmaceutical compns. comprising the amorphous and cryst. hemisulfate salt forms, methods for their manuf., and uses thereof for treating conditions assocd. with pyruvate kinase such as e.g., pyruvate kinase deficiency. Several crystal forms of

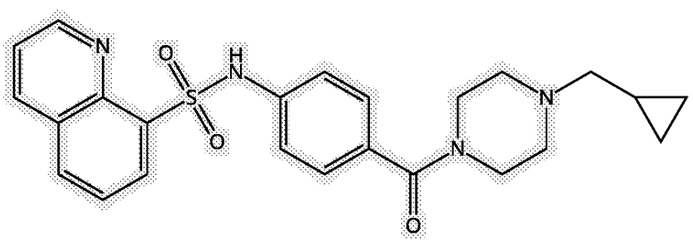
I·hemisulfate·sesquihydrate were prepd. and characterized using x-ray powder diffraction and thermal gravimetric anal. Pharmacokinetic evaluation of Cryst. Form A micronized and unmicronized, and cryst. free base of I administered orally to Sprague-Dawley rats resulted in AUCs 3.8 (micronized Form A) and 2.7 (unmicronized Form A) fold higher compared to cryst. free base.

IT 1260075-17-9P 2329710-90-7P 2329710-91-8P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(XRPD patterns; prepn. of amorphous and cryst. forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide useful for treatment of pyruvate kinase assocd. disorders)

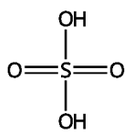
RN 1260075-17-9 CAPLUS
CN 8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]- (CA INDEX NAME)



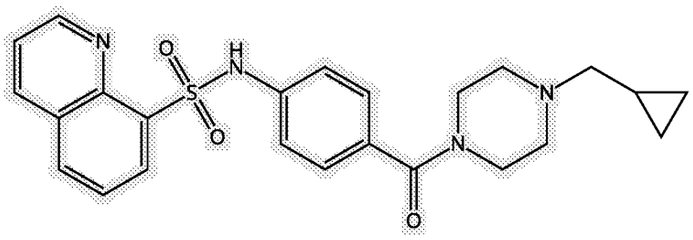
RN 2329710-90-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



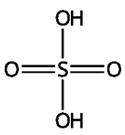
CM 2
CRN 7664-93-9
CMF H2 O4 S



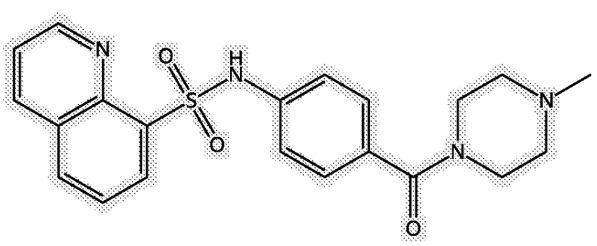
RN 2329710-91-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED
CM 1
CRN 1260075-17-9
CMF C24 H26 N4 O3 S



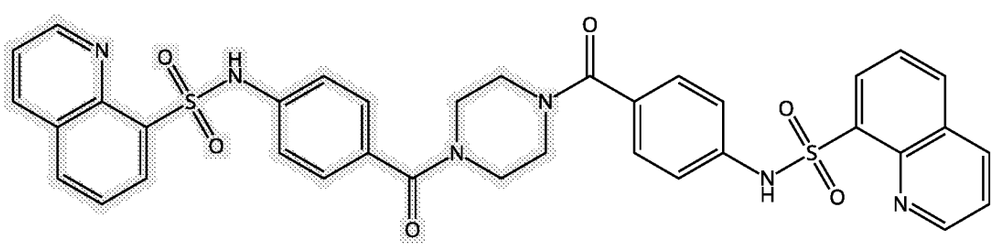
CM 2
CRN 7664-93-9
CMF H2 O4 S



IT 2329710-94-1P 2329710-95-2P
RL: BYP (Byproduct); PREP (Preparation)
(prepn. of amorphous and cryst. forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide useful for treatment of pyruvate kinase assocd. disorders)
RN 2329710-94-1 CAPLUS
CN 8-Quinolinesulfonamide, N-[4-[(4-methyl-1-piperazinyl)carbonyl]phenyl]- (CA INDEX NAME)



RN 2329710-95-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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NEWS	15	NOV 10	PS (Pharmaceutical Substances) Database Reloaded
NEWS	16	DEC 05	Expanded access to Taiwanese patent information provided by new full text database TWFULL and claims coverage in CAplus(SM)
NEWS	17	DEC 05	New Implementation of Derwent Drug File (DRUGU/DDFU) Makes Searching More Convenient
NEWS	18	DEC 23	New Interactive Claim Viewer in EPFULL and PCTFULL Makes Claim Analysis More Efficient
NEWS	19	DEC 30	2023 MeSH now available in MEDLINE on STNext
NEWS	20	FEB 03	January 2023 Update to Emtree(R) Now Available in Embase(R)
NEWS	21	FEB 17	Identification of Substances from Claims Simplified in CAS PatentPak - UPDATE
NEWS	22	FEB 23	Derwent World Patents Index - Manual Code revision 2023
NEWS	23	MAR 10	MEDLINE(R) Reloaded and MeSH Thesaurus Updated for 2023 on STNext
NEWS	24	MAR 23	Expanded Patent Authority Coverage in CA/CAplus Means Access to More Inventions, More Complete Patent Families

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FILE LAST UPDATED: 11 Apr 2023 (20230411/ED)

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provides more complete patent families, expanded invention
coverage. See NEWS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s (("St. John's wort"))

```
        101104 "ST"
         17061 "STS"
        116496 "ST"
                 ("ST" OR "STS")
          2396 "JOHNS"
         18444 "WORT"
          7755 "WORTS"
         20658 "WORT"
                 ("WORT" OR "WORTS")
L1        225 (("ST. JOHN'S WORT"))
                 ("ST"(W)"JOHNS"(W)"WORT")
```

=> s (("rifabutin") or ("rifapentin") or ("rifapentine") or ("nafcillin") or ("pexi
dartinib") or ("modafinil") or ("lorlatinib") or ("eslicarbazepine") or ("efavir
enz") or ("dipyrone") or ("dexamethsaone") or ("dabrafenib") or ("cetobamate") o
r ("bexarotene") or ("bosantan"))

```
          1944 "RIFABUTIN"
             1 "RIFABUTINS"
          1944 "RIFABUTIN"
                 ("RIFABUTIN" OR "RIFABUTINS")
            52 "RIFAPENTIN"
          1042 "RIFAPENTINE"
          1710 "NAFCILLIN"
             2 "NAFCILLINS"
```

```
          1710 "NAFCILLIN"
                 ("NAFCILLIN" OR "NAFCILLINS")
           170 "PEXIDARTINIB"
          1894 "MODAFINIL"
             3 "MODAFINILS"
          1894 "MODAFINIL"
                 ("MODAFINIL" OR "MODAFINILS")
           435 "LORLATINIB"
           532 "ESLICARBAZEPINE"
          7394 "EFAVIRENZ"
          1255 "DIPYRONE"
            10 "DIPYRONES"
          1262 "DIPYRONE"
                 ("DIPYRONE" OR "DIPYRONES")
             2 "DEXAMETHSAONE"
          1917 "DABRAFENIB"
             0 "CETOBAMATE"
          1474 "BEXAROTENE"
             2 "BOSANTAN"
L2       18640 (("RIFABUTIN") OR ("RIFAPENTIN") OR ("RIFAPENTINE") OR ("NAFCILL
               IN") OR ("PEXIDARTINIB") OR ("MODAFINIL") OR ("LORLATINIB") OR
               ("ESLICARBAZEPINE") OR ("EFAVIRENZ") OR ("DIPYRONE") OR ("DEXAME
               THSAONE") OR ("DABRAFENIB") OR ("CETOBAMATE") OR ("BEXAROTENE")
               OR ("BOSANTAN") )

=> s (("etravirine") or ("phenobarbital") or ("primidone"))

           1469 "ETRAVIRINE"
              1 "ETRAVIRINES"
           1469 "ETRAVIRINE"
                  ("ETRAVIRINE" OR "ETRAVIRINES")
          26417 "PHENOBARBITAL"
             27 "PHENOBARBITALS"
          26420 "PHENOBARBITAL"
                  ("PHENOBARBITAL" OR "PHENOBARBITALS")
           2324 "PRIMIDONE"
              3 "PRIMIDONES"
           2325 "PRIMIDONE"
                  ("PRIMIDONE" OR "PRIMIDONES")
L3       29021 (("ETRAVIRINE") OR ("PHENOBARBITAL") OR ("PRIMIDONE"))

=> s (("hemolytic anemia"))

          46821 "HEMOLYTIC"
             40 "HEMOLYTICS"
          46836 "HEMOLYTIC"
                  ("HEMOLYTIC" OR "HEMOLYTICS")
         113243 "ANEMIA"
           2739 "ANEMIAS"
         113785 "ANEMIA"
                  ("ANEMIA" OR "ANEMIAS")
L4       10500 (("HEMOLYTIC ANEMIA"))
                  ("HEMOLYTIC"(W)"ANEMIA")

=> s L1 or L2 or L3

L5       46580 L1 OR L2 OR L3

=> s L4 (L) L5

L6           6 L4 (L) L5

=> display L6 1-6 ibib abs hitstr


L6   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER:        2022:877943  CAPLUS Full-text
DOCUMENT NUMBER:         178:275647
TITLE:                   Switch from dabrafenib/trametinib combination therapy
                         to encorafenib/binimetinib combination therapy with
                         transition of serum lactate dehydrogenase level in
                         melanoma: A case report
```

AUTHOR(S): Sato, Takahiko; Noto, Mai; Yamada, Masayuki; Kono, Michihiro
CORPORATE SOURCE: Department of Dermatology and Plastic Surgery, Akita University Graduate School of Medicine, Akita, Japan
SOURCE: Dermatologic Therapy (2022), 35(4), e15301
CODEN: DETHFE; ISSN: 1529-8019
DIGITAL OBJECT ID: 10.1111/dth.15301
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The present article describes about switch from dabrafenib/trametinib combination therapy to encorafenib/binimetinib combination therapy with transition of serum lactate dehydrogenase level in melanoma. A 43-yr-old man with a 15-mm brownish-black nodule on the right lower leg had visited his neighborhood dermatol. He was diagnosed with melanoma by excisional biopsy and he received an addnl. excision and right inguinal sentinel lymph node (LN) biopsy. Two sentinel LNs detected, so he underwent an inguinal lymphadenectomy. As the primary tumor was BRAFV600E-pos., he was treated with a combination of dabrafenib (300 mg/day) and trametinib (2 mg/day). After the start of DT, all the metastatic lesions that had been detected by PET-CT and CECT completely disappeared within 3 mo and the LDH levels fell steadily and normalized within 5 mo. Our case coincidentally showed an example of the timing for switching from DT to EB, changes in LDH levels and long recurrencefree survival.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 2017:55497 CAPLUS Full-text
DOCUMENT NUMBER: 168:446594
TITLE: A Review of Pharmacogenetics of Antimalarials and Associated Clinical Implications
AUTHOR(S): Elewa, Hazem; Wilby, Kyle John
CORPORATE SOURCE: College of Pharmacy, Qatar University, Doha, Qatar
SOURCE: European Journal of Drug Metabolism and Pharmacokinetics (2017), 42(5), 745-756
CODEN: EJDPD2; ISSN: 0378-7966
DIGITAL OBJECT ID: 10.1007/s13318-016-0399-1
PUBLISHER: Springer France
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB Genetic variability in drug-metabolizing enzymes and drug transporters is known to influence the pharmacokinetics of many drugs. Antimalarial drugs are a class of agents known to utilize metabolic and elimination pathways prone to genetic variation. This paper aims to review the genetic variants affecting antimalarial medications and discuss their clin. implications. Data were identified for the genes coding for the cytochrome P 450 (CYP) enzymes: CYP2C8, CYP2C19, CYP2A6, CYP2D6, CYP2B6, and the P-glycoprotein drug transporter. Adverse effects of amodiaquine were more common in patients with decreased CYP2C8 metab. CYP2C19 variants influenced the metab. of proguanil but no differences in efficacy outcomes were obsd. Ultra-metabolizers of CYP2A6 showed increased incidence of adverse effects of artesunate (prodrug for active metabolite, dihydroartemisinin). In the presence of efavirenz, mutations in CYP2B6 influenced the no. of patients achieving day-7 lumefantrine concns. above accepted therapeutic cut-offs. Lumefantrine concns. were also influenced by ABCB1 variants in the presence of nevirapine. The most crit. pharmacogenetic consideration identified was the assocn. of glucose-6-phosphate dehydrogenase deficiency with development of hemolytic anemia and decreased Hb levels in patients treated with primaquine or a combination of chlorproguanil-dapsone-artesunate. These findings demonstrate a need for close monitoring of patients originating from populations where genetic variation in metabolizing enzymes is prevalent, so as to ensure that optimal clin. outcomes are achieved. Future studies should det. which populations are at greatest risk of potential treatment failures and/or adverse effects, which drugs are most susceptible to genetic variation in metabolizing enzymes, and the impact of genetic influence on the efficacy and safety of first-line treatment regimens.

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 2002:321113 CAPLUS Full-text
DOCUMENT NUMBER: 138:170
TITLE: Diclofenac activates T cells in the direct popliteal lymph node assay and selectively induces IgG1 and IgE against co-injected TNP-OVA
AUTHOR(S): Gutting, Bradford W.; Updyke, Lawrence W.; Amacher, David E.
CORPORATE SOURCE: Groton Laboratories, Drug Safety Evaluation, Pfizer Global Research and Development, Groton, CT, 06340, USA
SOURCE: Toxicology Letters (2002), 131(3), 167-180
CODEN: TOLED5; ISSN: 0378-4274
DIGITAL OBJECT ID: 10.1016/S0378-4274(02)00029-2
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently assocd. with immune-mediated hypersensitivity reactions. The NSAID diclofenac is assocd. with several distinct allergic and autoimmune-like reactions including anaphylaxis, idiosyncratic hepatotoxicity and autoimmune hemolytic anemia. The aim of this study was to examine the immunostimulating potential of diclofenac in the direct popliteal lymph node assay (PLNA) and reporter antigen PLNA. In BALB/c mice, diclofenac caused dose-dependent increases in PLN wt. and PLN cellularity in the direct PLNA; 0.25 mg was non-immunostimulating whereas 0.50-1.00 mg caused a significant PLN reaction. In the direct PLNA, diclofenac also increased the percent of T cells in the PLN with activated phenotypes (CD44highCD62Llow and CD44highCD62Lhigh). Finally, the magnitude of the diclofenac-induced direct PLN reaction was significantly reduced when the assay was conducted in T-cell-deficient mice. When co-injected with the reporter antigen TNP-Ficoll (trinitrophenyl Ficoll), 0.50 mg diclofenac caused significant increases in PLN wt., PLN cellularity, and induced IgM and IgG1 anti-TNP antibody forming cells (AFCs) in the PLN. In a final set of studies, a TNP-OVA PLNA was conducted using diclofenac, phenobarbital (neg. control) and streptozotocin (pos. control). As expected, phenobarbital (1.00 mg) failed to cause an increase in PLN cellularity or induce AFCs in the PLN. Streptozotocin (1.00 mg) caused significant increases in PLN cellularity, IgM AFCs, and selectively induced IgG2a and IgG2b AFCs against TNP-OVA. Likewise, diclofenac caused dose-dependent increases (0.25-1.00 mg) in PLN cellularity and IgM AFCs. However, in contrast to streptozotocin, diclofenac caused a selective dose-dependent increase in both IgG1 and IgE AFCs. Finally, an increase in the intracellular level of IL-4, but not INFγ, was detected in CD4+ PLN cells following the injection of diclofenac mixed with TNP-OVA. Collectively, these data suggest that diclofenac: (i) induces a T-cell-dependent direct PLN reaction that; (ii) provides non-cognate help for IgG AFC prodn. when co-injected with TNP-Ficoll, possibly through the formation of neo-antigens; and (iii) possesses intrinsic adjuvant activity that selectively induces IL-4 mediated prodn. of IgG1 and IgE against co-injected TNP-OVA.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 1996:585619 CAPLUS Full-text
DOCUMENT NUMBER: 125:292511
ORIGINAL REFERENCE NO.: 125:54423a,54426a
TITLE: Use of anti-inflammatory and analgesic drugs in dogs and cats
AUTHOR(S): Watson, Adj; Nicholson, A.; Church, Db; Pearson, Mrb
CORPORATE SOURCE: Department Veterinary Clinical Sciences, University Sydney, 2006, Australia
SOURCE: Australian Veterinary Journal (1996), 74(3), 203-210
CODEN: AUVJA2; ISSN: 0005-0423

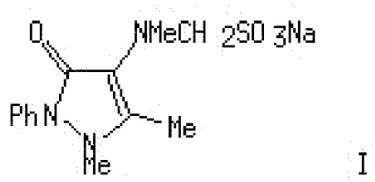
DIGITAL OBJECT ID: 10.1111/j.1751-0813.1996.tb15405.x
PUBLISHER: Australian Veterinary Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Responses (486) were collated from a survey of 5054 Australian veterinarians on their use of anti-inflammatory and analgesic drugs in dogs and cats. Almost all respondents used glucocorticoids (usually prednisolone) to treat allergic, pruritic dermatoses in dogs, while two-thirds also gave fatty acid supplements and one-half used antihistamines. Almost 60% of respondents initially injected a glucocorticoid (frequently a long-acting prepn.) when treating inflammatory skin diseases in dogs. More than 90% of respondents used glucocorticoids to treat immune-mediated hemolytic anemia or thrombocytopenia, and about one-third also gave cytotoxic drugs. Administration of prednisolone on alternate days was generally favored for long-term enteral steroid therapy. Phenylbutazone was the most preferred treatment for painful or inflammatory musculoskeletal disorders of dogs, but aspirin and pentosan polysulfate were also used widely. Regarding the use of analgesics drugs generally, both narcotic analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) were used more widely in dogs than in cats, but alpha-2 agonists were used similarly in both species. The most commonly used narcotic analgesics were pethidine and buprenorphine in both species, while the NSAIDs used most often were flunixin and dipyrone in dogs and ketoprofen in cats. More than 80% of respondents generally used analgesic drugs with potentially painful surgical procedures, with doses given usually before anesthetic recovery. Analgesic use rates varied with the condition, ranging from 94% for patients with acute severe trauma, through 60% for cruciate ligament repair and 29% for perineal herniorrhaphy, to about 5% for ovariohysterectomy and dog castration. The three clin. signs most frequently nominated as indicators of pain in dogs and cats were (in descending order) vocalization, response to handling or palpating the affected area, and mental depression. Other items mentioned frequently were behavioral changes and immobility (in both species), inappetence/anorexia in cats, and altered respiration in dogs.
OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS RECORD (25 CITINGS)

L6 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 1995:533321 CAPLUS Full-text
DOCUMENT NUMBER: 122:281125
ORIGINAL REFERENCE NO.: 122:50963a,50966a
TITLE: Overview of toxicological data on rifabutin
AUTHOR(S): Brughera, Marco; Scampini, Giovanna; Newman, A. John; Castellino, Silvana; Sammartini, Umberto; Mazue, Guy
CORPORATE SOURCE: R and D/Toxicology Dpt, Pharmacia Farmitalia Carlo Erba, Milan, 20014, Italy
SOURCE: Experimental and Toxicologic Pathology (1995), 47(1), 1-9
CODEN: ETPAEK; ISSN: 0940-2993
DIGITAL OBJECT ID: 10.1016/S0940-2993(11)80273-3
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 16 refs. Rifabutin is a wide spectrum antibiotic particularly active on atypical and rifampicin-resistant mycobacteria. Rifabutin is more potent than rifampicin on Mycobacterium tuberculosis in vitro. Its mode of action is characterized by a high intracellular penetration in treated individuals. Clin. trials have proven the therapeutic value of rifabutin esp. in AIDS patients with concomitant MAC. The preclin. safety evaluation of this compd. included single and repeated dose toxicity studies of up to one year in rodents and non-rodents, reprodn. and carcinogenicity studies and mutagenicity tests. During toxicol. studies the most significant finding after repeated administration of rifabutin was the presence of multinucleated hepatocytes (MNH) in rats. This is a species specific finding which did not affect the life span of the hepatocytes. As shown in carcinogenicity studies, there was no tendency to further proliferative changes. Another specific histol. feature among the species studied was the presence of a lipofuscin-like brown pigment, which was seen in many organs. This is a common finding with amphiphilic compds., such as rifabutin, which bind lipids and proteins, forming membrane-bound complexes. Even in

carcinogenicity studies this change did not constitute a stimulus to cell proliferation and did not cause any secondary changes. In rodents, there was a mild hemolytic anemia at doses higher than 10 mg/kg/day. At doses ranging from 160-200 mg/kg/day rifabutin inhibited the functions of the male gonads in rats. This effect was reflected in a redn. of implantations obsd. in the fertility studies. Doses of 40 mg/kg/day did not induce any embryotoxic effects or changes in reproductive performance. The drug was not genotoxic and was devoid of carcinogenic potential. The exposure levels in the animals used for toxicol. tests were higher than those reached in man at therapeutic doses.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L6 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2023 ACS on STN
ACCESSION NUMBER: 1981:24697 CAPLUS Full-text
DOCUMENT NUMBER: 94:24697
ORIGINAL REFERENCE NO.: 94:3957a,3960a
TITLE: Toxicology, pharmacokinetics and metabolism of dipyrone
AUTHOR(S): Kramer, M.
CORPORATE SOURCE: Hoechst A.-G., Frankfurt/Main, Fed. Rep. Ger.
SOURCE: Dipyrone, Symp. Proc. (1980), Meeting Date 1978, 19-22. Editor(s): Ovcharov, R.; Pola, Wolfgang. Schattauer: Stuttgart, Fed. Rep. Ger.
CODEN: 44QDAZ
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

AB With the administration of dipyrone (I) [68-89-3] to rats in doses of 100 and 300 mg/kg for 6 mo, no functional or morphol. changes were found. In doses of 900 mg/kg, dipyrone elicited a rise in reticulocyte count and enlargement of the spleen and thyroid. In a similar study in dogs at 300 and 600 mg/kg symptoms of hemolytic anemia were seen. Dipyrone showed no carcinogenic potential. The metabolic decompn. of dipyrone in man is similar to that in the rat. The metabolic decompn. of dipyrone in man is similar to that of rat. At least 7 metabolites are formed in human serum and at least 6 metabolites occur in the urine. Chief among these are 4-methylaminoantipyrine [519-98-2], 4-aminoantipyrine [83-07-8], 4-acetylaminoantipyrine [83-15-8], and 4-formylaminoantipyrine [1672-58-8].

=> s (("mitapivat") or ("AG-348") or ("AG348") or ("AG 348"))

```
            26 "MITAPIVAT"
        542460 "AG"
         13945 "AGS"
        553281 "AG"
                 ("AG" OR "AGS")
         19429 "348"
            10 "AG-348"
                 ("AG"(W)"348")
             3 "AG348"
        542460 "AG"
         13945 "AGS"
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        553281 "AG"
                 ("AG" OR "AGS")
         19429 "348"
            10 "AG 348"
                 ("AG"(W)"348")
L7          30 (("MITAPIVAT") OR ("AG-348") OR ("AG348") OR ("AG 348"))

=> s L5 and L7

L8           0 L5 AND L7

=> log hold

COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
                                                   ENTRY          SESSION
FULL ESTIMATED COST                               350.85           351.13

 SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 17:05:07 ON 12 APR 2023
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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:30 AM
L2	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L3	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L4	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT,	OR	ON	ON	2022/07/07 11:31 AM

			JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L5	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L6	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L7	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:57 PM
L8	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:58 PM
L9	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2022/07/07 01:01 PM

			JPO; DERWENT)				
L10	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:02 AM
L11	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L12	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L15	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:05 AM
L18	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L19	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L20	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE,	OR	ON	ON	2022/07/08 10:06 AM

			BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L21	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L22	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L23	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L24	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L25	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL,	OR	ON	ON	2022/07/08 10:06 AM

			NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L26	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L27	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L28	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L29	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L30	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L32	116351	(("anemia") OR ("hemolytic anemia"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 09:49 AM
L33	8	L32 SAME L30	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 09:49 AM
L34	0	"2019104134"	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 10:16 AM
L35	19	"2019104134"	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2023/01/20 10:16 AM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L36	134023	(("bosentan") OR ("etravirine") OR ("phenobarbital") OR ("sotorasib") OR ("primidone") OR ("lorlatinib") OR ("efavirenz") OR ("cenobamate") OR ("dabrafenib"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/20 04:27 PM
L37	6	L15 AND L36	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/20 04:28 PM
L38	31667	(("SN38") OR ("SN-38"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2023/03/21 12:37 PM

			JPO; DERWENT; IBM_TDB)				
L39	3545	(("solution")) SAME L38	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/21 12:37 PM
L40	560	(("mg/mL")) SAME L39	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/21 12:37 PM
L41	511492	(("bosentan") OR ("etravirine") OR ("phenobarbital") OR ("sotorasib") OR ("primidone") OR ("lorlatinib") OR ("efavirenz") OR ("cenobamate") OR ("dabrafenib") OR ("bexarotene") OR ("dexamethasone") OR ("dipyrone") OR ("eslicarbazepine") OR ("modafinil") OR ("nafcillin") OR ("pexidartinib") OR ("rifabutin") OR ("rifapentine") OR ("sotorasib") OR ("St John's Wort") OR ("St John's Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/05 03:37 PM
L42	8	L15 AND L41	(US-PGPUB; USPAT;	OR	ON	ON	2023/04/05

Ex. 2001-0138

			FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				03:37 PM
L43	0	L2 SAME L15	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/05 03:45 PM
L44	4	L2 AND L15	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/05 03:45 PM
L45	31	"11102994"	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2023/04/05 03:54 PM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L46	157018	(("rifabutin") OR ("rifapentin") OR ("rifapentine") OR ("nafcillin") OR ("pexidartinib") OR ("modafinil") OR ("lorlatinib") OR ("eslicarbazepine") OR ("efavirenz") OR ("dipyrone") OR ("dexamethsaone") OR ("dabrafenib") OR ("cetobamate") OR ("bexarotene") OR ("bosantan"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L47	0	(("St. John's Wort"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L48	0	(("St. Johns Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L49	0	(("St. John's Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2023/04/12 05:00 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L50	0	(("St. John's Wort"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L51	70428	(("ETRAVIRINE") OR ("PHENOBARBITAL") OR ("PRIMIDONE"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
L52	109157	(("hemolytic anemia"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2023/04/12 05:01 PM

			JPO; DERWENT; IBM_TDB)				
L53	201121	L46 OR L51	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
L54	272	L52 SAME L53	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
L55	1	(L52 SAME L53).clm.	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
L56	42	L52 WITH L53	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR,	OR	ON	ON	2023/04/12 05:02 PM

			HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L57	109244	(("hemolytic anemia"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/17 10:47 AM
L58	18	L57 SAME L19	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/17 10:47 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:30 AM
L2	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L3	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 11:31 AM
L4	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT,	OR	ON	ON	2022/07/07 11:31 AM

			JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L5	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L6	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/07 11:32 AM
L7	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:57 PM
L8	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/07 12:58 PM
L9	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2022/07/07 01:01 PM

			JPO; DERWENT)				
L10	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:02 AM
L11	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L12	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:03 AM
L15	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:05 AM
L18	140	(("pyruvate kinase")) NEAR (("disease") OR ("disorder"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L19	9062	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L20	0	L1 SAME L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE,	OR	ON	ON	2022/07/08 10:06 AM

			BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L21	7	L1 AND L2	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L22	19383	(("pyruvate kinase"))	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L23	8	L2 SAME L5	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L24	519	(("CYP 3A4") OR ("CYP3A4/5") OR ("CYP3A5") OR ("CYP 3A4") OR ("CYP 3A5")) WITH (("inducer") OR ("agonist") OR ("activator"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L25	209323	(("ketoconazole") OR ("itraconazole") OR ("ritonavir") OR ("boceprevir") OR ("clarithromycin") OR ("voriconazole"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL,	OR	ON	ON	2022/07/08 10:06 AM

			NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L26	95	L7 SAME L8	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/07/08 10:06 AM
L27	732	(("yang") near2 ("hua")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L28	0	(("prakash") near2 ("chandra agarwal")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L29	0	(("iyer") near2 ("varsha venkatachalam")).in.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/08 10:06 AM
L30	94	(("mitapivat") OR ("AG-348") OR ("AG348") OR ("AG 348"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/07/08 10:06 AM
L32	116351	(("anemia") OR ("hemolytic anemia"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 09:49 AM
L33	8	L32 SAME L30	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 09:49 AM
L34	0	"2019104134"	(US-PGPUB; USPAT)	OR	ON	ON	2023/01/20 10:16 AM
L35	19	"2019104134"	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2023/01/20 10:16 AM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L36	134023	(("bosentan") OR ("etravirine") OR ("phenobarbital") OR ("sotorasib") OR ("primidone") OR ("lorlatinib") OR ("efavirenz") OR ("cenobamate") OR ("dabrafenib"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/20 04:27 PM
L37	6	L15 AND L36	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/20 04:28 PM
L38	31667	(("SN38") OR ("SN-38"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2023/03/21 12:37 PM

			JPO; DERWENT; IBM_TDB)				
L39	3545	(("solution")) SAME L38	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/21 12:37 PM
L40	560	(("mg/mL")) SAME L39	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/03/21 12:37 PM
L41	511492	(("bosentan") OR ("etravirine") OR ("phenobarbital") OR ("sotorasib") OR ("primidone") OR ("lorlatinib") OR ("efavirenz") OR ("cenobamate") OR ("dabrafenib") OR ("bexarotene") OR ("dexamethasone") OR ("dipyrone") OR ("eslicarbazepine") OR ("modafinil") OR ("nafcillin") OR ("pexidartinib") OR ("rifabutin") OR ("rifapentine") OR ("sotorasib") OR ("St John's Wort") OR ("St John's Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/05 03:37 PM
L42	8	L15 AND L41	(US-PGPUB; USPAT;	OR	ON	ON	2023/04/05

			FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				03:37 PM
L43	0	L2 SAME L15	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/05 03:45 PM
L44	4	L2 AND L15	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/04/05 03:45 PM
L45	31	"11102994"	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2023/04/05 03:54 PM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L46	157018	(("rifabutin") OR ("rifapentin") OR ("rifapentine") OR ("nafcillin") OR ("pexidartinib") OR ("modafinil") OR ("lorlatinib") OR ("eslicarbazepine") OR ("efavirenz") OR ("dipyrone") OR ("dexamethsaone") OR ("dabrafenib") OR ("cetobamate") OR ("bexarotene") OR ("bosantan"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L47	0	(("St. John's Wort"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L48	0	(("St. Johns Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:00 PM
L49	0	(("St. John's Wart"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2023/04/12 05:00 PM

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			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
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L52	109157	(("hemolytic anemia"))	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2023/04/12 05:01 PM

			JPO; DERWENT; IBM_TDB)				
L53	201121	L46 OR L51	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
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L55	1	(L52 SAME L53).clm.	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/12 05:01 PM
L56	42	L52 WITH L53	(US-PGPUB; USPAT; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR,	OR	ON	ON	2023/04/12 05:02 PM

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L57	109244	(("hemolytic anemia"))	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/17 10:47 AM
L58	18	L57 SAME L19	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/04/17 10:47 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Ex. 2001-0155

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(12) **United States Patent**
Iyer et al.

(10) **Patent No.: US 11,878,049 B1**
(45) **Date of Patent: Jan. 23, 2024**

(54) **MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450**

(71) Applicant: **Agios Pharmaceuticals, Inc.**, Cambridge, MA (US)

(72) Inventors: **Varsha Venkatachalam Iyer**, Boston, MA (US); **Chandra Agarwal Prakash**, North Andover, MA (US); **Hua Yang**, Acton, MA (US)

(73) Assignee: **Agios Pharmaceuticals, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 414 days.

(21) Appl. No.: **16/900,610**

(22) Filed: **Jun. 12, 2020**

Related U.S. Application Data

(60) Provisional application No. 62/861,600, filed on Jun. 14, 2019.

(51) **Int. Cl.**
A61K 38/45 (2006.01)
A61K 45/06 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 38/45*** (2013.01); *A61K 45/06* (2013.01); *C12Y 207/0104* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/4709; A61K 31/496
See application file for complete search history.

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Assistant Examiner — George W Kosturko
(74) *Attorney, Agent, or Firm* — McCarter & English, LLP; Michael J. DeGrazia

(57) **ABSTRACT**

Described herein are methods of treating pyruvate kinase deficiency (PKD), sickle cell disease or thalassemia with mitapivat or a pharmaceutically acceptable salt thereof, or use of the drug for the treatment of these conditions, in combination with or in the absence of with a secondary drug, such as an inducer or an inhibitor of cytochrome P450. Various doses and dosing regimens of mitapivat in monotherapy and in concomitant medications are described.

19 Claims, 4 Drawing Sheets

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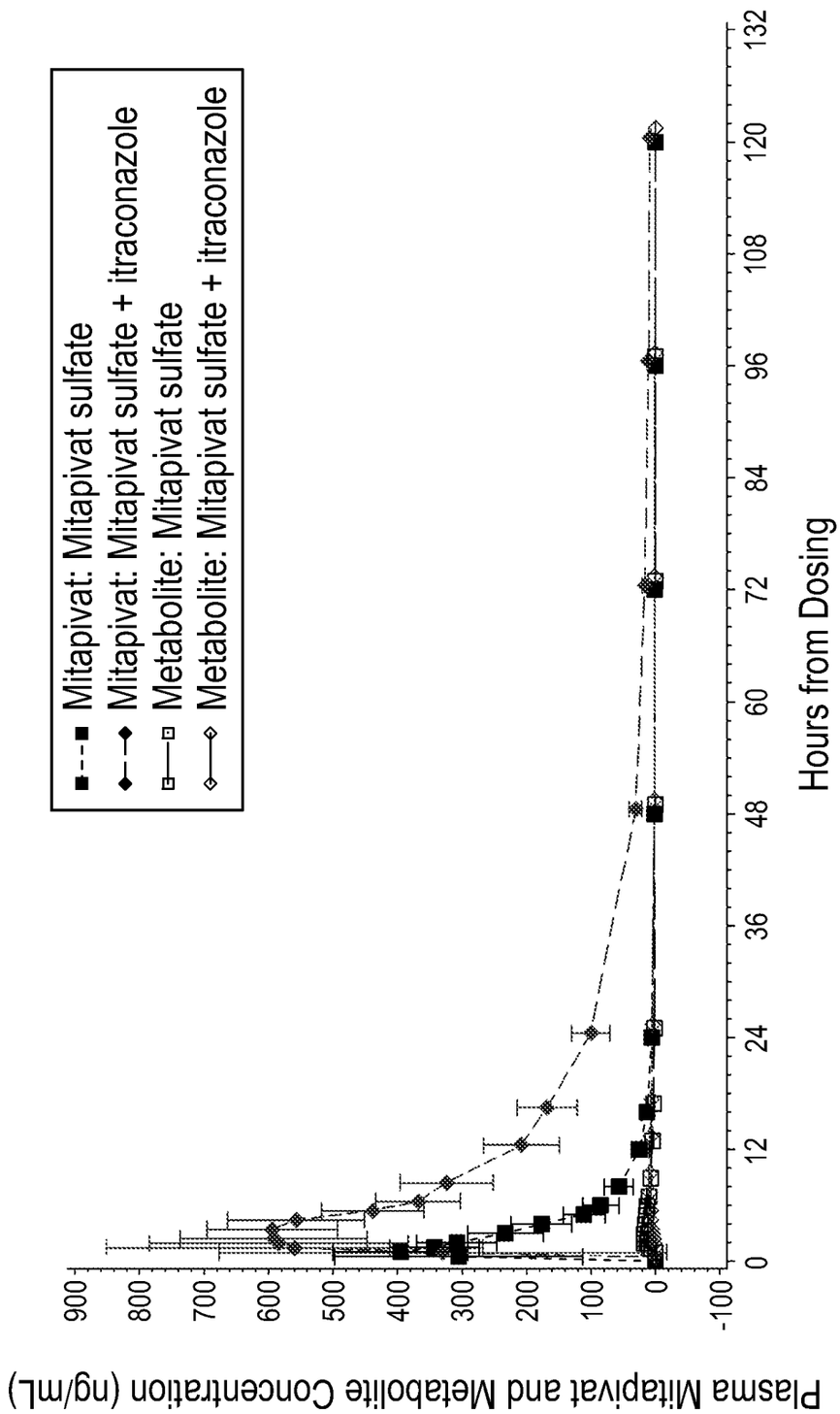

Mitapivat: Mitapivat sulfate
Mitapivat: Mitapivat sulfate + itraconazole
Metabolite: Mitapivat sulfate
Metabolite: Mitapivat sulfate + itraconazole
Plasma Mitapivat and Metabolite Concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
-100
0
12
24
36
48
60
72
84
96
108
120
132
Hours from Dosing

FIG. 1

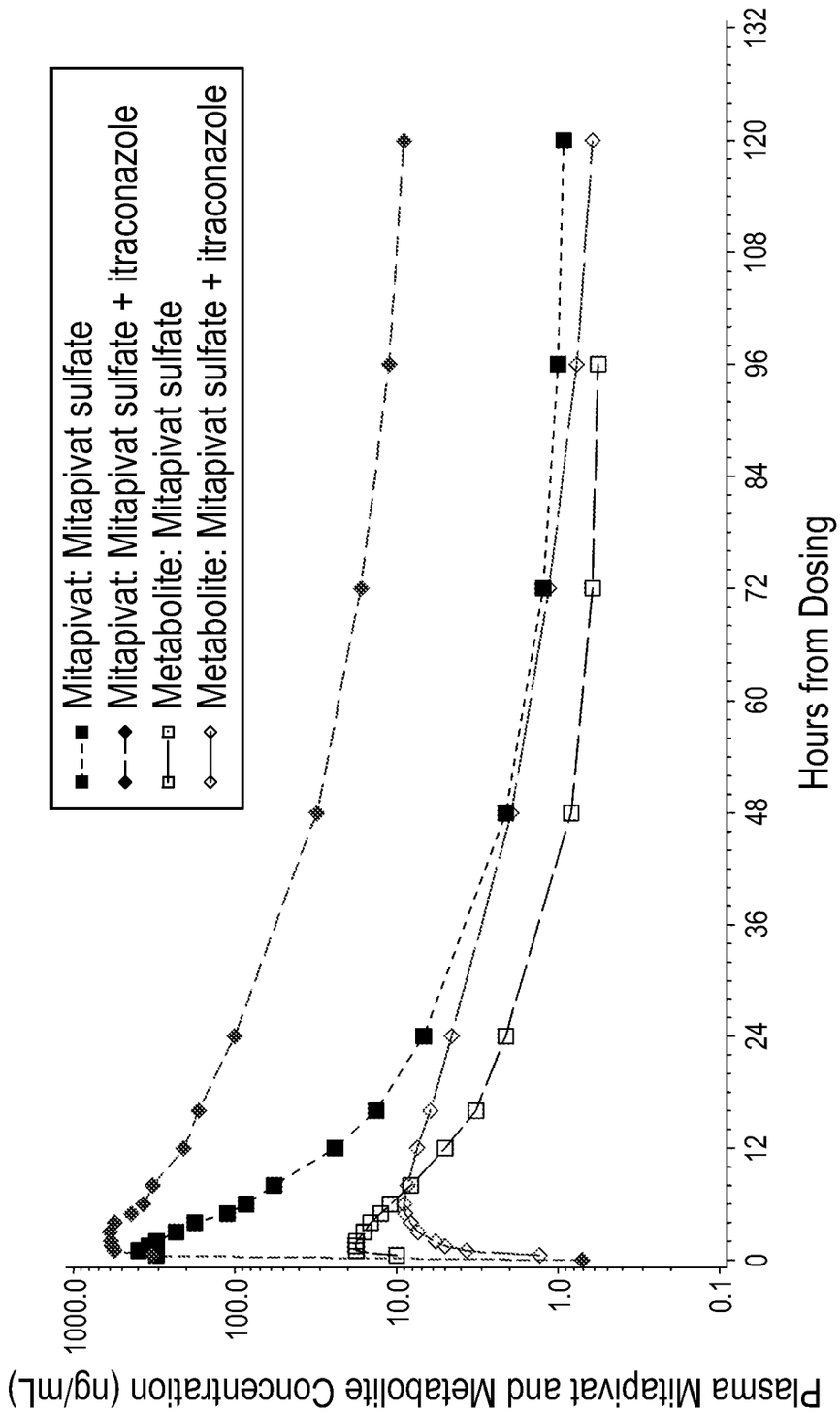

Mitapivat: Mitapivat sulfate
Mitapivat: Mitapivat sulfate + itraconazole
Metabolite: Mitapivat sulfate
Metabolite: Mitapivat sulfate + itraconazole
Plasma Mitapivat and Metabolite Concentration (ng/mL)
1000.0
100.0
10.0
1.0
0.1
0
12
24
36
48
60
72
84
96
108
120
132
Hours from Dosing

FIG. 2

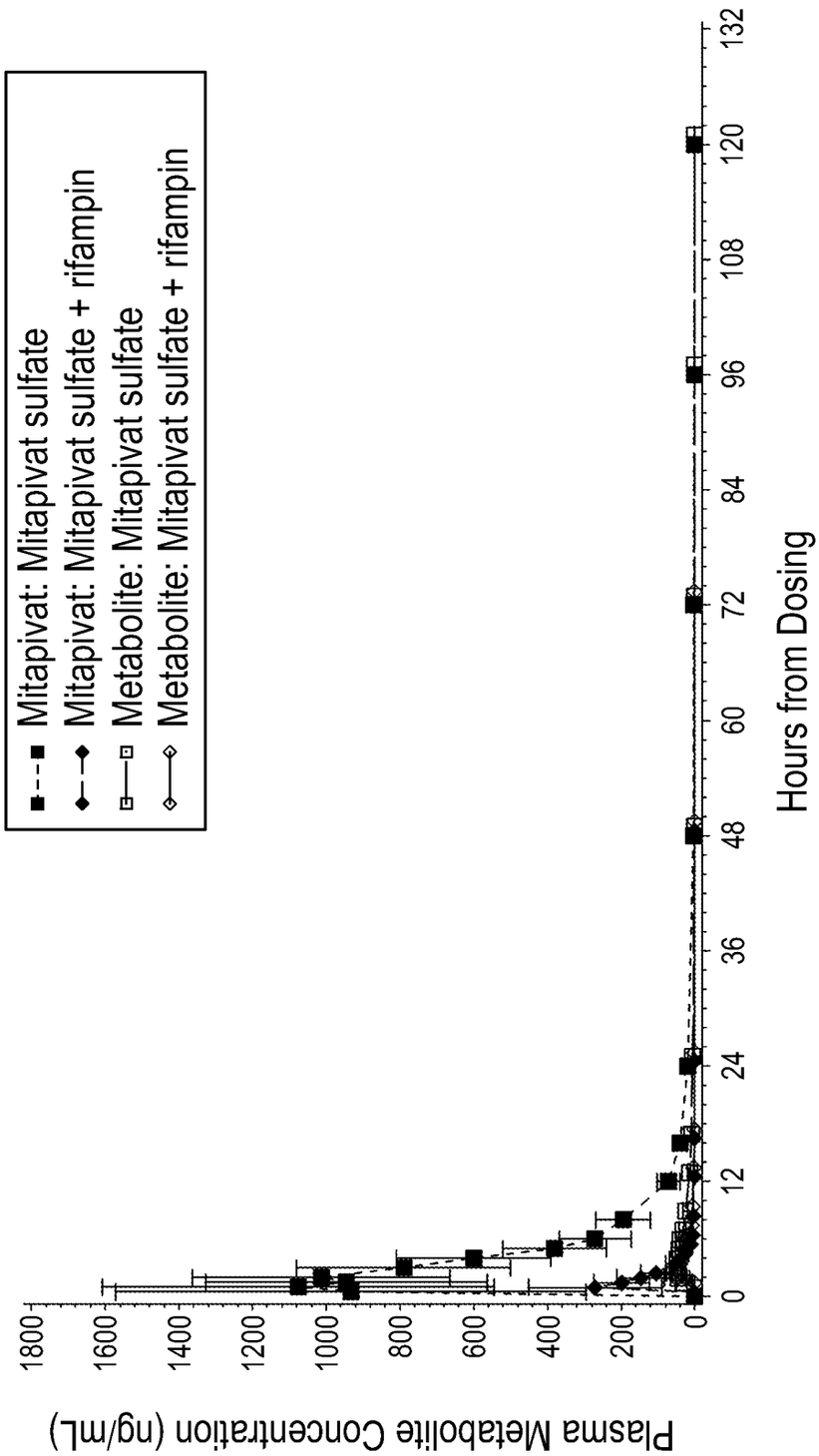

Mitapivat: Mitapivat sulfate
Mitapivat: Mitapivat sulfate + rifampin
Metabolite: Mitapivat sulfate
Metabolite: Mitapivat sulfate + rifampin
Plasma Metabolite Concentration (ng/mL)
0
200
400
600
800
1000
1200
1400
1600
1800
Hours from Dosing
0
12
24
36
48
60
72
84
96
108
120
132

FIG. 3

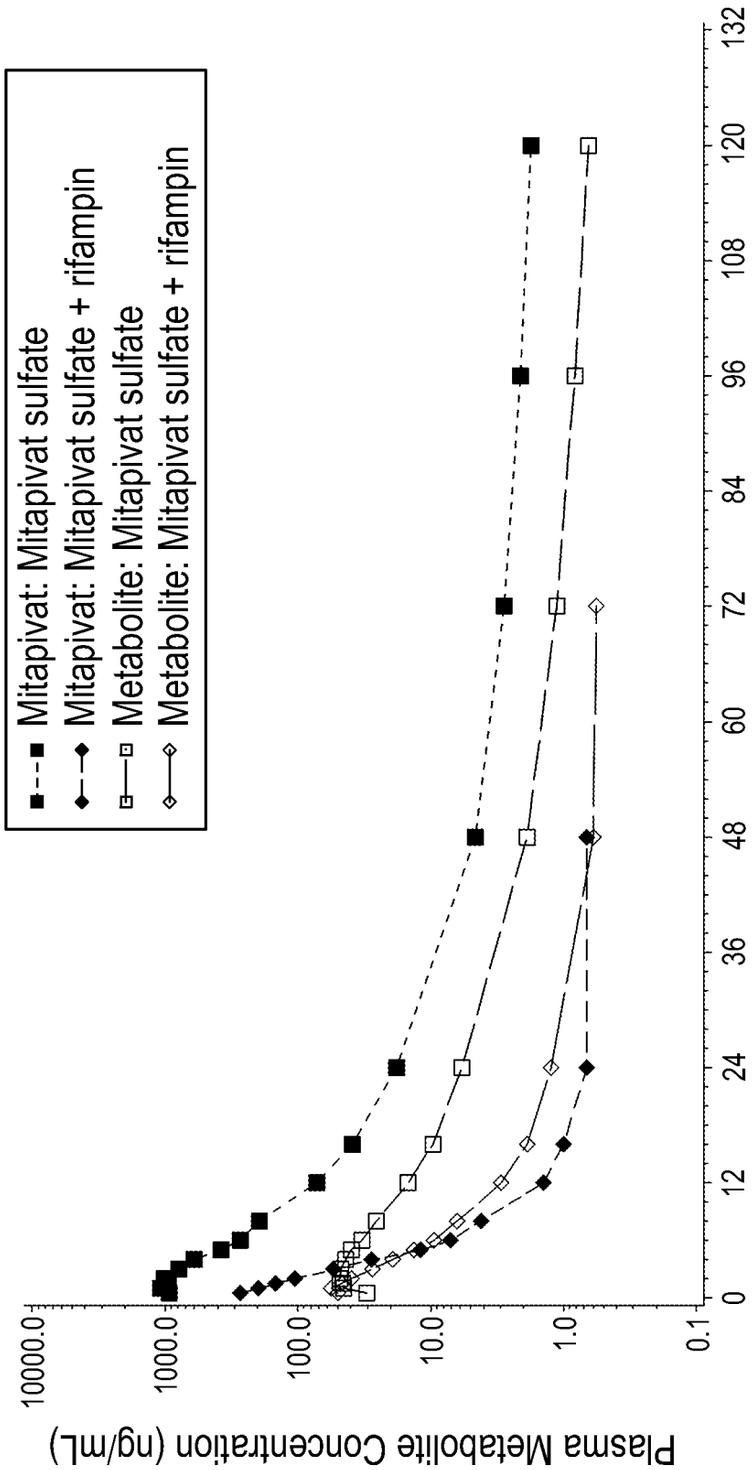

Mitapivat: Mitapivat sulfate
Mitapivat: Mitapivat sulfate + rifampin
Metabolite: Mitapivat sulfate
Metabolite: Mitapivat sulfate + rifampin
Plasma Metabolite Concentration (ng/mL)
10000.0
1000.0
100.0
10.0
1.0
0.1
0
12
24
36
48
60
72
84
96
108
120
132
Hours from Dosing

FIG. 4

MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

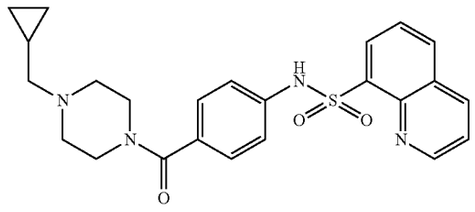
RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 62/861,600, filed Jun. 14, 2019, the entire teachings of which are incorporated herein by reference.

BACKGROUND

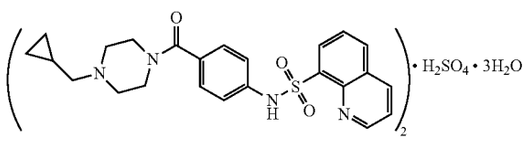
Pyruvate kinase deficiency (PKD) is a disease of the red blood cells caused by a deficiency of the pyruvate kinase R (PKR) enzyme due to recessive mutations of PKLR gene. PKR activators can be beneficial to treat PKD, thalassemia (e.g., beta-thalassemia), abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, anemia (e.g., congenital anemias (e.g., enzymopathies), hemolytic anemia (e.g., hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, anemia of chronic diseases, non-spherocytic hemolytic anemia or hereditary spherocytosis). Treatment of PKD is supportive, including blood transfusions, splenectomy, chelation therapy to address iron overload, and/or interventions for other disease-related morbidity. Currently, however, there is no approved medicine that treats the underlying cause of PKD, and thus the etiology of life-long hemolytic anemia.

Mitapivat, also known as AG-348 or by its chemical name N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl) quinoline-8-sulfonamide, and is represented by the following structural formula:



is an allosteric activator of pyruvate kinase R (PKR). See e.g., International Patent Application Publication Nos. WO 2011/002817 and WO 2016/201227.

Mitapivat sulfate is represented by the following structural formula:



and is currently in Phase 2 and Phase 3 clinical trials as a disease-altering therapy in patients with PKD, hemolytic anemia and thalassemia. See, e.g., U.S. Clinical Trials Identifier Nos. NCT03692052, NCT03559699, NCT03548220, NCT03853798, and NCT02476916.

SUMMARY

Non-clinical studies described in Example 1 show that the PKR activator, mitapivat, is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5) enzymes (i.e., >90%), with minor contributions from other detoxification enzymes, namely CYP2C8, CYP2C9, and CYP1A2. It has also been found that in a clinical trial, total exposure of mitapivat increased in the presence of itraconazole, a strong CYP3A4A and p-gp inhibitor, compared with dosing of mitapivat sulfate alone. It has further been found that total exposure of mitapivat decreased in the presence of rifampin, a strong CYP3A4A and p-gp inducer, compared with dosing of mitapivat sulfate alone.

Accordingly, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor. In another aspect, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof and a p-glycoprotein (p-gp) inhibitor. As used herein, "CYP3A4/5" means cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In some embodiments, the pharmaceutically acceptable salt is mitapivat sulfate.

Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5) . In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g., alpha-thalassemia and beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In some embodiments, the inhibitor of CYP3A4/5 is a moderate CYP3A4/5 inhibitor. In some embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inhibitor.

In another embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5) . In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g., alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In another

embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In some embodiments, the inducer of CYP3A4/5 is a moderate CYP3A4/5 inducer. In some embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inducer.

Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g., alpha-thalassemia and beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a moderate p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a mild p-glycoprotein inhibitor.

The present disclosure further provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or p-glycoprotein inhibitor.

Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In yet another embodiment, the present disclosure relates to a method of treating thalassemia (e.g., alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In yet another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In some embodiments, the inducer of CYP3A4/5 is a strong inducer of CYP3A4/5. In some embodiments, the inducer of CYP3A4/5 is a moderate inducer of CYP3A4/5. In some embodiments, the inhibitor of CYP3A4/5 is a strong inhibitor of CYP3A4/5. In some embodiments, the inhibitor of CYP3A4/5 is a moderate inhibitor of CYP3A4/5.

In another embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In yet another embodiment, the present disclosure relates to a method of treating thalassemia (e.g., alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In yet another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a strong p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a mild p-glycoprotein inhibitor.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing Arithmetic Mean (SD) Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 20 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 200 mg itraconazole (Treatment Period 2) on linear scale (Part 1). "Metabolite" refers to the CYP3A4 metabolite of mitapivat (see Example 2).

FIG. **2** is a graph showing Arithmetic Mean Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 20 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 200 mg itraconazole (Treatment Period 2) on semi-log scale (Part 1) (see Example 2).

FIG. **3** is a graph showing Arithmetic Mean (SD) Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 50 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 600 mg rifampin on linear scale (Treatment Period 2, Part 2, see Example 2).

FIG. **4** is a graph showing Arithmetic Mean Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 50 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 600 mg rifampin on semi-log scale (Treatment Period 2, Part 2, see Example 2)

DETAILED DESCRIPTION

Definitions

"CYP3A4/5 modulator" refers to any substance, including, but not limited to a small molecule (with a molecular weight of ≤1000 Da, or ≤750 Da, or ≤500 Da), a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a polysaccharide, a peptide, a polypeptide, a protein, an antibody, an aptamer, a natural or synthetic plant-based substance, or a complex or a composition comprising any combination of the aforementioned substances, that can modify or alter the activity and/or expression levels of the enzyme cytochrome P450 3A4 (CYP3A4; EC 1.14.13.97) or 3A5 (CYP3A5; EC1.14.14.1). Briefly, the cytochrome P450 (CYP) is a superfamily of detoxification enzymes that are

responsible for the oxidative and reductive metabolic transformation of drug medications and the ultimate "clearance", which is the elimination of the drug from the body as determined by the measured plasma levels of the drug and optionally, the drug metabolites, such as the metabolite known to be formed by CYP3A4/5. CYP3A4 and CYP3A5 are two of such enzymes and are largely prevalent in the liver.

A CYP3A4/5 modulator may be a CYP3A4/5 inducer or a CYP3A4/5 inhibitor. A "CYP3A4/5 inducer" or "inducer of CYP3A4/5" is a CYP3A4/5 modulator as defined above that can increase, enhance, stimulate, induce, accelerate or augment the CYP3A4/5 activity from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, e.g., the level of the CYP3A4/5 activity and/or expression prior to the exposure or contact with the CYP3A4/5 inducer, including all ranges and values therebetween not expressly mentioned above. The CYP3A4/5 inducer activity may cause mitapivat or a pharmaceutically acceptable salt thereof that is co-administered with the CYP3A4/5 inducer to be metabolized and eliminated more quickly from the body, as determined by the measured plasma levels of the compound and its metabolites.

A "CYP3A4/5 inhibitor" or "inhibitor of CYP3A4/5" is a CYP3A4/5 modulator as defined above that can decrease, reduce, inhibit, decelerate, attenuate, or suppress the CYP3A4/5 activity and/or expression from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, e.g., the level of the CYP3A4/5 activity and/or expression prior to the exposure or contact with the CYP3A4/5 inhibitor, including all ranges and values therebetween not expressly mentioned above. The CYP3A4/5 inhibitor may cause mitapivat or a pharmaceutically acceptable salt thereof that is co-administered with the CYP3A4/5 inhibitor to be metabolized and eliminated more slowly from the body, as determined by the measured plasma levels of the compound and its metabolites.

If an investigational drug is a CYP inducer, it can be classified as a strong, moderate, or mild inducer based on its effect on an index CYP substrate. The convention is to categorize CYP induction in the following ways:

A strong inducer decreases the AUC of a sensitive index CYP by ≥80 percent.

A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥50 to <80 percent.

A mild inducer decreases the AUC of a sensitive index CYP substrate by ≥20 to <50 percent.

A CYP inhibitor can be classified as a strong, moderate, or mild inhibitor based on its effect on an index CYP substrate. A strong inhibitor increases the AUC of a sensitive index CYP substrate ≥5-fold. A moderate inhibitor increases the AUC of a sensitive index CYP substrate by ≥2- to <5-fold. A mild inhibitor increases the AUC of a sensitive index CYP substrate by ≥1.25- to <2-fold.

A p-glycoprotein inhibitor refers to any substance, including, but not limited to a small molecule (with a molecular weight of ≤1000 Da, or ≤750 Da, or ≤500 Da), a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a polysaccharide, a peptide, a polypeptide, a protein, an antibody, an aptamer, a natural or synthetic plant-based substance, or a complex or a composition comprising any combination of the aforementioned substances, that can decrease, reduce, inhibit, decelerate, attenuate, or suppress the p-glycoprotein activity and/or expression from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, e.g., the level of the p-glycoprotein. In some embodiments, the p-glycoprotein inhibitor is a strong p-glycoprotein inhibitor, selected from the group consisting of amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine ticagrelor, and erapamil.

The terms "effective amount" and "therapeutically effective amount" are used interchangeably throughout the present disclosure, whether referring to mitapivat or a pharmaceutically acceptable salt thereof, a CYP3A4/5 inducer, or a CYP3A4/5 inhibitor.

An "effective amount" of mitapivat or a pharmaceutically acceptable thereof is an amount sufficient to provide a therapeutic benefit in the treatment of pyruvate kinase deficiency (PKD), thalassemia (e.g., alfa-thalassemia, beta-thalassemia or non-transfusion-dependent thalassemia), abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, anemia (e.g., congenital anemias (e.g., enzymopathies), hemolytic anemia (e.g., hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, chronic hemolytic anemia, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, anemia of chronic diseases, non-spherocytic hemolytic anemia or hereditary spherocytosis), as well as all other conditions disclosed in the section "Diseases, Disorders and Conditions" in the present disclosure, i.e., conditions that are responsive to treatment with a PKR activator such as mitapivat or a pharmaceutically acceptable salt thereof. Such diseases, disorders and conditions are hereinafter referred as "a PKR activator-responsive condition" when referring to any one of these conditions or "PKR activator-responsive conditions" when referring to these conditions collectively. Additionally or alternatively, an "effective amount" of mitapivat or a pharmaceutically acceptable salt thereof is an amount sufficient to delay or minimize one or more effects or symptoms associated with these conditions. In one aspect, an "effective amount" of mitapivat or a pharmaceutically acceptable salt thereof means an amount of mitapivat or a pharmaceutically acceptable salt thereof, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "effective amount" can encompass an amount that improves overall therapy, reduces or avoids effects, symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, an "effective amount" of mitapivat or a pharmaceutically acceptable salt thereof is an amount sufficient for eliciting measurable activation of wild-type or mutant PKR. In certain embodiments, an "effective amount" of mitapivat or a pharmaceutically acceptable salt thereof is an amount sufficient for regulating 2,3-diphosphoglycerate levels in blood in need thereof or for treating PKR activator-responsive conditions or treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (e.g., liver diseases). In certain embodiments, an effective amount of mitapivat or a pharmaceutically acceptable salt thereof is an amount sufficient for eliciting measurable activation of wild-type or

mutant PKR and for regulating 2,3-diphosphoglycerate levels in blood in need thereof or for treating PKR activator-responsive conditions or treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (e.g., liver diseases). In one aspect, the effective amount is the amount required to generate a subject's hemoglobin response of ≥1.0 g/dL (such as ≥1.5 g/dL or ≥2.0 g/dL) increase in Hb concentration from baseline. In one aspect, the subject's baseline Hb concentration is the average of all available Hb concentrations before treatment with a compound described herein. In certain aspects, the effective amount is the amount required to reduce the patient's transfusion burden. In one aspect, the effective amount of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is between about 0.01-100 mg/kg body weight/day of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate), e.g., about 0.1-100 mg/kg body weight/day.

Concomitant medications will be commonly used with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate). An "effective amount" of the drug (e.g., an effective amount of a CYP3A4/5 inducer or an effective amount of a CYP3A4/5 inhibitor) being co-administered with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is an amount sufficient to provide a desired therapeutic benefit. Drugs that are being co-administered with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate), including some of the current antiarrhythmics, antibiotics, antidepressants, antifungals, calcium channel blockers, H_2 receptor antagonists, non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, etc., will sometimes be CYP3A4/5 inducers or CYP3A4/5 inhibitors. In such instances, the amount of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) or the amount of the drug being co-administered should be adjusted to reduce effects of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and the co-administered drug.

In one aspect, an effective amount of a CYP3A4/5 inducer is between about 0.1-1000 mg/kg/day of a CYP3A4/5 inducer, e.g., about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

In one aspect, an effective amount of a CYP3A4/5 inhibitor is between about 0.1-1000 mg/kg/day of a CYP3A4/5 inhibitor, e.g., about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

In one aspect, an effective amount of a p-gp inhibitor is between about 0.1-1000 mg/kg/day of a p-gp inhibitor, e.g., about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

As used herein, reduction in transfusion burden means at least 20% reduction in the number of RBC units transfused within at least 5 weeks of treatment. In certain embodiments, the reduction in transfusion burden is ≥33% reduction in the number of RBC units transfused within at least 5 weeks of treatment. In certain embodiments, reduction of transfusion burden is ≥33% reduction in the number of RBC units transfused within at least 10 weeks (e.g., at least 20 weeks or at least 24 weeks) of treatment.

The term "activating" as used herein means an agent that (measurably) increases the activity of wild type pyruvate kinase R (wt PKR) or causes wild type pyruvate kinase R (wt PKR) activity to increase to a level that is greater than wt PKR's basal levels of activity or an agent that (measurably) increases the activity of a mutant pyruvate kinase R (mPKR) or causes mutant pyruvate kinase R (mPKR) activity to increase to a level that is greater than that mutant PKR's basal levels of activity, for examples, to a level that is 20%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of wild type PKR.

The terms "treatment," "treat," and "treating" refer to reversing, alleviating, reducing the likelihood of developing, or inhibiting the progress of a disease or disorder, or one or more effects or symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed, i.e., therapeutic treatment. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors), i.e., prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to reduce the likelihood of or delay their recurrence.

As used herein the terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate).

The term "pharmaceutically acceptable salt" when referring to a pharmaceutically acceptable salt of mitapivat, refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art, for example, Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19. Pharmaceutically acceptable salts of mitapivat include those derived from suitable inorganic and organic acids. Examples of pharmaceutically acceptable acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, besylate bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, gentisate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, tosylate p-toluenesulfonate, undecanoate, valerate salts, and the like. Preferably, a pharmaceutically acceptable salt of mitapivat is a sulfate salt.

As used herein, the terms "about" and "approximately" are used herein to mean within the typical ranges of tolerance in the art. In one embodiment, "about" means within 2 standard deviations from the mean value. In one embodiment, "about" means ±10%. In one embodiment, "about" means ±5%. When "about" is present before a series of numbers of number ranges, it is understood that the term can apply to any and each of the numbers and ranges recited in the series.

Compositions and Administration

he effective amount of mitapivat, in accordance with a method of the invention, may be administered in the form of a pharmaceutical composition comprising mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate), together with a pharmaceutically acceptable carrier.

Pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

Pharmaceutically acceptable carriers used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Exemplary carriers, diluents, granulating and/or dispersing agents, surface active agents and/or emulsifiers, binding agents, preservatives, antioxidants, chelating agent, antifungal preservatives, alcohol preservatives, acidic preservatives, other types of preservatives, buffering agents, lubricating agents, and natural oils that can be included in a pharmaceutical composition of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) as disclosed in International Patent Application No. W02019/104134.

Pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, transmucosally, or in an ophthalmic preparation. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In one aspect, the pharmaceutical compositions provided herewith are orally administered in an orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include one or more substances selected from microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

A secondary drug can be co-administered with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate). The effective amount of a secondary drug that is co-administered with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate), such as a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor, if used in a method of the invention, may also be administered in the form of a pharmaceutical composition comprising the CYP3A4/5 inducer or the CYP3A4/5 inhibitor or the p-gp inhibitor, together with a pharmaceutically acceptable carrier. Pharmaceutical compositions of the secondary drug may be prepared and administered as described above for pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate).

In one aspect, mitapivat or a pharmaceutically acceptable salt thereof (e.g. mitapivat sulfate) is formulated as a tablet composition together with a pharmaceutically acceptable carrier, in accordance with the disclosures of International Patent Application No. W02019/104134.

In one embodiment, in therapies comprising mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and the secondary drug are administered "concurrently" to the subject, which means that the subject is administered both drugs on the same day on all days of the treatment period. In one embodiment, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and the secondary drug are administered "sequentially" to the subject, which means that the subject is administered either of the two drugs on all days of the treatment period, but not both drugs. In another embodiment, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and the secondary drug are administered "sequentially and concurrently" to the subject, which means that the subject is administered either of the two drugs on certain days of the treatment period, but not both drugs; and the subject is administered both drugs on the same day on other days of the treatment period.

Doses and Dosing Regimens

The amount of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) that may be combined with carrier materials to produce a composition in a single dosage form will vary depending upon the subject to be treated and the particular mode of administration. For example, a specific dosage and treatment regimen for any particular subject will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of mitapivat or a pharmaceutically acceptable salt thereof will also depend upon the particular form (e.g., free base, salt form, crystalline form, etc.) in the composition. In one aspect, a provided composition may be formulated such that a dosage equivalent to about 0.001 to about 100 mg/kg body weight/day of mitapivat or a pharmaceutically acceptable salt thereof (e.g., about 0.5 to about 100 mg/kg of mitapivat or a pharmaceutically acceptable salt thereof) can be administered to a subject receiving these compositions. Alternatively, dosages equivalent to 1 mg/kg and 1000 mg/kg of mitapivat or a pharmaceutically acceptable salt thereof every 4 to 120 hours is also acceptable.

In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose of equivalent to about 2 mg to about 3000 mg of mitapivat. In certain embodiments, the dose is an oral dose. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 2 mg to about 3000 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 350 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 200 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 100 mg of mitapivat. In certain embodiments, mitapivat or a pharma-

ceutically acceptable salt thereof is formulated equivalent to about 5 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 10 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 15 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 20 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 25 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 30 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 35 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 40 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 45 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 50 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 55 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 60 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 65 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 70 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 75 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 80 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 85 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 90 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 95 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 100 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 110 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 120 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 130 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 140 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 150 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 160 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 170 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 180 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 190 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 200 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 210 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 220 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 230 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 240 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 250 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 260 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 270 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 280 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 290 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 300 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 300 to 360 mg of mitapivat. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 2 mg to about 3000 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 500 mg of mitapivat of per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 200 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 10 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose of about 15 mg equivalent to mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 45 mg of mitapivat per day. In certain embodiments, mitapivat or a

pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat thereof per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 90 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 110 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 120 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 130 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 140 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 150 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 160 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 170 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 180 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 190 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 200 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 210 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 220 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 230 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 240 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 250 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 260 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 270 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 280 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 290 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 300 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 300-360 mg of mitapivat per day. Dosing can be once, twice, or three times daily. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 10 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 15 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 45 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 65 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 75 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about

85 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 90 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 95 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat twice per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 10 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 15 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 45 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 65 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 75 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 85 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 95 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 110 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 120 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 130 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 140 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 150 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 160 mg to about 200 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 200 mg to about 360 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat once every other day. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 70% to about 80%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 60% to about 70%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 50% to about 60%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 40% to about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 30% to about 40%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 20% to about 30%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 10% to about 20%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat to the dose equivalent to about 200 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or

a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat to the dose equivalent to about 150 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat to the dose equivalent to about 100 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat to the dose equivalent to about 50 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat to the dose equivalent to about 25 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat to the dose equivalent to about 10 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat to the dose equivalent to about 5 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg of mitapivat to the dose equivalent to about 2.5 mg.

In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 70% to about 80%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 60% to about 70%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 50% to about 60%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 40% to about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 30% to about 40%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 20% to about 30%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 10% to about 20%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof from twice daily to once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof from once daily to once every other day.

In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat twice daily to the dose equivalent to about 200 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat twice daily to the dose equivalent to about 150 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat twice daily to the dose equivalent to about 100 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat twice daily to the dose equivalent to about 50 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat twice daily to the dose equivalent to about 25 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat twice daily to the dose equivalent to about 10 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat twice daily to the dose equivalent to about 5 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg twice daily of mitapivat to the dose equivalent to about 2.5 mg twice daily.

In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat once daily to the dose equivalent to about 200 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat once daily to the dose equivalent to about 150 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat once daily to the dose equivalent to about 100 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat once daily to the dose equivalent to about 50 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat once daily to the dose equivalent to about 25 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat once daily to the dose equivalent to about 10 mg once daily. In certain embodiments, for any

of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat once daily to the dose equivalent to about 5 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg once daily of mitapivat to the dose equivalent to about 2.5 mg once daily.

In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat twice daily to the dose equivalent to about 200 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat twice daily to the dose equivalent to about 150 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat twice daily to the dose equivalent to about 100 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat twice daily to the dose equivalent to about 50 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat twice daily to the dose equivalent to about 25 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat twice daily to the dose equivalent to about 10 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat twice daily to the dose equivalent to about 5 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg twice daily of mitapivat to the dose equivalent to about 2.5 mg once daily.

In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 200 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 150 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 100 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 5 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 20 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 50 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 75 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is present in a tablet composition in an amount equivalent to about 100 mg of mitapivat. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

As used herein, the dose amount of mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) is based on the equivalence to the free-base form of mitapivat. For example, "mitapivat or pharmaceutically acceptable salt thereof present in the composition in an amount equivalent to about 2.0 mg of mitapivat" means about 2.0 mg of free-base mitapivat or about 2.33 mg of mitapivat sulfate having the structural formula as depicted in the background of the present disclosure.

Methods of Treatment (Mitapivat Monotherapy and Concomitant Medications)

In one aspect, the present disclosure provides methods of treating a disease, disorder or condition with mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor; use of mitapivat and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for the manufacture of a medicament for treating a disease, disorder or condition; and mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for use in treating a disease, disorder or condition. The disease, disorder or condition treated is pyruvate kinase deficiency (PKD), sickle cell disease, or thalassemia as further discussed in the following embodiments, and any one disease, disorder or condition described in the section "Diseases, Disorders and Conditions" provided in the present disclosure.

In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia.

In one embodiment, the method of any one of the preceding embodiments further comprises:

(a) monitoring the subject for an effect of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer; and

(b) in the event that an effect of the drug-drug interaction is present, adjusting the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and/or the

effective amount of the CYP3A4/5 inducer being administered to the subject to reduce the effect.

In some embodiments, the adjustment is to reduce the dose of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose and dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. Details of the dose and/or dose frequency adjustment are shown in the dose and dose regime section.

In one embodiment, the method of the preceding embodiment further comprises:

(c) repeating (a) and (b) until there are no further detectable symptoms of the drug-drug interaction.

Steps (a) and (b) can be repeated as many times as necessary until there are no further detectable symptoms of the drug-drug interaction. In one embodiment, step (a) comprises measuring and analyzing the pharmacokinetic (PK) such as AUC (i.e., area under the plasma concentration-time curve, such as AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, $AUC_{\%estrap}$) and C_{max} values (i.e., the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administrated and before the administration of a second dose). In one embodiment, step (a) comprises measuring and analyzing other PK parameters such as but not limited to C_L/F (i.e., apparent total body clearance of the drug from plasma), V_z/F (i.e., apparent volume of distribution during terminal phase after non-intravenous administration) , $t_{1/2}$ (elimination half-life), t_{last}, t_{max} (time to reach maximum (peak) plasma concentration following drug administration), etc.

A "drug-drug interaction" as used herein refers to a change in concentration in a patient of a first drug (e.g., mitapivat) and consequential change in the effect of the first drug on the subject/patient resulting from administration of a second drug (e.g., a CYP3A4/5 inducer, a CYP3A4/5 inhibitor). The change in concentration and consequential change in effect of the first drug resulting from the second drug typically occurs because of a change in activity or expression level of a detoxification enzyme that acts to clear the first drug from the patient (such as CYP3A4/5), wherein the change in activity or expression level of the detoxification enzyme is caused by the second drug. An increase in activity or expression level of the detoxification enzyme will tend to decrease the concentration of the first drug in the patient and its consequential effect on the patient, whereas a decrease in activity or expression level of the detoxification enzyme will tend to increase the concentration of the first drug in the patient and its consequential effect on the patient.

An "effect of a drug-drug interaction" as used herein refers to a detectable and measurable effect, such as a detectable symptom, on the subject/patient caused by the drug-drug interaction. Where the concentration of the first drug is increased, such as when mitapivat is co-administered with a CYP3A4/5 inhibitor, the "effect" typically refers to undesired phenomena such as an overdose of the first drug, liver failure, kidney failure, and the prevalence of side effects and adverse reactions. Where the concentration of the first drug is decreased, such as when mitapivat is co-administered with a CYP3A4/5 inducer, the "effect" typically refers to a decrease in the therapeutic efficacy of the first drug (e.g., mitapivat). Exemplary effects of a drug-drug interaction as used herein further include headache, insomnia, nausea, viral upper respiratory tract infection, arthralgia, diarrhoea, fatigue, hot flush, influenza, vomiting, cough, dizziness, oropharyngeal pain, pyrexia, back pain, dysmenorrhoea, and gastroenteritis, and dyspepsia, hypertriglyceridemia, hemolytic anemia, hemolysis, dizziness, etc.

In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5) or a p-gp inhibitor. In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia.

In one embodiment, the method of any one of the suitable preceding embodiments further comprises:

(a) monitoring the subject for a symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor; and

(b) in the event that a symptom of the drug-drug interaction is present, adjusting the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and/or the effective amount of the CYP3A4/5 inhibitor being administered to the subject to reduce the effect.

In some embodiments, the adjustment is to reduce the dose of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose and dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. Details of the dose and/or dose frequency adjustment are shown in the dose and dose regime section.

In one embodiment, the method of the preceding embodiment further comprises:

(c) repeating (a) and (b) until there are no further detectable symptoms of the drug-drug interaction.

Likewise, steps (a) and (b) can be repeated as many times as necessary until here are no further detectable symptoms of the drug-drug interaction. Ways of monitoring the subject for a symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor as recited in step (a) are as described above.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the CYP3A4/5 inducer (or inhibitor) sequentially.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the CYP3A4/5 inducer (or inhibitor) concurrently.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the

CYP3A4/5 inducer (or inhibitor) sequentially and concurrently. As used herein, "co-administered" or "in combination with" encompasses administration of mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer (or inhibitor) sequentially and concurrently, or at different intervals. In another embodiments, for the method of any one of the embodiments, the CYP3A4/5 inducer is a mild CYP3A4/5 inducer. In another embodiments, for the method of any one of the embodiments, the CYP3A4/5 inhibitor is a mild CYP3A4/5 inhibitor. In another embodiments, for the methods of any one of the embodiments, the CYP3A4/5 inhibitor is a moderate CYP3A4/5 inhibitor.

In another aspect, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor; use of mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for the manufacture of a medicament for treating disease, disorder or a condition; and mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for use in treating a disease, disorder or a condition.

As used herein, "in the absence of" when referring to a secondary drug co-administered with mitapivat (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor), refers to levels of the secondary drug in the subject/patient that are sufficiently low that such that any change in the levels of the detoxification enzymes for mitapivat and the secondary drug results in no detectable symptoms of a drug-drug interaction between mitapivat and the secondary drug.

In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In some embodiments, the thalassemia is alpha thalassemia. In some embodiments, the thalassemia is beta thalassemia.

In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a CYP3A4/5 inducer, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer. In certain embodiments, the CYP3A4/5 inducer is a strong CYP3A4/5 inducer. In certain embodiments, the CYP3A4/5 inducer is a moderate CYP3A4/5 inducer. In some embodiments, the CYP3A4/5 inducer is terminated at least 30 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 28 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 25 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 21 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 15 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In certain embodiment, the thalassemia is alpha-thalassemia. In certain embodiment, the thalassemia is beta-thalassemia.

In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a CYP3A4/5 inhibitor, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor. In certain embodiments, the CYP3A4/5 inhibitor is a strong CYP3A4/5 inhibitor. In certain embodiments, the CYP3A4/5 inhibitor is a moderate CYP3A4/5 inhibitor. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 21 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 15 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodi-

ments, the CYP3A4/5 inhibitor is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 3 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 2 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 1 day prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor.

In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor.

In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor. In certain embodiment, the thalassemia is alpha-thalassemia. In certain embodiment, the thalassemia is beta-thalassemia.

In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a p-gp inhibitor, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the p-gp inhibitor. In certain embodiments, the p-gp inhibitor is a strong p-gp inhibitor (e.g. amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine ticagrelor, and erapamil). In some embodiments, the p-gp inhibitor inhibitor is terminated at least 21 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 15 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 3 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 2 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor is terminated at least 1 day prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 1 mg to about 2500 mg, or about 5 mg to 2500 mg, or about 30 mg to 2500 mg, or about 5 mg to about 700 mg, or about 15 mg to about 700 mg, about 5 mg to about 360 mg, about 5 mg to about 300 mg, about 50 mg to about 300 mg, about 120 mg to about 360 mg, about 120 mg to about 300 mg, about 5 mg to about 120 mg, about 5 mg, about 20 mg, about 50 mg, about 100 mg, about 120 mg , about 200 mg, about 300 mg, or about 360 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 1 mg to about 2500 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg to 2500 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg to about 360 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg to about 300 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 50 mg to about 300 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 20 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 50 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 100 mg of mitapivat or a pharmaceutically acceptable salt thereof.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof once daily.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof twice daily.

In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject a sulfate salt of mitapivat, such as a sulfate salt of mitapivat having the structural formula depicted in the background of the present disclosure.

In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a strong inducer of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a moderate inducer of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a mild inducer of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a strong CYP3A4/5 inducer selected from a group consisting of apalutamide, enzalutamide, mitotane, phenytoin, efavirenz, nevirapine, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, henytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, and troglitazone.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a moderate CYP3A4/5 inducer selected from a group consisting of bosentan, etravirine, phenobarbital, and primidone.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a mild CYP3A4/5 inducer selected from a group consisting of armodafinil, modafinil, and rufinamide.

In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is selected from the group consisting of aminoglutethimide, bexarotene, bosentan, carbamazepine, dexamethasone, efavirenz, fosphenytoin, griseofulvin, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's Wort, avasimibe, dabrafenib, mifepristone, etravirine, armodafninil, glycerol phenylbutyrate, asunaprevir, rifunamide, oritavancin, clobazam, felbamate, eslicarbazepine acetate, and genistein.

In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is rifampin. In one aspect, rifampin is administered to the subject in the form of a capsule composition. In one aspect, about 0.1-1000 mg of rifampin is administered to the subject. In one aspect, about 100-1000 mg of rifampin is administered to the subject.

In one embodiment, the method of any one of the suitable preceding embodiments comprises administering about 600 mg of rifampin to the subject. In one aspect, the method of any one of the suitable preceding embodiments comprises administering about 600 mg of rifampin to the subject once daily.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a strong inhibitor of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a moderate inhibitor of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a mild inhibitor of CYP3A4/5.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is selected from the group consisting of toamiodarone, amprenavir, aprepitant, atazanavir, chloramphenicol, clarithromycin, conivaptan, cyclosporine, darunavir, dasatinib, delavirdine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, quinupristin, saquinavir, tamoxifen, telithromycin, troleandomycin, verapamil, voriconazole, grapefruit, Seville oranges, limes, pomelos, fruit juices, and vegetables from mustard green family.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a strong CYP3A4/5 inhibitor selected from a group consisting of boceprevir, cobicistat, danoprevir, elvitegravir, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, telithromycin, troleandomycin, nelfinavir, clarithromycin, nefazodone, saquinavir, suboxone, and voriconazole.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a moderate CYP3A4/5 inhibitor selected from a group consisting of aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inhibitor selected from a group consisting of chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor.

As used herein, the terms "weak inhibitor" and "mild inhibitor" are used interchangeably.

As used herein, the terms "weak inducer" and "mild inducer" are used interchangeably.

In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is itraconazole. In one aspect, about 0.1-1000 mg of itraconazole is administered to the subject. In one aspect, itraconazole is administered in the form of an oral solution. In one aspect, about 50-500 mg of itraconazole is administered to the subject.

In one embodiment, the method of any one of the suitable preceding embodiments comprises administering about 200 mg of itraconazole to the subject. In one aspect, about 0.1-1000 mg of itraconazole is administered to the subject. In one aspect, about 50-500 mg of itraconazole is administered to the subject. In one aspect, about 200 mg of itraconazole is administered to the subject. In one aspect, about 200 mg of itraconazole is administered to the subject once daily. In one aspect, about 100 mg of itraconazole is administered to the subject. In one aspect, about 100 mg of itraconazole is administered to the subject once daily. In one aspect, itraconazole is administered in the form of an oral solution.

Diseases, Disorders and Conditions

Pyruvate kinase deficiency (PKD) is a glycolytic enzymopathy that results in life-long hemolytic anemia. In certain embodiments, the subject having PKD is a patient having at least 2 mutant alleles in PKLR gene. In certain embodiments, the subject having PKD is a patient having at least 2 mutant alleles in PKLR gene and at least one is a missense mutation. See Canu et al., Blood Cells, Molecules and Diseases 2016, 57, pp. 100-109. In certain embodiments, a subject having PKD has an Hb concentration less than or equal to 10.0 g/dL. In certain embodiments, the subject having PKD is an adult not under regular transfusion (e.g., having had no more than 4 transfusion episodes in the 12-month period up to the treatment). In certain embodiments, the subject having PKD is an adult transfusion independent (e.g., having no more than 3 units of RBCs transfused in the 12-month period prior to the treatment). In

certain embodiments, the subject having PKD is an adult under regular transfusion (e.g., having had at least 4 transfusion episodes (e.g., at least 6 transfusion episodes) in the 12-month period prior to the treatment). In certain embodiments, the subject having PKD has a total number of at least 5 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 10 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 15 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 20 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 25 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 30 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 40 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 50 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 60 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 70 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD is not homozygous for the R479H mutation or does not have 2 non-missense mutations in the PKLR gene. In certain embodiments, the subject having PKD, under regular transfusion, has hemoglobin (Hb) ≤12.0 g/dL (if male) or ≤11.0 g/dL (if female), prior to the treatment. In certain embodiments, the subject having PKD, under regular transfusion, has transfusion occurring on average less than or equal to once every three weeks. In certain embodiments, the subject having PKD has received at least 0.8 mg (e.g., at least 1.0 mg)folic acid daily (e.g., for at least 21 days) prior to the treatment. In certain embodiments, the subject with PKD under regular transfusion achieves a reduction in transfusion burden (e.g., at least 33% reduction in the number of RBC units transfused) during the 5 weeks, 10 weeks, 15 weeks, 20 weeks, or 24 weeks, 28 weeks, or 32 weeks of treatment. In certain embodiments, the subject having PKD, not under regular transfusion (having had no more than 4 transfusion episodes in the 12-month period prior to the treatment and/or no transfusion in the 3 months prior to the treatment), has hemoglobin (Hb) ≤10.0 g/dL regardless of gender prior to the treatment. In certain embodiments, the subject having PKD has undergone splenectomy. In certain embodiment, the subject having PKD is a child 18 years old or younger. In certain embodiments, the child is transfusion dependent.

Exemplified conditions related to PKD include, but are not limited to, anemias, cholecystolithiasis, gallstones, tachycardia, hemochromatosis, icteric sclera, splenomegaly, leg ulcers, jaundice, fatigue, and shortness of breath. As described herein, PKD is a deficiency of PKR. In certain embodiments, the deficiency of PKR is associated with a PKR mutation.

In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 1.0 g/dL increase in Hb concentration after the treatment compared to the baseline of prior to the treatment. In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 1.5 g/dL increase in Hb concentration from baseline prior to the treatment. In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 2.0 g/dL increase in Hb concentration from baseline prior to the treatment.

In an embodiment, the mutant PKR is selected from the group consisting of A31V, A36G, G37Q, R40W, R40Q, L73P, S80P, P82H, R86P, I90N, T93I, G95R, M107T, G111R, A115P, S120F, H121Q, S130P, S130Y, V134D, R135D, A137T, G143S, I153T, A154T, L155P, G159V, R163C, R163L, T164N, G165V, L167M, G169G, E172Q, W201R, I219T, A221Y, D221N, G222A, I224T, G232C, N253D, G263R, G263W, E266K, V269F, L272V, L272P, G275R, G275R, E277K, V280G, D281N, F287V, F287L, V288L, D293N, D293V, A295I, A295V, I310N, I314T, E315K, N316K, V320L, V320M, S330R, D331N, D331G, D331E, G332S, V335M, A336S, R337W, R337P, R337Q, D339N, D339Q, G341A, G341D, I342F, K348N, A352D, I357T, G358R, G358E, R359C, R359H, C360Y, N361D, G364D, K365M, V368F, T371I, L374P, S376I, T384M, R385W, R385K, E387G, D390N, A392T, N393D, N393S, N393K, A394S, A394D, A394V, V395L, D397V, G398A, M403I, G406R, E407K, E407G, T408P, T408A, T408I, K410E, G411S, G411A, Q421K, A423A, A423A, R426W, R426Q, E427A, E427N, A431T, R449C, I457V, G458D, A459V, V460M, A468V, A468G, A470D, T477A, R479C, R479H, S485F, R486W, R486L, R488Q, R490W, I494T, A495T, A495V, R498C, R498H, A503V, R504L, Q505E, V506I, R510Q, G511R, G511E, R518S, R531C, R532W, R532Q, E538D, G540R, D550V, V552M, G557A, R559G, R559P, N566K, M568V, R569Q, R569L, Q58X, E174X, W201X, E241X, R270X, E440X, R486X, Q501X, L508X, R510X, E538X, R559X. These mutations are described in Canu et.al., Blood Cells, Molecules and Diseases 2016, 57, pp. 100-109. In an embodiment, the mutant PKR is selected from G332S, G364D, T384M, K410E, R479H, R479K, R486W, R532W, R510Q, and R490W. In certain embodiments, the mutant PKR is selected from A468V, A495V, I90N, T408I, and Q421K, and R498H. In certain embodiments, the mutant PKR is R532W, K410E, or R510Q. In certain embodiments, the mutant PKR is R510Q, R486W, or R479H.

In other aspects, provided are methods of treating a disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in treating disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for treating a disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof. In one aspect, the disease to be treated is hemolytic anemia.

Thalassemia is an inherited blood disorder in which the normal ratio of α- to β-globin production is disrupted due to a disease-causing variant in 1 or more of the globin genes. In certain embodiments, Alpha-globin aggregates (as found

in β-thalassemia) readily precipitate, which disrupts the red blood cell (RBC) membrane and results in oxidative stress. In certain embodiments, Beta-globin tetramers (Hb H, found in a-thalassemia) are generally more soluble, but are still unstable and can form precipitates. The imbalance of the globin chain synthesis can lead to a net reduction in Hb concentrations and has dramatic effects on the survival of RBC precursors, ultimately resulting in their premature destruction in the bone marrow and in extramedullary sites (Cappellini et al., 2014). In certain embodiments, the disorder results in large numbers of red blood cells being destroyed, which leads to anemia. In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia. In other embodiments, the thalassemia is non-transfusion-dependent thalassemia. In other embodiments, the thalassemia is beta thalassemia intermedia. In other embodiments, the thalassemia is Hb E beta thalassemia. In other embodiments, the thalassemia is beta thalassemia with mutations of 1 or more alfa genes.

In certain embodiments, the subject is an adult subject with thalassemia. In certain embodiments, the subject has thalassemia such as β-thalassemia intermedia, Hb E β-thalassemia, α-thalassemia (Hb H disease), or β-thalassemia with mutations of 1 or more α genes. In certain embodiments, the subject has non-transfusion-dependent thalassemia. In certain embodiments, the subject has non-transfusion-dependent alpha thalassemia. In certain embodiments, the subject has beta-thalassemia or non-transfusion-dependent beta-thalassemia. In certain embodiments, the subject is an adult male subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject is a female subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject is an adult female subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 6.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 7.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 8.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 9.0 g/dL. In certain aspects, the subject having non-transfusion-dependent thalassemia does not have a known history (e.g., has been diagnosed in the past) of Hb S or Hb C forms of thalassemia. In certain embodiments, the term "non-transfusion dependent" thalassemia refers to subjects with thalassemia having no more than 4 (e.g., five) units of RBCs transfused during a 24-week period up to the first day of administration of mitapivat and/or no RBC transfusions in the 8 weeks prior to the first day of administration of mitapivat. In certain embodiment, the subject is an adult over 18 years old. In certain embodiment, the subject is a child 18 years old or younger.

As used herein, sickle cell disease (SCD), Hemoglobin SS disease, and sickle cell anemia are used interchangeably. Sickle cell disease (SCD) is an inherited blood disorder caused by the presence of sickle hemoglobin (HbS). In certain embodiments, subjects with SCD have abnormal hemoglobin, called hemoglobin S or sickle hemoglobin, in their red blood cells. In certain embodiments, people having SCD have at least one abnormal gene causing the body to make hemoglobin S. In certain embodiments, people having SCD have two hemoglobin S genes, Hemoglobin SS.

In other aspects, provided herein are methods for treating anemia in a subject in need thereof comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in treating anemia in a subject in need thereof. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for treating anemia. In one aspect, the anemia to be treated is dyserythropoietic anemia.

In certain embodiments, the anemia is a dyserythropoietic anemia such as congenital dyserythropoietic anemia type I, II, III, or IV. In certain embodiments, the anemia is hemolytic anemia. In certain embodiments, the hemolytic anemia is a congenital and/or hereditary form of hemolytic anemia such as PKD, sickle cell disease, thalassemias (e.g., alpha or beta or non-transfusion-dependent thalassemia), hereditary spherocytosis, hereditary elliptocytosis), paroxysmal nocturnal hemoglobinuria, abeta-liproteinemia (Bassen-Kornzweig syndrome). In certain embodiments, the hemolytic anemia is acquired hemolytic anemia such as autoimmune hemolytic anemia, drug-induced hemolytic anemia. In certain embodiments, the hemolytic anemia is anemia as part of a multi-system disease, such as the anemia of Congenital Erythropoietic Purpura, Fanconi, Diamond-Blackfan.

As used herein, the term "anemia" refers to a deficiency of red blood cells (RBCs) and/or hemoglobin. As used herein, anemia includes all types of clinical anemia, for example (but not limited to): microcytic anemia, iron deficiency anemia, hemoglobinopathies, heme synthesis defect, globin synthesis defect, sideroblastic defect, normocytic anemia, anemia of chronic disease, aplastic anemia, hemolytic anemia, macrocytic anemia, megaloblastic anemia, pernicious anemia, dimorphic anemia, anemia of prematurity, Fanconi anemia, hereditary spherocytosis, sickle cell disease, warm autoimmune hemolytic anemia, cold agglutinin hemolytic anemia, osteopetrosis, thalassemia, and myelodysplastic syndrome.

In certain embodiments, anemia can be diagnosed on a complete blood count. In certain embodiments, anemia can be diagnosed based on the measurement of one or more markers of hemolysis (e.g., RBC count, hemoglobin, reticulocytes, schistocytes, lactate Dehydrogenase (LDH), haptoglobin, bilirubin, and ferritin) and/or hemosiderinuria mean corpuscular volume (MCV) and/or red cell distribution width (RDW). In the context of the present invention, anemia is present if an individual has a hemoglobin (Hb) less than the desired level, for example, the Hb concentration of less than 14 g/dL, more preferably of less than 13 g/dL, more preferably of less than 12 g/dL, more preferably of less than 11 g/dL, or most preferably of less than 10 g/dL.

In certain embodiments, provided herein is a method of increasing the amount of hemoglobin in a subject by administering an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). In certain embodiments, also provided herein is a method of increasing the amount of hemoglobin in a subject having thalassemia comprising administering to the subject an effective amount

of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Further provided is a method of increasing the amount of hemoglobin in subjects having non-transfusion-dependent thalassemia comprising administering an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor) to the subject. In certain embodiments, the provided methods increase hemoglobin concentration in the subject. In certain embodiments, the provided methods increase Hb concentration to a desired level, for example, above 10 g/dL, more preferably above 11 g/dL, more preferably above 12 g/dL, more preferably above 13 g/dL, or most preferably above 14 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 0.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 1.0 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 1.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 2.0 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 2.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 3.0 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 3.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 4.0 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 4.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 5.0 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 5.5 g/dL. In certain embodiments, the provided methods increase Hb concentration by at least about 6.0 g/dL. In certain embodiments, the increase in Hb concentration is determined from baseline at one or more assessment between week 1 and week 20 (e.g., between week 2 and week 15, between week 3 and week 15, and between week 4 and week 12) of treatment with an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). In certain embodiments, the provided methods increase Hb concentration as described above in female subjects having thalassemia (e.g., beta-thalassemia or non-transfusion-dependent thalassemia). In certain embodiments, the provided methods increase Hb concentration from baseline to about 12 g/dL in female subjects having thalassemia (e.g., beta-thalassemia or non-transfusion-dependent thalassemia). In certain embodiments, the provided methods increase Hb concentration as described above in male subjects having thalassemia (e.g., beta-thalassemia or non-transfusion-dependent thalassemia). In certain embodiments, the provided methods increase Hb concentration from baseline to about 13 g/dL in male subjects having thalassemia (e.g., beta-thalassemia or non-transfusion-dependent thalassemia).

In some aspects, provided herein are methods for treating hemolytic anemia in a subject in need thereof comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in treating hemolytic anemia in a subject in need thereof. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for treating hemolytic anemia. In one aspect, the hemolytic anemia to be treated is hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, or anemia as part of a multi-system disease.

In some aspects, provided herein are methods for activating wild-type or mutant PKR in red blood cells in a subject in need thereof comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in activating wild-type or mutant PKR in red blood cells in a subject in need thereof. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for activating wild-type or mutant PKR in red blood cells.

Mitapivat is an activator of PKR mutants having lower activities compared to the wild type, thus are useful for methods of the present disclosure. Such mutations in PKR can affect enzyme activity (catalytic efficiency), regulatory properties (modulation by fructose bisphosphate (FBP)/ATP), and/or thermostability of the enzyme. Examples of such mutations are described in Valentini et al., JBC 2002. Some examples of the mutants that are activated by the compounds described herein include G332S, G364D, T384M, R479H, R479K, R486W, R532W, R510Q, and R490W. Without being bound by theory, in certain embodiments, mitapivat affects the activities of PKR mutants by activating FBP non-responsive PKR mutants, restoring thermostability to mutants with decreased stability, or restoring catalytic efficiency to impaired mutants.

In certain embodiments, mitapivat increases the affinity of PKR to phosphoenolpyruvate (PEP). In certain embodiments, mitapivat restores the ability of RBCs to cover PEP and ADP to pyruvate and ATP.

In certain embodiments, provided herein are methods of reducing transfusion frequency of a subject with PKD comprising administering to the subject mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). In certain embodiments, the transfusion frequency is reduced by at least 5% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 10% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 15% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 20% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 25% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 30% in the number of RBC units

transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 35% in the number of RBC units transfused over at least 15 weeks. In certain embodiments, the transfusion frequency is reduced by at least 40% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 5% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 10% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 15% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 20% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 25% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 30% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 35% in the number of RBC units transfused over at least 20 weeks. In certain embodiments, the transfusion frequency is reduced by at least 40% in the number of RBC units transfused over at least 20 weeks.

In some aspects, provided herein are methods of evaluating the efficacy of mitapivat therapy (monotherapy or concomitant medications with a CYP3A4/5 inducer or a CYP3A4/5 inhibitor) in a subject, the method comprising: administering to the subject mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor); and acquiring a value for the level of mitapivat, the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in the subject, to thereby evaluate the efficacy of the mitapivat therapy. In some aspects, the value for the level is acquired by analyzing the plasma concentration of mitapivat and optionally, the metabolite known to be formed by CYP3A4/5. In some aspects, the level of 2,3-DPG is acquired by analyzing the blood concentration of 2,3-DPG. In some aspects, the level of ATP is acquired by analyzing the blood concentration of ATP. In some aspects, the activity of PKR is acquired by analyzing the blood concentration of a ^{13}C-label in the blood. In some aspects, the analysis is performed by sample analysis of bodily fluid. In some aspects, the bodily fluid is blood. In some aspects, the analysis is performed by mass spectroscopy. In some aspects, the analysis is performed by LC-MS.

In some aspects, provided herein are methods of treating a subject, the method comprising: administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (e.g., a CYP3A4/5 inducer or a CYP3A4/5 inhibitor); and acquiring a value for the level of mitapivat and optionally its metabolite known to be formed by CYP3A4/5, the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in the subject, to thereby treat the subject.

EXEMPLIFICATIONS

As depicted in the Examples below, the drug-drug interactions between mitapivat sulfate and a CYP3A4/5 inducer (e.g., rifampin) or a CYP3A4/5 inhibitor (e.g., itraconazole) are studied. Mitapivat can be synthesized using the procedures described in International Patent Application Publication Nos. WO 2011/002817 and WO 2016/201227.

Example 1: Mitapivat sulfate is primarily metabolized by CYP3A4

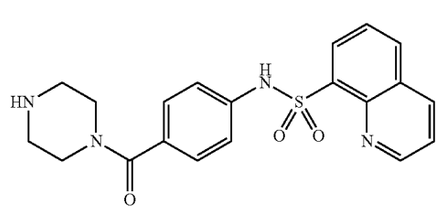
CYP-enzyme phenotyping using human liver microsomes and recombinant CYP enzymes revealed that mitapivat sulfate was primarily metabolized by CYP3A4/5 (>90%), with minor contributions from CYP2C9, CYP2C8, and CYP1A2. There was evidence of metabolism-dependent inhibition of CYP2C19 (largely reversible) and CYP3A4 (largely irreversible). Mitapivat sulfate was found to be a substrate and inhibitor for P-gp but not for breast cancer resistance protein (BCRP) and was found to be a potential inducer of human CYP2B6 and CYP3A4. Mitapivat sulfate appeared to be a mild inhibitor of CYP2C8, CYP2C9, xYP2C19, CYP2D6, and CYP3A4/5 enzymes (testosterone 6β-hydroxylation), bile salts export pump (BSEP), organic anion transporting polypeptide (OATP)1B1, organic anion transporter (OAT)3, and organic cation transporter (OCT)2, and of uridine-5'-diphospho-glucuronosyltransferase (UGT) 1A3, 1A4, and 1A9. Mitapivat sulfate does not appear to be an inhibitor of multidrug resistance-associated protein (MRP)2, MRP3, OATP1B3, and OAT1. The metabolite was found to be a mild inhibitor of CYP2C9 and CYP2C19 and was not an inhibitor of P-gp or BCRP under tested concentrations.

Example 2: Drug-drug Interaction (DDI) Studies of Mitapivat Sulfate and a CYP3A4 Inducer or a CYP3A4 Inhibitor

Twenty-eight (28) healthy, adult male and female (non-childbearing potential) subjects were enrolled in the study in total; 14 subjects in each study part (Parts 1 and 2). A minimum of 8 female subjects were enrolled in the study (i.e., a minimum of 4 female subjects per study part). Each subject participated in either Part 1 or Part 2, but not both.

Part 1

On Day 1 of Treatment Period 1, a single oral dose of 20 mg mitapivat sulfate was administered. Serial blood samples for plasma assay of mitapivat concentrations and its CYP3A4 metabolite, referred to herein as the "Metabolite" (structure below),



were collected from predose to 120 hours following administration of mitapivat sulfate. In Treatment Period 2, an oral dose of 200 mg itraconazole was administered once daily (QD) for 9 consecutive days (Day 1 through Day 9 of Treatment Period 2) with a single oral dose of 20 mg mitapivat sulfate coadministered on Day 5. Serial blood samples for plasma assay of mitapivat and the Metabolite concentrations were collected from predose to 120 hours following coadministration of mitapivat sulfate and itraconazole on Day 5.

In Treatment Period 1, mitapivat sulfate was administered orally with approximately 240 mL of water. In Treatment Period 2, on Days 1 to 4, itraconazole was administered alone immediately followed by approximately 220 mL of water, and on Day 5, itraconazole was administered first (no water) and was immediately followed by mitapivat sulfate administration with approximately 220 mL of water. Study drugs (mitapivat sulfate and itraconazole) were administered following an overnight fast of at least 10 hours on Day 1 of Treatment Period 1 (mitapivat sulfate only) and Day 5 of Treatment Period 2 (mitapivat sulfate and itraconazole), and subjects remained fasted for 4 hours after dosing. On all other dosing days, itraconazole was administered following a predose fast of at least 4 hours and subjects remained fasted for at least 2 hours after dosing.

Part 2

On Day 1 of Treatment Period 1, a single oral dose of 50 mg mitapivat sulfate was administered. Serial blood samples for plasma assay of mitapivat and the Metabolite concentrations were collected from predose to 120 hours following administration of mitapivat sulfate. In Treatment Period 2, an oral dose of 600 mg rifampin was administered QD for 12 consecutive days (Day 1 through Day 12 of Treatment Period 2) with a single oral dose of 50 mg mitapivat sulfate coadministered on Day 8. Serial blood samples for plasma assay of mitapivat sulfate and the Metabolite concentrations were collected from predose to 120 hours following coadministration of mitapivat and rifampin on Day 8.

In Part 2, study drugs were administered with approximately 240 mL of water on all dosing days including the coadministration of mitapivat sulfate and rifampin on Day 8 of Treatment Period 2. Mitapivat sulfate and rifampin was administered following an overnight fast of at least 10 hours on Day 1 of Treatment Period 1 (mitapivat sulfate only) and Day 8 of Treatment Period 2 (both mitapivat sulfate and rifampin) and subjects remained fasted for 4 hours after dosing. On all other dosing days, rifampin was administered following a predose fast of at least 4 hours and subjects remained fasted for at least 2 hours after dosing. There was a washout period of 7 days between the mitapivat sulfate dose in Treatment Period 1 and the first itraconazole (Part 1) or rifampin (Part 2) dose in Treatment Period 2. All study drugs were consumed within 5 minutes for both Part 1 and Part 2.

Test and Reference Products, Dose, Duration and Mode of Administration

Part 1

Mitapivat sulfate (20 mg tablets) administered along with Itraconazole (also referred to as Sporanox®, 10 mg/mL oral solution, is considered as the test arm in this study. Mitapivat sulfate administered alone is considered as the reference arm in this study. In Period 1, a single oral dose of 20 mg mitapivat sulfate was administered orally with approximately 240 mL of water. In Period 2, on Day 5 (coadministration of itraconazole and mitapivat sulfate), 200 mg itraconazole (20 mL of 10 mg/mL oral solution) was administered first (no water) and was immediately followed by 20 mg mitapivat sulfate (1×20 mg tablet) administration with approximately 220 mL of water. On all other dosing days, itraconazole was administered alone immediately followed by approximately 220 mL of water. Each subject received 2 doses of mitapivat sulfate and 9 doses of itraconazole in Part 1.

Part 2

Mitapivat sulfate (50 mg tablets) administered along with Rifampin (also referred to as Rifadin®, 300 mg capsules) is considered as the test arm in this study. Mitapivat sulfate (50 mg tablets) administered alone is considered as the reference arm in this study.

In Period 1, a single oral dose of 50 mg mitapivat sulfate was administered orally. In Period 2, subjects were administered 600 mg rifampin (2×300 mg capsules) QD on Day 1 to Day 12 inclusive, with 50 mg mitapivat sulfate (1×50 mg tablet) coadministered on Day 8. Study drugs were administered with approximately 240 mL of water on all dosing days including the coadministration of mitapivat sulfate and rifampin on Day 8 of Period 2.

Each subject received 2 doses of mitapivat sulfate and 12 doses of rifampin in Part 2.

Duration of Treatment:

The total duration of participation including the screening period for each subject was approximately 49 to 62 days for Part 1 and approximately 61 or 63 days in Part 2 of the study.

In each study part, Treatment Period 1 was approximately 6 days and Treatment Period 2 was approximately 12 days; a washout phase was 7 days between both treatment periods in each study part.

Criteria for Evaluation of Pharmacokinetics

In Parts 1 and 2, for mitapivat and the Metabolite, blood samples were obtained for all subjects to determine the plasma concentrations of mitapivat, and the Metabolite, before mitapivat sulfate dosing (0 hour) on Day 1 of Period 1 (Parts 1 and 2) and Day 5 (Part 1) or Day 8 (Part 2) of Period 2 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours postdose. Plasma concentrations of mitapivat and the Metabolite were determined using methods validated with respect to accuracy, precision, linearity, sensitivity, and specificity, with a lower limit of quantitation (LLOQ) of 0.5 ng/mL for both analytes. A noncompartmental PK approach was used to analyze individual plasma mitapivat and the Metabolite concentration time data (using Phoenix® WinNonlin® Version 7.0). The following PK parameters were calculated: AUC_{0-t}, AUC_{0-inf}, AUC_{0-24}, $AUC_{\%extrap}$, Cmax, CL/F (mitapivat only), Tlast, Tmax, t½, and Vz/F (mitapivat only).

Statistical Methods for Pharmacokinetics

The plasma concentrations of mitapivat and the Metabolite were listed and summarized by treatment and collection time for all subjects in the PK Population. Plasma concentrations were presented with the same level of precision as received from the bioanalytical laboratory including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, maximum, and median. Concentrations from excluded subjects were included in the plasma concentration tables, but were excluded from the summary statistics and noted as such in the tables. All BLQ values were presented as "BLQ" in the plasma concentration table listings and footnoted accordingly.

PK parameters were presented with a minimum of 3 significant figures. PK parameters were listed by subject, tabulated by treatment, and summarized using descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, geometric mean (Geom. Mean) and geometric mean coefficient of variation (Geom. CV%). Time-based parameters (i.e., Tmax and t½) and treatment:reference AUC and Cmax ratios were presented to 2 decimals. Excluded subjects were included in the PK parameter table listings, but were excluded from the summary statistics and noted as such in the tables.

To evaluate the effect of itraconazole and rifampin on mitapivat and the Metabolite (primary objective), plasma mitapivat and the Metabolite PK parameters (Cmax, AUC_{0-t}, and AUC_{0-inf}) were natural log (ln) transformed before analysis. The ln-transformed value of the PK parameters was analyzed using a linear mixed effect model for each study part separately with treatment as a fixed effect and subject as a random effect. The linear mixed effect model included treatment as a fixed effect and subject as a random effect. The inferential results (least-squares means [LSMs], difference between LSMs, and 90% confidence intervals [CIs] of the difference) were back transformed to the original scale. Geometric LSMs, geometric mean ratios (GMRs), and 90% CIs were presented. The GMR of the LSMs were calculated from the back-transformed difference between the treatment LSMs. The GMRs were expressed as a percentage relative to mitapivat sulfate given alone for both Part 1 and Part 2. The 90% CIs for the ratios were derived by back-transformation of the CIs obtained for the difference between the treatment LSMs. The CIs were expressed as a percentage relative to mitapivat sulfate given alone for both Part 1 and Part 2.

The median differences in Tmax for evaluation of the effect of itraconazole and rifampin on mitapivat and the Metabolite along with the range of the difference were calculated using the non parametric Wilcoxon Signed Rank test, and the p-value was presented. Note that Tmax was not ln-transformed for these analyses.

Pharmacokinetic Results

Part 1

Mean plasma mitapivat and the Metabolite concentration-time profiles following 20 mg mitapivat sulfate administered alone (Period 1) or coadministered with multiple doses of 200 mg itraconazole (Period 2) on linear and semi-log scales are presented in FIGS. **1** and **2**.

Mitapivat

Mitapivat plasma concentrations were detectable in all subjects at 0.5 hour (the first scheduled postdose sample) in both Periods 1 and 2. Mitapivat was still detectable up to the last sample time at 120 hours postdose in the majority of subjects in Period 1 and in all subjects in Period 2.

Measurable predose mitapivat concentrations were present in all but 2 subjects in Period 2 (two subjects were BLQ). As used herein, BLQ refers to below the limit of quantification. These predose concentrations were <5% of the Cmax, so PK calculations were performed.

Mitapivat concentrations exhibited a characteristic multi-compartmental pharmacokinetic profile. When coadministered with itraconazole, mitapivat concentrations rose to a higher mean peak with a delay in time to peak by approximately 2 hours compared to when the drug was administered alone. The post-peak decline of the multi-compartmental behavior was slower after coadministration with itraconazole when compared to mitapivat administered alone. Overall, higher mitapivat concentrations were experienced for a longer time period when mitapivat was coadministered with itraconazole.

The Metabolite

When mitapivat was administered alone, the Metabolite plasma concentrations were detectable in all but 1 subject at 0.5 hour. The Metabolite remained detectable all but 1 subject up to 48 hours postdose, with quantifiable the Metabolite out to 72 hours in 3 subjects and 96 hours in 1 subject. In Period 2 (coadministration with itraconazole), the Metabolite concentrations were delayed relative to administration of mitapivat alone. Concentrations were not measurable in all subjects until 1.5 hours postdose. Maximum concentrations were also reduced. However, the Metabolite residence was prolonged in the presence of itraconazole, with concentrations still detectable in all but 1 subject throughout the 120-hour sampling interval (in 1 subject the last measurable concentration was at 96 hours postdose).

The statistical comparisons of mitapivat PK parameters following 20 mg mitapivat sulfate administered alone (Period 1) or coadministered with multiple doses of 200 mg itraconazole (Period 2) PK parameters are summarized below in Table 1.

TABLE 1

Summary of Statistical Comparisons of Plasma Mitapivat Pharmacokinetic Parameters Following 20 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 200 mg Itraconazole Versus Administered Alone (Part 1)

	Mitapivat Sulfate + Itraconazole (Test)		Mitapivat sulfate alone (Reference)				
Parameter (unit)	Geometric LSM	n	Geometric LSM	n	GMR	90% Confidence Interval	Intra-subject CV %
AUC_{0-t} (ng*hr/mL)	8860	14	1885	14	4.6998	4.2519-5.1949	15.05
AUC_{0-inf} (ng*hr/mL)	9475	14	1942	14	4.8780	4.4154-5.3890	14.97
C_{max} (ng/mL)	704.3	14	412.5	14	1.7074	1.5815-1.8433	11.48

Mitapivat sulfate alone: 20 mg mitapivat sulfate (1 × 20 mg tablet) at Hour 0 on Day 1 (Period 1)
Mitapivat sulfate + itraconazole: 200 mg itraconazole (20 mL of 10 mg/mL oral solution) QD on Days 1 to Day 9 inclusive (within ± 1 hour of dosing time on Day 1) with 20 mg mitapivat sulfate (1 × 20 mg tablet) coadministered at Hour 0 on Day 5 (Period 2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed effect model.
Geometric Mean Ratio (GMR) = test/reference
Intra-subject CV % = 100 × (square root (exp[MSE] − 1), where MSE = Residual variance from linear mixed effect model.

The coadministration of 200 mg itraconazole with 20 mg mitapivat sulfate increased mitapivat exposure relative to when mitapivat sulfate was administered alone. The geometric mean AUC_{0-t} and AUC_{0-inf} ratios of mitapivat in the presence and absence of itraconazole were 4.7 and 4.9, respectively. The geometric mean Cmax ratio of mitapivat in the presence and absence of itraconazole was 1.7. The intra-subject variability was low at approximately 15% for AUCs and 11% for Cmax.

The statistical comparisons of the Metabolite PK parameters following 20 mg mitapivat sulfate administered alone (Period 1) or coadministered with multiple doses of 200 mg itraconazole (Period 2) PK parameters are summarized below in Table 2.

TABLE 2

Summary of Statistical Comparisons of Plasma Metabolite Pharmacokinetic Parameters Following 20 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 200 mg Itraconazole Versus Administered Alone (Part 1)

	Mitapivat Sulfate + Itraconazole (Test)		Mitapivat sulfate alone (Reference)				
Parameter (unit)	Geometric LSM	n	Geometric LSM	n	GMR	90% Confidence Interval	Intra-subject CV %
AUC_{0-t} (ng*hr/mL)	300.0	14	197.1	14	1.5218	1.4268-1.6231	9.65

TABLE 2-continued

Summary of Statistical Comparisons of Plasma Metabolite Pharmacokinetic Parameters Following 20 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 200 mg Itraconazole Versus Administered Alone (Part 1)

Parameter (unit)	Mitapivat Sulfate + Itraconazole (Test) Geometric LSM	n	Mitapivat sulfate alone (Reference) Geometric LSM	n	GMR	90% Confidence Interval	Intra-subject CV %
$AUC_{0\text{-}inf}$ (ng*hr/mL)	338.6	14	216.2	14	1.5661	1.4784-1.6590	8.63
C_{max} (ng/mL)	9.110	14	18.79	14	0.4849	0.4441-0.5295	13.20

Mitapivat sulfate alone: 20 mg mitapivat sulfate (1 × 20 mg tablet) at Hour 0 on Day 1 (Period 1)
Mitapivat sulfate + itraconazole: 200 mg itraconazole (20 mL of 10 mg/mL oral solution) QD on Days 1 to Day 9 inclusive (within ± 1 hour of dosing time on Day 1) with 20 mg mitapivat sulfate (1 × 20 mg tablet) coadministered at Hour 0 on Day 5 (Period 2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed effect model.
Geometric Mean Ratio (GMR) = test/reference
Intra-subject CV % = 100 × (square root (exp[MSE] − 1), where MSE = Residual variance from linear mixed effect model.

The coadministration of 200 mg itraconazole with 20 mg mitapivat sulfate increased total Metabolite exposure relative to when mitapivat sulfate was administered alone. The geometric mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ ratios of the Metabolite in the presence and absence of itraconazole were 1.5 and 1.6, respectively. The geometric mean Cmax ratio of the Metabolite in the presence and absence of itraconazole was 0.5. The intra-subject variability was low at approximately 9% to 10% for AUCs and 13% for Cmax.

Part 2

Mean plasma mitapivat and metabolite the Metabolite concentration-time profiles following 50 mg mitapivat sulfate administered alone (Period 1) or coadministered with multiple doses of 600 mg rifampin (Period 2) on linear and semi-log scales are presented in FIGS. **3** and **4**.

Mitapivat

Mitapivat plasma concentrations were detectable in all subjects at 0.5 hour (the 1st scheduled postdose sample) when given alone or with rifampin. Mitapivat was still detectable up to the last sample time at 120 hours postdose in all but 1 subject when given alone had a BLQ concentration at 120 hours). When coadministered with rifampin, detectable mitapivat concentrations were not present in any sample collections from any subject beyond 24 hours postdose (except 1 subject with detectable mitapivat at 48 hours).

Mitapivat concentrations increased to a lower and slightly earlier peak when coadministered with rifampin compared to when administered alone. The peak arithmetic mean mitapivat concentrations were observed at a nominal time of approximately 1 hour postdose for Period 1 and 0.5 hour postdose for Period 2. The mean concentrations of mitapivat then declined in a multi exponential manner for both periods; however, the post-peak initial decline in mitapivat concentrations was more rapid and to lower levels when coadministered with rifampin compared to dosing alone.

The Metabolite

The Metabolite plasma concentrations were detectable at 0.5 hour postdose in all subjects after mitapivat sulfate was given alone and in all but 1 subject (1 subject was reported as BLQ) when mitapivat sulfate was coadministered with rifampin. The Metabolite was still detectable in all but 4 subjects up to the last scheduled sampling time of 120 hours postdose when mitapivat sulfate was given alone. When mitapivat sulfate was coadministered with rifampin, the Metabolite remained detectable in all subjects up to 24 hours postdose, with quantifiable the Metabolite out to 48 hours in 6 subjects and 72 hours in 1 subject. No Metabolite concentrations were detectable in samples collected beyond 72 hours.

The peak arithmetic mean Metabolite concentrations were observed at a nominal time of approximately 2 hours postdose with mitapivat sulfate given alone and 1 hour when mitapivat sulfate was coadministered with rifampin. When mitapivat sulfate was given alone, higher mean concentrations the Metabolite were observed over the initial 1 hour postdose. Metabolite concentrations were higher when mitapivat sulfate was coadministered with rifampin beyond 1 hour. The mean concentrations of the Metabolite then declined in a multi exponential fashion for both treatments. Decline in Metabolite concentrations was more rapid when mitapivat sulfate was coadministered with rifampin.

The statistical comparisons of mitapivat PK parameters following 50 mg mitapivat sulfate administered alone (Period 1) or coadministered with multiple doses of 600 mg rifampin (Period 2) PK parameters are summarized below in Table 3.

TABLE 3

Summary of Statistical Comparisons of Plasma Mitapivat Pharmacokinetic Parameters Following 50 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 600 mg Rifampin Versus Administered Alone (Part 2)

Parameter (unit)	Mitapivat sulfate + rifampin (Test) Geometric LSM	n	Mitapivat sulfate alone (Reference) Geometric LSM	n	GMR	90% Confidence Interval	Intra-subject CV %
$AUC_{0\text{-}t}$ (ng*hr/mL)	486.4	14	5565	14	0.0874	0.0719-0.1062	29.73
$AUC_{0\text{-}inf}$ (ng*hr/mL)	496.4	14	5681	14	0.0874	0.0719-0.1062	29.84
C_{max} (ng/mL)	292.4	14	1263	14	0.2316	0.1933-0.2773	27.45

Mitapivat sulfate alone: 50 mg mitapivat sulfate (1 × 50 mg tablet) at Hour 0 on Day 1 (Period 1)
Mitapivat sulfate + rifampin: 600 mg rifampin (2 × 300 mg capsules) QD on Day 1 to Day 12 inclusive (within ± 1 hour of dosing time on Day 1) with 50 mg mitapivat sulfate (1 × 50 mg tablet) coadministered at Hour 0 on Day 8 (Period 2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed effect model.
Geometric Mean Ratio (GMR) = test/reference
Intra-subject CV % = 100 × (square root (exp[MSE] − 1), where MSE = Residual variance from linear mixed effect model.

The coadministration of 600 mg rifampin with 50 mg mitapivat sulfate decreased mitapivat exposure relative to when mitapivat sulfate was administered alone. The geometric mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ ratios of mitapivat in the presence and absence of rifampin were 0.09. The geometric mean Cmax ratio of mitapivat in the presence and absence of rifampin was 0.23. The intra-subject variability was low at approximately 30% for AUCs and 27% for Cmax.

The statistical comparisons of Metabolite PK parameters following 50 mg mitapivat sulfate administered alone (Period 1) or co-administered with multiple doses of 600 mg rifampin (Period 2) PK parameters are summarized below in Table 4.

TABLE 4

Summary of Statistical Comparisons of Plasma Metabolite Pharmacokinetic Parameters Following 50 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 600 mg Rifampin Versus Administered Alone (Part 2)

	Mitapivat sulfate + rifampin (Test)		Mitapivat sulfate alone (Reference)				
Parameter (unit)	Geometric LSM	n	Geometric LSM	n	GMR	90% Confidence Interval	Intra-subject CV %
AUC_{0-t} (ng*hr/mL)	230.5	14	623.0	14	0.3700	0.3316-0.4129	16.50
AUC_{0-inf} (ng*hr/mL)	244.9	14	662.6	14	0.3696	0.3321-0.4113	16.08
C_{max} (ng/mL)	64.47	14	53.80	14	1.1983	1.0642-1.3492	17.86

Mitapivat sulfate alone: 50 mg mitapivat sulfate (1 × 50 mg tablet) at Hour 0 on Day 1 (Period 1)
Mitapivat sulfate + rifampin: 600 mg rifampin (2 × 300 mg capsules) QD on Day 1 to Day 12 inclusive (within ± 1 hour of dosing time on Day 1) with 50 mg mitapivat sulfate (1 × 50 mg tablet) coadministered at Hour 0 on Day 8 (Period 2)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed effect model.
Geometric Mean Ratio (GMR) = test/reference
Intra-subject CV % = 100 × (square root (exp[MSE] − 1), where MSE = Residual variance from linear mixed effect model.

The coadministration of 600 mg rifampin with 50 mg mitapivat sulfate decreased the Metabolite exposure relative to when mitapivat sulfate was administered alone. The geometric mean AUC0-t and AUC0-inf ratios of the Metabolite in the presence versus absence of rifampin were 0.37. The geometric mean Cmax ratio of the Metabolite in the presence versus absence of rifampin was 1.2. The intra-subject variability was low at approximately 16% to 18% for AUCs and Cmax.

Conclusions

Total exposure of mitapivat increased in the presence of itraconazole compared to dosing of mitapivat sulfate alone.

Total exposure of mitapivat decreased in the presence of rifampin compared to dosing of mitapivat sulfate alone.

Example 3. Development of a PBPK Model for Mitapivat Sulfate to Evaluate the Potential for Drug-Drug Interactions

Part I

A physiologically based pharmacokinetic model (hereinafter "PBPK" model) for mitapivat sulfate based on the currently available in-vitro and clinical PK data is being developed. The developed PBPK model will be used to assess DDI liability with mitapivat sulfate acting as a victim of CYP3A4-mediated metabolism as well as a perpetrator of CYP and transporter mediated DDI.

Specifically, a PBPK model that includes a simple first order absorption model will be developed. Full PBPK and minimal PBPK distribution models will be evaluated, both of which consider liver and intestinal metabolism. The fraction of mitapivat sulfate absorbed will be estimated from mass balance data from the [14C] human ADME study (Clinical Study AG348-C-009). In-vitro data will be used to assign the relative contribution of CYP3A4 to the clearance of mitapivat sulfate. K_I and K_{inact} values for mechanism based inhibition of CYP3A4 and CYP3A4 induction (Emax and EC50) data by mitapivat sulfate will be incorporated within the PBPK model to assess the net DDI effects at steady state. Once an mitapivat sulfate PBPK model has been verified against the available clinical data, a series of DDI simulations assessing mitapivat sulfate as a victim or perpetrator of DDI will be performed in healthy volunteers.

Experiments with mitapivat sulfate as a victim

The impact of the co-administration of the strong CYP3A4 inhibitor, itraconazole, on the PK of mitapivat sulfate will be determined based on the following single and multiple-dose administration of 5, 20 and 50 mg BID.

The impact of the co-administration of the strong CYP3A4 inhibitor, ketoconazole, on the PK of mitapivat sulfate will be determined based following single and multiple-dose administration of 5, 20 and 50 mg BID.

The impact of the co-administration of the moderate CYP3A4 inhibitor fluconazole on the PK of mitapivat sulfate will be determined based on the following single and multiple dose administration of 5, 20 and 50 mg BID.

The impact of the co-administration of the mild CYP3A4 inhibitor cimetidine on the PK of mitapivat sulfate will be determined based on the following single- and multiple dose administration of 5, 20 and 50 mg BID.

The impact of the co-administration of the strong CYP3A4 inducer, rifampin, on the PK of mitapivat sulfate will be determined based on the following single and multiple dose administration of 5, 20 and 50 mg BID.

The impact of the co-administration of the moderate CYP3A4 inducer efavirenz on the PK of mitapivat sulfate will be determined following single and multiple dose administration of 5, 20 and 50 mg BID.

Experiments with mitapivat sulfate as perpetrator

The extent to which 5 to 50 mg BID mitapivat sulfate affects the systemic exposure of CYP3A4 substrate midazolam when co-administered with mitapivat sulfate will be determined.

The effect of 5 to 50 mg mitapivat sulfate on the systemic exposures of CYP2B6 substrate bupropion when co-administered will be determined. CYP2B6 induction (Emax and EC50) data by mitapivat sulfate will be incorporated within the PBPK model. Sensitivity analysis will be conducted to gauge the impact of the uncertainty around Emax and EC50 on the predicted DDIs.

The effect of 5 to 50 mg AG mitapivat sulfate BID on the systemic exposures of CYP2C9 substrate warfarin when co-administered will be determined. CYP2C9 induction (Emax and EC50) data by mitapivat sulfate will be incorporated within the PBPK model. Sensitivity analysis will be conducted to gauge the impact of the uncertainty around Emax and EC50 on the predicted DDIs.

The effect of 5 to 50 mg mitapivat sulfate BID on the systemic exposures of CYP2C8/CYP3A4 substrate repaglinide when co-administered will be determined. CYP2C8 induction (Emax and EC50) data by mitapivat sulfate will be incorporated within the PBPK model. Sensitivity analysis will be conducted to gauge the impact of the uncertainty around Emax and EC50 on the predicted DDIs.

The effect of 5 to 50 mg mitapivat sulfate BID on the systemic exposures of CYP2C19 substrate omeprazole when co-administered will be determined. CYP2C19 induction (Emax and EC50) data by mitapivat sulfate will be incorporated within the PBPK model. Sensitivity analysis will be conducted to gauge the impact of the uncertainty around Emax and EC50 on the predicted DDIs.

The effect of mitapivat sulfate (5 to 50 mg BID) on the systemic exposures of OATP1B1/OATP1B3 (rosuvastatin), P-gp (digoxin), metformin (MATE1 and OCT2), OAT3 (methotrexate) substrate drugs when co-administered will be determined. The respective IC50 values for inhibition of OATP1B1, P-gp, MATE1, OCT2 and OAT3 by mitapivat sulfate will be incorporated within the PBPK model. Sensitivity analysis will be performed to assess the impact of these parameters on the DDI liability of mitapivat sulfate.

Part II

The first order absorption component of the previously developed PBPK model will be extended using available pH solubility data to include the ADAM model. The recovery of mitapivat sulfate plasma concentration profiles after single and multiple dosing (up to 50 mg BID) to healthy volunteer subjects will be demonstrated. Once verified against the available clinical data, the modified PBPK model will be used to assess the impact of an increase in gastric pH on the pharmacokinetics of mitapivat sulfate via manipulation of system parameters (gastric pH).

While a number of embodiments have been described, the scope of this disclosure is to be defined by the appended claims, and not by the specific embodiments that have been represented by way of example. The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

What is claimed is:

1. A method of treating hemolytic anemia in a subject, comprising administering to the subject about 10 mg/day, about 40 mg/day, about 100 mg/day, or about 200 mg/day of mitapivat or a pharmaceutically acceptable salt thereof and a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5).

2. The method of claim **1**, wherein the subject is administered about 10 mg/day of mitapivat or a pharmaceutically acceptable salt thereof.

3. The method of claim **2**, wherein the subject is administered about 5 mg of mitapivat or a pharmaceutically acceptable salt thereof twice per day.

4. The method of claim **1**, wherein the subject is administered about 40 mg/day of mitapivat or a pharmaceutically acceptable salt thereof.

5. The method of claim **4**, wherein the subject is administered about 20 mg of mitapivat or a pharmaceutically acceptable salt thereof twice per day.

6. The method of claim **1**, wherein the subject is administered about 100 mg/day of mitapivat or a pharmaceutically acceptable salt thereof.

7. The method of claim **6**, wherein the subject is administered about 50 mg of mitapivat or a pharmaceutically acceptable salt thereof twice per day.

8. The method of claim **1**, wherein the subject is administered about 200 mg/day of mitapivat or a pharmaceutically acceptable salt thereof.

9. The method of claim **6**, wherein the subject is administered about 100 mg of mitapivat or a pharmaceutically acceptable salt thereof twice per day.

10. The method of claim **1**, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition.

11. The method of claim **3**, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition.

12. The method of claim **5**, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition.

13. The method of claim **7**, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition.

14. The method of claim **9**, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition.

15. The method of claim **10**, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

16. The method of claim **11**, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

17. The method of claim **12**, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

18. The method of claim **13**, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

19. The method of claim **14**, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate.

* * * * *

Bibliographic Data

Application No: 16/900,610

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /GEORGE W KOSTURKO/ Examiner's Signature | Initials

Title: MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/12/2020	424	1621	128748-01502
RULE			

APPLICANTS

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INVENTORS

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Chandra Agarwal Prakash, North Andover, MA, UNITED STATES

Hua Yang, Acton, MA, UNITED STATES

CONTINUING DATA

This application has PRO of 62861600 06/14/2019

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

06/18/2020

STATE OR COUNTRY

UNITED STATES

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UNITED STATES

FILING FEE RECEIVED

$1,720

Bibliographic Data

Application No: 16/900,610

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /GEORGE W KOSTURKO/ (Examiner's Signature) ____ (Initials)

Title: MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/12/2020	424	1628	128748-01502
RULE			

APPLICANTS

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Chandra Agarwal Prakash, North Andover, MA, UNITED STATES

Hua Yang, Acton, MA, UNITED STATES

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06/18/2020

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Bibliographic Data

Application No: 16/900,610

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This application has PRO of 62861600 06/14/2019

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06/18/2020

STATE OR COUNTRY

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$1,720

Electronic Acknowledgement Receipt	
EFS ID:	39709998
Application Number:	16900610
International Application Number:	
Confirmation Number:	1054
Title of Invention:	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450
First Named Inventor/Applicant Name:	Varsha Venkatachalam Iyer
Customer Number:	86738
Filer:	Steven G. Davis
Filer Authorized By:	
Attorney Docket Number:	128748-01502
Receipt Date:	12-JUN-2020
Filing Date:	
Time Stamp:	18:23:19
Application Type:	Utility under 35 USC 111(a)

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Payment Type	DA
Payment was successfully received in RAM	$1720
RAM confirmation Number	E20206BI23490036
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	128748-01502_-_Application_Data_Sheet_Fillable_PDF.pdf	1255683 50404fac34bcaf473e2152102a58aa24e989cadb	no	9
Warnings:					
Information:					
2	Nonpublication request from applicant	Nonpublication_Request.pdf	17330 639a8ba90447c12ffe8c2572751b550b7a5f8e33	no	1
Warnings:					
Information:					
3	Transmittal of New Application	Utility_Patent_Application_Transmittal.pdf	32100 91e7743ee623b3e3f56304c7a76a66338ae9bbe2	no	1
Warnings:					
Information:					
4	Specification	06122020_SPECIFICATION_.pdf	268736 3891c6d042fffd63732040701fd44ba810171573	no	70
Warnings:					
Information:					
5	Drawings-only black and white line drawings	06122020_FIGURES_FOR_FILING.pdf	745862 e8526be9c56c2aab29f775b0d5ae03c6490aea8c	no	4
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	34922 b74e49cf202e9c61d17b902eebe0cd2ccf4d32a9	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	2354633

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
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Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

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Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

City	Acton	State/Province	MA	Country of Residence i	US

Mailing Address of Inventor:

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Postal Code	02139	**Country** i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	86738		
Email Address	docket@mccarter.com	Add Email	Remove Email

Application Information:

Title of the Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450		
Attorney Docket Number	128748-01502	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☒ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	◯ Limited Recognition (37 CFR 11.9)
Customer Number	86738		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62/861600	2019-06-14

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Agios Pharmaceuticals, Inc.		
Mailing Address Information For Applicant:			
Address 1	88 Sidney Street		
Address 2			
City	Cambridge	**State/Province**	MA
Country	US	Postal Code	02139
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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Signature:

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NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Steven G. Davis/			Date (YYYY-MM-DD)	2020-06-12
First Name	Steven	Last Name	Davis	Registration Number	39,652

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	128748-01502
	Application Number	
Title of Invention	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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NONPUBLICATION REQUEST UNDER 35 U.S.C. 122(b)(2)(B)(i)		
	First Named Inventor	Varsha Venkatachalam Iyer
	Title	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450
	Attorney Docket Number	128748-01502

I hereby certify that the invention disclosed in the attached application **has not and will not be** the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

I hereby request that the attached application not be published under 35 U.S.C. 122(b).

/Steven G. Davis/	June 12, 2020
Signature	Date
Steven G. Davis, Ph.D.	39,652
Typed or printed name	Registration Number, if applicable
(617) 449-6580	
Telephone Number	

This request must be signed in compliance with 37 CFR 1.33(b) and submitted with the application **upon filing.**

Applicant may rescind this nonpublication request at any time. If applicant rescinds a request that an application not be published under 35 U.S.C. 122(b), the application will be scheduled for publication at eighteen months from the earliest claimed filing date for which a benefit is claimed.

If applicant subsequently files an application directed to the invention disclosed in the attached application in another country, or under a multilateral international agreement, that requires publication of applications eighteen months after filing, the applicant **must** notify the United States Patent and Trademark Office of such filing within forty-five (45) days after the date of the filing of such foreign or international application. **Failure to do so will result in abandonment of this application (35 U.S.C. 122(b)(2)(B)(iii)).**

PTO/AIA/15 (10-17)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	128748-01502
First Named Inventor	Varsha Venkatachalam Iyer
Title	MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] **Specification** [*Total Pages* 70]
   Both the claims and abstract must start on a new page.
   (See MPEP § 608.01(a) for information on the preferred arrangement)
5. [X] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 4]
6. **Inventor's Oath or Declaration** [*Total Pages*]
   (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [X] **Application Data Sheet** * *See note below.*
   See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [ ] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [X] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] **Other:**

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 86738 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Steven G. Davis/	Date	June 12, 2020
Name (Print/Type)	Steven G. Davis, Ph.D.	Registration No. (Attorney/Agent)	39,652

MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

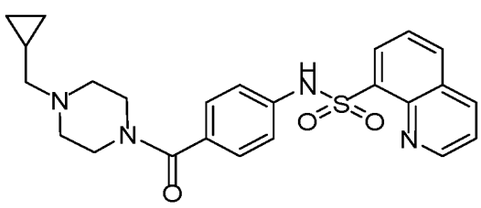
RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 62/861,600, filed June 14, 2019, the entire teachings of which are incorporated herein by reference.

BACKGROUND

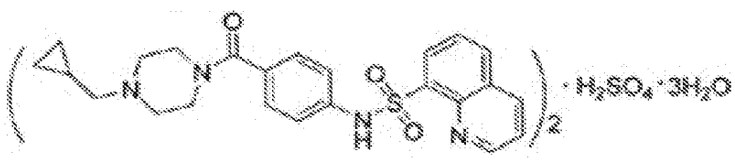
[0001] Pyruvate kinase deficiency (PKD) is a disease of the red blood cells caused by a deficiency of the pyruvate kinase R (PKR) enzyme due to recessive mutations of PKLR gene. PKR activators can be beneficial to treat PKD, thalassemia (*e.g.*, beta-thalassemia), abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, anemia (*e.g.*, congenital anemias (*e.g.*, enzymopathies), hemolytic anemia (*e.g.* hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, anemia of chronic diseases, non-spherocytic hemolytic anemia or hereditary spherocytosis). Treatment of PKD is supportive, including blood transfusions, splenectomy, chelation therapy to address iron overload, and/or interventions for other disease-related morbidity. Currently, however, there is no approved medicine that treats the underlying cause of PKD, and thus the etiology of life-long hemolytic anemia.

[0002] Mitapivat, also known as AG-348 or by its chemical name *N*-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide, and is represented by the following structural formula:



is an allosteric activator of pyruvate kinase R (PKR). See *e.g.*, International Patent Application Publication Nos. WO 2011/002817 and WO 2016/201227.

[0003] Mitapivat sulfate that is represented by the following structural formula:



is currently in Phase 2 and Phase 3 clinical trials as a disease-altering therapy in patients with PKD, hemolytic anemia and thalassemia. See *e.g.*, U.S. Clinical Trials Identifier Nos. NCT03692052, NCT03559699, NCT03548220, NCT03853798, and NCT02476916.

SUMMARY

[0004] Non-clinical studies described in Example 1 show that the PKR activator, mitapivat, is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5) enzymes (*i.e.*, >90%), with minor contributions from other detoxification enzymes, namely CYP2C8, CYP2C9, and CYP1A2. It has also been found that in a clinical trial, total exposure of mitapivat increased in the presence of itraconazole, a strong CYP3A4A and p-gp inhibitor, compared with dosing of mitapivat sulfate alone. It has further been found that total exposure of mitapivat decreased in the presence of rifampin, a strong CYP3A4A and p-gp inducer, compared with dosing of mitapivat sulfate alone.

[0005] Accordingly, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor. In another aspect, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof and a p-glycoprotein (p-gp) inhibitor. As used herein, "CYP3A4/5" means cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In some embodiments, the pharmaceutically acceptable salt is mitapivat sulfate.

[0006] Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5) . In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a

pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g. alpha-thalassemia and beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5). In some embodiments, the inhibitor of CYP3A4/5 is a moderate CYP3A4/5 inhibitor. In some embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inhibitor.

[0007] In another embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5) . In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g. alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4/5 (CYP3A4/5). In some embodiments, the inducer of CYP3A4/5 is a moderate CYP3A4/5 inducer. In some embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inducer.

[0008] Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure

relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating thalassemia (e.g. alpha-thalassemia and beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating hemolytic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of a p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a moderate p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a mild p-glycoprotein inhibitor.

[0009] The present disclosure further provides methods of treating a disease, disorder or a condition with mitapivat or a pharmaceutically acceptable salt thereof in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or p-glycoprotein inhibitor.

[0010] Specifically, in one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In yet another embodiment, the present disclosure relates to a method of treating thalassemia (e.g. alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In yet another embodiment, the present disclosure relates to a method of treating hemylotic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer or an inhibitor of cytochrome P450 3A4/5 (CYP3A4/5), respectively. In some embodiments, the inducer of CYP3A4/5 is a strong inducer of CYP3A4/5. In some embodiments, the inducer of

CYP3A4/5 is a moderate inducer of CYP3A4/5. In some embodiments, the inhibitor of CYP3A4/5 is a strong inhibitor of CYP3A4/5. In some embodiments, the inhibitor of CYP3A4/5 is a moderate inhibitor of CYP3A4/5.

[0011] In another embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In yet another embodiment, the present disclosure relates to a method of treating thalassemia (e.g. alpha-thalassemia and/or beta-thalassemia) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In yet another embodiment, the present disclosure relates to a method of treating hemylotic anemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-glycoprotein inhibitor. In some embodiments, the p-glycoprotein inhibitor is a strong p-glycoprotein inhibitor. In some embodiments, In some embodiments, the p-glycoprotein inhibitor is a mild p-glycoprotein inhibitor.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graph showing Arithmetic Mean (SD) Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 20 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 200 mg itraconazole (Treatment Period 2) on linear scale (Part 1). **"Metabolite"** refers to the CYP3A4 metabolite of mitapivat (see Example 2).

Figure 2 is a graph showing Arithmetic Mean Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 20 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 200 mg itraconazole (Treatment Period 2) on semi-log scale (Part 1) (see Example 2).

Figure 3 is a graph showing Arithmetic Mean (SD) Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 50 mg mitapivat sulfate alone

(Treatment Period 1) and co-administered with multiple doses of 600 mg rifampin on linear scale (Treatment Period 2, Part 2, see Example 2).

Figure 4 is a graph showing Arithmetic Mean Plasma Mitapivat and Metabolite Concentration-Time Profiles following administration of 50 mg mitapivat sulfate alone (Treatment Period 1) and co-administered with multiple doses of 600 mg rifampin on semi-log scale (Treatment Period 2, Part 2, see Example 2)

DETAILED DESCRIPTION

Definitions

[0012]
"CYP3A4/5 modulator" refers to any substance, including, but not limited to a small molecule (with a molecular weight of ≤ 1000 Da, or ≤ 750 Da, or ≤ 500 Da), a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a polysaccharide, a peptide, a polypeptide, a protein, an antibody, an aptamer, a natural or synthetic plant-based substance, or a complex or a composition comprising any combination of the aforementioned substances, that can modify or alter the activity and/or expression levels of the enzyme cytochrome P450 3A4 (CYP3A4; EC 1.14.13.97) or 3A5 (CYP3A5; EC1.14.14.1). Briefly, the cytochrome P450 (CYP) is a superfamily of detoxification enzymes that are responsible for the oxidative and reductive metabolic transformation of drug medications and the ultimate "clearance", which is the elimination of the drug from the body as determined by the measured plasma levels of the drug and optionally, the drug metabolites, such as the metabolite known to be formed by CYP3A4/5. CYP3A4 and CYP3A5 are two of such enzymes and are largely prevalent in the liver.

[0013] A CYP3A4/5 modulator may be a CYP3A4/5 inducer or a CYP3A4/5 inhibitor. A "CYP3A4/5 inducer" or "inducer of CYP3A4/5" is a CYP3A4/5 modulator as defined above that can increase, enhance, stimulate, induce, accelerate or augment the CYP3A4/5 activity from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, *e.g.*, the level of the CYP3A4/5 activity and/or expression prior to the exposure or contact with the CYP3A4/5 inducer, including all ranges and values therebetween not expressly mentioned above. The CYP3A4/5 inducer activity may cause mitapivat or a pharmaceutically acceptable

salt thereof that is co-administered with the CYP3A4/5 inducer to be metabolized and eliminated more quickly from the body, as determined by the measured plasma levels of the compound and its metabolites.

[0014] A "CYP3A4/5 inhibitor" or "inhibitor of CYP3A4/5" is a CYP3A4/5 modulator as defined above that can decrease, reduce, inhibit, decelerate, attenuate, or suppress the CYP3A4/5 activity and/or expression from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, *e.g.*, the level of the CYP3A4/5 activity and/or expression prior to the exposure or contact with the CYP3A4/5 inhibitor, including all ranges and values therebetween not expressly mentioned above. The CYP3A4/5 inhibitor may cause mitapivat or a pharmaceutically acceptable salt thereof that is co-administered with the CYP3A4/5 inhibitor to be metabolized and eliminated more slowly from the body, as determined by the measured plasma levels of the compound and its metabolites.

[0015] If an investigational drug is a CYP inducer, it can be classified as a strong, moderate, or mild inducer based on its effect on an index CYP substrate. The convention is to categorize CYP induction in the following ways:

[0016] A strong inducer decreases the AUC of a sensitive index CYP by ≥ 80 percent.

[0017] A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥ 50 to < 80 percent.

[0018] A mild inducer decreases the AUC of a sensitive index CYP substrate by ≥ 20 to < 50 percent."

[0019] A CYP inhibitor can be classified as a strong, moderate, or mild inhibitor based on its effect on an index CYP substrate. A strong inhibitor increases the AUC of a sensitive index CYP substrate ≥ 5-fold. A moderate inhibitor increases the AUC of a sensitive index CYP substrate by ≥ 2- to < 5-fold. A mild inhibitor increases the AUC of a sensitive index CYP substrate by ≥ 1.25- to < 2- fold."

[0020] A p-glycoprotein inhibitor refers to any substance, including, but not limited to a small molecule (with a molecular weight of ≤ 1000 Da, or ≤ 750 Da, or ≤ 500 Da), a

nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a polysaccharide, a peptide, a polypeptide, a protein, an antibody, an aptamer, a natural or synthetic plant-based substance, or a complex or a composition comprising any combination of the aforementioned substances, that can decrease, reduce, inhibit, decelerate, attenuate, or suppress the p-glycoprotein activity and/or expression from its existing state or native state, such as by at least about 0.1%, 0.2%, 0.5%, 1%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% and 100% or more relative to a reference level, *e.g.*, the level of the p-glycoprotein. In some embodiments, the p-glycoprotein inhibitor is a strong p-glycoprotein inhibitor, selected from the group consisting of amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine ticagrelor, and erapamil.

[0021] The terms "effective amount" and "therapeutically effective amount" are used interchangeably throughout the present disclosure, whether referring to mitavipat or a pharmaceutically acceptable thereof, a CYP3A4/5 inducer, or a CYP3A4/5 inhibitor.

[0022] An "effective amount" of mitavipat or a pharmaceutically acceptable thereof is an amount sufficient to provide a therapeutic benefit in the treatment of pyruvate kinase deficiency (PKD), thalassemia (*e.g.*, alfa-thalassemia, beta-thalassemia or non-transfusion-dependent thalassemia), abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, anemia (*e.g.*, congenital anemias (*e.g.*, enzymopathies), hemolytic anemia (*e.g.* hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, chronic hemolytic anemia, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, anemia of chronic diseases, non-spherocytic hemolytic anemia or hereditary spherocytosis), as well as all other conditions disclosed in the section "Diseases, Disorders and Conditions" in the present disclosure, *i.e.* conditions that are responsive to treatment with a PKR activator such as mitavipat or a pharmaceutically acceptable thereof. Such diseases, disorders and conditions are hereinafter referred as "a PKR activator-responsive condition" when referring to any one of these conditions or "PKR activator-responsive conditions" when referring to these conditions collectively. Additionally or alternatively, an "effective amount" of mitavipat or a pharmaceutically acceptable thereof is an amount sufficient to delay or minimize one or more effects or symptoms associated with these conditions. In one aspect, an "effective amount" of mitavipat or a pharmaceutically

acceptable thereof means an amount of mitavipat or a pharmaceutically acceptable thereof, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "effective amount" can encompass an amount that improves overall therapy, reduces or avoids effects, symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, an "effective amount" of mitavipat or a pharmaceutically acceptable thereof is an amount sufficient for eliciting measurable activation of wild-type or mutant PKR. In certain embodiments, an "effective amount" of mitavipat or a pharmaceutically acceptable thereof is an amount sufficient for regulating 2,3-diphosphoglycerate levels in blood in need thereof or for treating PKR activator-responsive conditions or treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (*e.g.*, liver diseases). In certain embodiments, an effective amount of mitavipat or a pharmaceutically acceptable thereof is an amount sufficient for eliciting measurable activation of wild-type or mutant PKR and for regulating 2,3-diphosphoglycerate levels in blood in need thereof or for treating PKR activator-responsive conditions or treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (e.g., liver diseases). In one aspect, the effective amount is the amount required to generate a subject's hemoglobin response of $\geq$1.0 g/dL (such as $\geq$1.5 g/dL or $\geq$2.0 g/dL) increase in Hb concentration from baseline. In one aspect, the subject's baseline Hb concentration is the average of all available Hb concentrations before treatment with a compound described herein. In certain aspects, the effective amount is the amount required to reduce the patient's transfusion burden. In one aspect, the effective amount of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is between about 0.01-100 mg/kg body weight/day of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate), *e.g.,* about 0.1-100 mg/kg body weight/day.

[0023] Concomitant medications will be commonly used with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate). An "effective amount" of the drug (*e.g.*, an effective amount of a CYP3A4/5 inducer or an effective amount of a CYP3A4/5 inhibitor) being co-administered with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is an amount sufficient to provide a desired therapeutic benefit. Drugs that are being co-administered with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate), including some of the current antiarrhythmics, antibiotics, antidepressants, antifungals, calcium channel blockers, H_2 receptor antagonists, non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, etc., will

sometimes be CYP3A4/5 inducers or CYP3A4/5 inhibitors. In such instances, the amount of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) or the amount of the drug being co-administered should be adjusted to reduce effects of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) and the co-administered drug.

[0024] In one aspect, an effective amount of a CYP3A4/5 inducer is between about 0.1-1000 mg/kg/day of a CYP3A4/5 inducer, *e.g.,* about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

[0025] In one aspect, an effective amount of a CYP3A4/5 inhibitor is between about 0.1-1000 mg/kg/day of a CYP3A4/5 inhibitor, *e.g.,* about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

[0026] In one aspect, an effective amount of a p-gp inhibitor is between about 0.1-1000 mg/kg/day of a p-gp inhibitor, *e.g.,* about 1.0-1000 mg/kg/day, depending on the drug that is co-administered with.

[0027] As used herein, reduction in transfusion burden means at least 20% reduction in the number of RBC units transfused within at least 5 weeks of treatment. In certain embodiments, the reduction in transfusion burden is ≥33% reduction in the number of RBC units transfused within at least 5 weeks of treatment. In certain embodiments, reduction of transfusion burden is ≥33% reduction in the number of RBC units transfused within at least 10 weeks (e.g., at least 20 weeks or at least 24 weeks) of treatment.

[0028] The term "activating" as used herein means an agent that (measurably) increases the activity of wild type pyruvate kinase R (wt PKR) or causes wild type pyruvate kinase R (wt PKR) activity to increase to a level that is greater than wt PKR's basal levels of activity or an agent that (measurably) increases the activity of a mutant pyruvate kinase R (mPKR) or causes mutant pyruvate kinase R (mPKR) activity to increase to a level that is greater than that mutant PKR's basal levels of activity, for examples, to a level that is 20%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of wild type PKR.

[0029] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, reducing the likelihood of developing, or inhibiting the progress of a disease or disorder, or one or more effects or symptoms thereof, as described herein. In some embodiments,

treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to reduce the likelihood of or delay their recurrence.

[0030] As used herein the terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate).

[0031] The term "pharmaceutically acceptable salt" when referring to a pharmaceutically acceptable salt of mitapivat, refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art, for example, Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19. Pharmaceutically acceptable salts of mitapivat include those derived from suitable inorganic and organic acids. Examples of pharmaceutically acceptable acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, besylate bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, gentisate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, tosylate p-toluenesulfonate, undecanoate, valerate salts, and the like. Preferably, a pharmaceutically acceptable salt of mitapivat is a sulfate salt.

[0032] As used herein, the terms "about" and "approximately" are used herein to mean within the typical ranges of tolerance in the art. In one embodiment, "about" means within 2 standard deviations from the mean value. In one embodiment, "about" means ±10%. In one embodiment, "about" means ±5%. When "about" is present before a series of numbers of number ranges, it is understood that the term can applies to any and each of the numbers and ranges recited in the series.

Compositions and Administration

[0033]
he effective amount of mitapivat, in accordance with a method of the invention, may be administered in the form of a pharmaceutical composition comprising mitapivat or a pharmaceutically acceptable salt thereof (*e.g.* mitapivat sulfate), together with a pharmaceutically acceptable carrier.

[0034] Pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0035] Pharmaceutically acceptable carriers used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Exemplary carriers, diluents, granulating and/or dispersing agents, surface active agents and/or emulsifiers, binding agents, preservatives, antioxidants, chelating agent, antifungal preservatives, alcohol preservatives, acidic preservatives, other types of preservatives, buffering agents, lubricating agents, and natural oils that can be included in a pharmaceutical composition of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) as disclosed in International Patent Application No. WO2019/104134.

[0036] Pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) may be administered orally, parenterally, by inhalation spray,

topically, rectally, nasally, buccally, transmucosally, or in an ophthalmic preparation. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In one aspect, the pharmaceutical compositions provided herewith are orally administered in an orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include one or more substances selected from microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0037] A secondary drug can be co-administered with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.* mitapivat sulfate). The effective amount of a secondary drug that is co-administered with mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate), such as a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor, if used in a method of the invention, may also be administered in the form of a pharmaceutical composition comprising the CYP3A4/5 inducer or the CYP3A4/5 inhibitor or the p-gp inhibitor, together with a pharmaceutically acceptable carrier. Pharmaceutical compositions of the secondary drug may be prepared and administered as described above for pharmaceutical compositions of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate).

[0038] In one aspect, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.* mitapivat sulfate) is formulated as a tablet composition together with a pharmaceutically acceptable carrier, in accordance with the disclosures of International Patent Application No. WO2019/104134.

[0039] In one embodiment, in therapies comprising mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) and a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) and the secondary drug are administered "concurrently" to the

subject, which means that the subject is administered both drugs on the same day on all days of the treatment period. In one embodiment, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) and the secondary drug are administered "sequentially" to the subject, which means that the subject is administered either of the two drugs on all days of the treatment period, but not both drugs. In another embodiment, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) and the secondary drug are administered "sequentially and concurrently" to the subject, which means that the subject is administered either of the two drugs on certain days of the treatment period, but not both drugs; and the subject is administered both drugs on the same day on other days of the treatment period.

Doses and Dosing Regimens

[0040] The amount of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) that may be combined with carrier materials to produce a composition in a single dosage form will vary depending upon the subject to be treated and the particular mode of administration. For example, a specific dosage and treatment regimen for any particular subject will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of mitapivat or a pharmaceutically acceptable salt thereof will also depend upon the particular form (*e.g.*, free base, salt form, crystalline form, etc.) in the composition. In one aspect, a provided composition may be formulated such that a dosage equivalent to about 0.001 to about 100 mg/kg body weight/day of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, about 0.5 to about 100 mg/kg of mitapivat or a pharmaceutically acceptable salt thereof) can be administered to a subject receiving these compositions. Alternatively, dosages equivalent to 1 mg/kg and 1000 mg/kg of mitapivat or a pharmaceutically acceptable salt thereof every 4 to 120 hours is also acceptable.

[0041] In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose of equivalent to about 2 mg to about 3000 mg of mitapivat. In certain embodiments, the dose is an oral dose. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 2 mg to about 3000 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 350 mg of mitapivat.

In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 200 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg to about 100 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 5 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 10 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 15 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 20 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 25 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 30 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 35 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 40 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 45 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 50 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 55 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 60 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 65 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 70 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 75 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 80 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 85 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 90 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 95 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 100 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt

thereof is formulated equivalent to about 110 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 120 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 130 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 140 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 150 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 160 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 170 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 180 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 190 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 200 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 210 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 220 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 230 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 240 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 250 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 260 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 270 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 280 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 290 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 300 mg of mitapivat. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated equivalent to about 300 to 360 mg of mitapivat. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

[0042] In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 2 mg to about 3000 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 500 mg of mitapivat of per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 200 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg to about 10 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose of about 15 mg equivalent to mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 45 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat thereof per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat per day. In certain

embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 90 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 110 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 120 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 130 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 140 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 150 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 160 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 170 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 180 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 190 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 200 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 210 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 220 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 230 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 240 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 250 mg of mitapivat per day. In certain

embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 260 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 270 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 280 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 290 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 300 mg of mitapivat per day. In certain embodiments, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 300-360 mg of mitapivat per day. Dosing can be once, twice, or three times daily. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 10 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 15 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 45 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt

thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 65 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 75 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 85 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 90 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 95 mg of mitapivat thereof twice per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat twice per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 10 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 15 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 25 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 30 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 35 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 40 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for

administration at a dose equivalent to about 45 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 50 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 55 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 60 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 65 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 70 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 75 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 80 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 85 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 95 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 110 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 120 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 130 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 140 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 150 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 160 mg to about 200 mg of mitapivat thereof once per day. In another aspect, mitapivat or a pharmaceutically acceptable salt thereof is

formulated for administration at a dose equivalent to about 200 mg to about 360 mg of mitapivat thereof once per day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 20 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereofis formulated for administration at a dose equivalent to about 50 mg of mitapivat once every other day. In one aspect, mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 100 mg of mitapivat once every other day. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

[0043] In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 70% to about 80%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 60% to about 70%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 50% to about 60%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 40% to about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 30% to about 40%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 20% to about 30%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 10% to about 20%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof by about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat to the dose equivalent to about 200 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat to the dose equivalent to about 150 mg. In certain embodiments,

for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat to the dose equivalent to about 100 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat to the dose equivalent to about 50 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat to the dose equivalent to about 25 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat to the dose equivalent to about 10 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat to the dose equivalent to about 5 mg. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg of mitapivat to the dose equivalent to about 2.5 mg.

[0044] In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 70% to about 80%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 60% to about 70%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 50% to about 60%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 40% to about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 30% to about 40%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 20% to about 30%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose

frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 10% to about 20%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof by about 50%. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof from twice daily to once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof from once daily to once every other day.

[0045] In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat twice daily to the dose equivalent to about 200 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat twice daily to the dose equivalent to about 150 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat twice daily to the dose equivalent to about 100 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat twice daily to the dose equivalent to about 50 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat twice daily to the dose equivalent to about 25 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat twice daily to the dose equivalent to about 10 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat twice daily to the dose equivalent to about 5 mg twice daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg twice daily of mitapivat to the dose equivalent to about 2.5 mg twice daily.

[0046] In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat once daily to the dose equivalent to about 200 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat once daily to the dose equivalent to about 150 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 200 mg of mitapivat once daily to the dose equivalent to about 100 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat once daily to the dose equivalent to about 50 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat once daily to the dose equivalent to about 25 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat once daily to the dose equivalent to about 10 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat once daily to the dose equivalent to about 5 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg once daily of mitapivat to the dose equivalent to about 2.5 mg once daily.

[0047] In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 400 mg of mitapivat twice daily to the dose equivalent to about 200 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 300 mg of mitapivat twice daily to the dose equivalent to about 150 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from

the dose equivalent to about 200 mg of mitapivat twice daily to the dose equivalent to about 100 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 100 mg of mitapivat twice daily to the dose equivalent to about 50 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 50 mg of mitapivat twice daily to the dose equivalent to about 25 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 20 mg of mitapivat twice daily to the dose equivalent to about 10 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 10 mg of mitapivat twice daily to the dose equivalent to about 5 mg once daily. In certain embodiments, for any of the methods presented herein, further comprising reducing the dose of mitapivat or a pharmaceutically acceptable salt thereof from the dose equivalent to about 5 mg twice daily of mitapivat to the dose equivalent to about 2.5 mg once daily.

[0048] In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 200 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 150 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 1 to about 100 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 5 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 20 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 50 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is present in the tablet composition in an amount equivalent to about 75 mg of mitapivat. In some embodiments, mitapivat or a pharmaceutically acceptable

salt thereof (*e.g.*, mitapivat sulfate) is present in a tablet composition in an amount equivalent to about 100 mg of mitapivat. In certain embodiment, the pharmaceutically acceptable salt of mitapivat is mitapivat sulfate.

[0049] As used herein, the dose amount of mitapivat or a pharmaceutically acceptable salt thereof (*e.g.*, mitapivat sulfate) is based on the equivalence to the free-base form of mitapivat. For example, "mitapivat or pharmaceutically acceptable salt thereof present in the composition in an amount equivalent to about 2.0 mg of mitapivat" means about 2.0 mg of free-base mitapivat or about 2.33 mg of mitapivat sulfate having the structural formula as depicted in the background of the present disclosure.

Methods of Treatment (Mitipivat Monotherapy and Concomitant Medications)

[0050] In one aspect, the present disclosure provides methods of treating a disease, disorder or condition with mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor; use of mitapivat and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for the manufacture of a medicament for treating a disease, disorder or condition; and mitapivat or a pharmaceutically acceptable salt thereof and a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for use in treating a disease, disorder or condition. The disease, disorder or condition treated is pyruvate kinase deficiency (PKD), sickle cell disease, or thalassemia as further discussed in the following embodiments, and any one disease, disorder or condition described in the section "Diseases, Disorders and Conditions" provided in the present disclosure.

[0051] In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0052] In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0053] In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of

mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia.

[0054] In one embodiment, the method of any one of the preceding embodiments further comprises:

(a) monitoring the subject for an effect of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer; and

(b) in the event that an effect of the drug-drug interaction is present, adjusting the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and/or the effective amount of the CYP3A4/5 inducer being administered to the subject to reduce the effect.

[0055] In some embodiments, the adjustment is to reduce the dose of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose and dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. Details of the dose and/or dose frequency adjustment are shown in the dose and dose regime section.

[0056] In one embodiment, the method of the preceding embodiment further comprises:

(c) repeating (a) and (b) until there are no further detectable symptoms of the drug-drug interaction.

Steps (a) and (b) can be repeated as many times as necessary until there are no further detectable symptoms of the drug-drug interaction. In one embodiment, step (a) comprises measuring and analyzing the pharmacokinetic (PK) such as AUC (*i.e.*, area under the plasma concentration-time curve, such as $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%estrap}$) and C_{max} values (*i.e.*, the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administrated and before the administration of a second dose). In one embodiment, step (a) comprises measuring and analyzing other PK parameters such as but not limited to C_l/F (*i.e.*, apparent total body clearance of the drug from plasma), V_z/F (*i.e.*, apparent volume of distribution during

terminal phase after non-intravenous administration) , $t_{1/2}$ (elimination half-life), t_{last}, t_{max} (time to reach maximum (peak) plasma concentration following drug administration), etc.

[0057] A "drug-drug interaction" as used herein refers to a change in concentration in a patient of a first drug (*e.g.*, mitipivat) and consequential change in the effect of the first drug on the subject/patient resulting from administration of a second drug (*e.g.*, a CYP3A4/5 inducer, a CYP3A4/5 inhibitor). The change in concentration and consequential change in effect of the first drug resulting from the second drug typically occurs because of a change in activity or expression level of a detoxification enzyme that acts to clear the first drug from the patient (such as CYP3A4/5), wherein the change in activity or expression level of the detoxification enzyme is caused by the second drug. An increase in activity or expression level of the detoxification enzyme will tend to decrease the concentration of the first drug in the patient and its consequential effect on the patient, whereas a decrease in activity or expression level of the detoxification enzyme will tend to increase the concentration of the first drug in the patient and its consequential effect on the patient.

[0058] An "effect of a drug-drug interaction" as used herein refers to a detectable and measurable effect, such as a detectable symptom, on the subject/patient caused by the drug-drug interaction. Where the concentration of the first drug is increased, such as when mitapivat is co-administered with a CYP3A4/5 inhibitor, the "effect" typically refers to undesired phenomena such as an overdose of the first drug, liver failure, kidney failure, and the prevalence of side effects and adverse reactions. Where the concentration of the first drug is decreased, such as when mitapivat is co-administered with a CYP3A4/5 inducer, the "effect" typically refers to a decrease in the therapeutic efficacy of the first drug (*e.g.*, mitapivat). Exemplary effects of a drug-drug interaction as used herein further include headache, insomnia, nausea, viral upper respiratory tract infection, arthralgia, diarrhoea, fatigue, hot flush, influenza, vomiting, cough, dizziness, oropharyngeal pain, pyrexia, back pain, dysmenorrhoea, and gastroenteritis, and dyspepsia. Hypertriglyceridemia, hemolytic anemia, hemolysis, dizziness, etc.

[0059] In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0060] In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0061] In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof and an effective amount of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5) or a p-gp inhibitor. In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia.

[0062] In one embodiment, the method of any one of the suitable preceding embodiments further comprises:

(a) monitoring the subject for a symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor; and

(b) in the event that a symptom of the drug-drug interaction is present, adjusting the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and/or the effective amount of the CYP3A4/5 inhibitor being administered to the subject to reduce the effect.

[0063] In some embodiments, the adjustment is to reduce the dose of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the adjustment is to reduce the dose and dose frequency of mitapivat or a pharmaceutically acceptable salt thereof. Details of the dose and/or dose frequency adjustment are shown in the dose and dose regime section.

[0064] In one embodiment, the method of the preceding embodiment further comprises:

(c) repeating (a) and (b) until there are no further detectable symptoms of the drug-drug interaction.

Likewise, steps (a) and (b) can be repeated as many times as necessary until here are no further detectable symptoms of the drug-drug interaction. Ways of monitoring the subject for

a symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor as recited in step (a) are as described above.

[0065] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the CYP3A4/5 inducer (or inhibitor) sequentially.

[0066] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the CYP3A4/5 inducer (or inhibitor) concurrently.

[0067] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof and the effective amount of the CYP3A4/5 inducer (or inhibitor) sequentially and concurrently. As used herein, "co-administered" or "in combination with" encompasses administration of mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer (or inhibitor) sequentially and concurrently, or at different intervals. In another embodiments, for the method of any one of the embodiments, the CYP3A4/5 inducer is a mild CYP3A4/5 inducer. In another embodiments, for the method of any one of the embodiments, the CYP3A4/5 inhibitor is a mild CYP3A4/5 inhibitor. In another embodiments, for the methods of any one of the embodiments, the CYP3A4/5 inhibitor is a moderate CYP3A4/5 inhibitor.

[0068] In another aspect, the present disclosure provides methods of treating a disease, disorder or a condition with mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor; use of mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for the manufacture of a medicament for treating disease, disorder or a condition; and mitapivat in the absence of a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor for use in treating a disease, disorder or a condition.

[0069] As used herein, "in the absence of" when referring to a secondary drug co-administered with mitapivat (*e.g.*, a CYP3A4/5 inducer or a CYP3A4/5 inhibitor or a p-gp inhibitor), refers to levels of the secondary drug in the subject/patient that are sufficiently low that such that any change in the levels of the detoxification enzymes for mitapivat and the

secondary drug results in no detectable symptoms of a drug-drug interaction between mitapivat and the secondary drug.

[0070] In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0071] In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0072] In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inducer of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In some embodiments, the thalassemia is alpha thalassemia. In some embodiments, the thalassemia is beta thalassemia.

[0073] In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a CYP3A4/5 inducer, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inducer. In certain embodiments, the CYP3A4/5 inducer is a strong CYP3A4/5 inducer. In certain embodiments, the CYP3A4/5 inducer is a moderate CYP3A4/5 inducer. In some embodiments, the CYP3A4/5 inducer is terminated at least 30 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 28 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 25 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 21 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 15 days prior to

the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inducer is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

[0074] In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0075] In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).

[0076] In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of an inhibitor of cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5). In certain embodiment, the thalassemia is alpha-thalassemia. In certain embodiment, the thalassemia is beta-thalassemia.

[0077] In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a CYP3A4/5 inhibitor, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the CYP3A4/5 inhibitor. In certain embodiments, the CYP3A4/5 inhibitor is a strong CYP3A4/5 inhibitor. In certain embodiments, the CYP3A4/5 inhibitor is a moderate CYP3A4/5 inhibitor. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 21 days prior

to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 15 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 3 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 2 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the CYP3A4/5 inhibitor is terminated at least 1 day prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

[0078] In one embodiment, the present disclosure relates to a method of treating pyruvate kinase deficiency (PKD) in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor.

[0079] In another embodiment, the present disclosure relates to a method of treating sickle cell disease in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor.

[0080] In yet another embodiment, the present disclosure relates to a method of treating thalassemia in a subject, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof in the absence of a p-gp inhibitor. In certain embodiment, the thalassemia is alpha-thalassemia. In certain embodiment, the thalassemia is beta-thalassemia.

[0081] In one embodiment, in accordance with the method of any one of the suitable preceding embodiments, administration of a p-gp inhibitor, if any, is terminated at a sufficient time interval prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof such that there is no detectable symptom of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof and the p-gp inhibitor. In certain embodiments, the p-gp inhibitor is a strong p-gp inhibitor (e.g. amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine ticagrelor, and erapamil). In some embodiments, the p-gp inhibitor inhibitor is terminated at least 21 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 15 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 14 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 10 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 7 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 5 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 3 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 2 days prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof. In some embodiments, the p-gp inhibitor inhibitor is terminated at least 1 day prior to the administration of the effective amount of mitapivat or a pharmaceutically acceptable salt thereof.

[0082] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 1 mg to about 2500 mg, or about 5 mg to 2500 mg, or about 30 mg to 2500 mg, or about 5 mg to about 700 mg, or about 15 mg to about 700 mg, about 5 mg to about 360 mg, about 5 mg to about 300 mg, about 50 mg to about 300 mg, about 120 mg to about 360 mg, about 120 mg to about 300 mg, about 5 mg to about 120 mg,

about 5 mg, about 20 mg, about 50 mg, about 100 mg, about 120 mg , about 200 mg, about 300 mg, or about 360 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0083] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 1 mg to about 2500 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0084] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about about 5 mg to 2500 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0085] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg to about 360 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0086] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg to about 300 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0087] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 50 mg to about 300 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0088] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 5 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0089] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 20 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0090] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 50 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0091] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject about 100 mg of mitapivat or a pharmaceutically acceptable salt thereof.

[0092] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof once daily.

[0093] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject the effective amount of mitapivat or a pharmaceutically acceptable salt thereof twice daily.

[0094] In one embodiment, the method of any one of the preceding embodiments comprises administering to the subject a sulfate salt of mitapivat, such as a sulfate salt of mitapivat having the structural formula depicted in the background of the present disclosure.

[0095] In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a strong inducer of CYP3A4/5.

[0096] In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a moderate inducer of CYP3A4/5.

[0097] In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is a mild inducer of CYP3A4/5.

[0098] In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a strong CYP3A4/5 inducer selected from a group consisting of apalutamide, enzalutamide, mitotane, phenytoin, efavirenz, nevirapine, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, henytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, and troglitazone.

[0099] In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a moderate CYP3A4/5 inducer selected from a group consisting of bosentan, etravirine, phenobarbital, and primidone.

[00100] In one embodiment, in the method of any one of the suitable preceding embodiments, the inducer of CYP3A4/5 is a mild CYP3A4/5 inducer selected from a group consisting of armodafinil, modafinil, and rufinamide.

[00101] In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is selected from the group consisting of aminoglutethimide, bexarotene, bosentan, carbamazepine, dexamethasone, efavirenz, fosphenytoin, griseofulvin, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's wort, avasimibe, dabrafenib, mifepristone, etravirine, armodafninil, glycerol phenylbutyrate, asunaprevir, rifunamide, oritavancin, clobazam, felbamate, eslicarbazepine acetate, and genistein.

[00102] In one embodiment, in the method of any one of the suitable preceding embodiments, the CYP3A4/5 inducer is rifampin. In one aspect, rifampin is administered to the subject in the form of a capsule composition. In one aspect, about 0.1-1000 mg of rifampin is administered to the subject. In one aspect, about 100-1000 mg of rifampin is administered to the subject.

[00103] In one embodiment, the method of any one of the suitable preceding embodiments comprises administering about 600 mg of rifampin to the subject. In one aspect, the method of any one of the suitable preceding embodiments comprises administering about 600 mg of rifampin to the subject once daily.

[00104] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a strong inhibitor of CYP3A4/5.

[00105] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a moderate inhibitor of CYP3A4/5.

[00106] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a mild inhibitor of CYP3A4/5.

[00107] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is selected from the group consisting of toamiodarone, amprenavir, aprepitant, atazanavir, chloramphenicol, clarithromycin, conivaptan, cyclosporine, darunavir, dasatinib, delavirdine, diltiazem, erythromycin,

fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, quinupristin, saquinavir, tamoxifen, telithromycin, troleandomycin, verapamil, voriconazole, grapefruit, Seville oranges, limes, pomelos, fruit juices, and vegetables from mustard green family.

[00108] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a strong CYP3A4/5 inhibitor selected from a group consisting of boceprevir, cobicistat, danoprevir, elvitegravir, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, telithromycin, troleandomycin, nelfinavir, clarithromycin, nefazodone, saquinavir, suboxone, and voriconazole.

[00109] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a moderate CYP3A4/5 inhibitor selected from a group consisting of aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

[00110] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is a mild CYP3A4/5 inhibitor selected from a group consisting of chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor.

[00111] As used herein, the terms “weak inhibitor” and ‘mild inhibitor” are used interchangeably.

[00112] As used herein, the terms “weak inducer” and ‘mild inducer” are used interchangeably.

[00113] In one embodiment, in the method of any one of the suitable preceding embodiments, the inhibitor of CYP3A4/5 is itraconazole. In one aspect, about 0.1-1000 mg of itraconazole is administered to the subject. In one aspect, itraconazole is administered in the form of an oral solution. In one aspect, about 50-500 mg of itraconazole is administered to the subject.

[00114] In one embodiment, the method of any one of the suitable preceding embodiments comprises administering about 200 mg of itraconazole to the subject. In one aspect, about 0.1-1000 mg of itraconazole is administered to the subject. In one aspect, about 50-500 mg of itraconazole is administered to the subject. In one aspect, about 200 mg of itraconazole is administered to the subject. In one aspect, about 200 mg of itraconazole is administered to the subject once daily. In one aspect, about 100 mg of itraconazole is administered to the subject. In one aspect, about 100 mg of itraconazole is administered to the subject once daily. In one aspect, itraconazole is administered in the form of an oral solution.

Diseases, Disorders and Conditions

[00115] Pyruvate kinase deficiency (PKD) is a glycolytic enzymopathy that results in life-long hemolytic anemia. In certain embodiments, the subject having PKD is a patient having at least 2 mutant alleles in PKLR gene. In certain embodiments, the subject having PKD is a patient having at least 2 mutant alleles in PKLR gene and at least one is a missense mutation. See Canu. et.al , Blood Cells, Molecules and Diseases **2016**, *57*, pp. 100-109. In certain embodiments, a subject having PKD has an Hb concentration less than or equal to 10.0 g/dL. In certain embodiments, the subject having PKD is an adult not under regular transfusion (e.g. having had no more than 4 transfusion episodes in the 12-month period up to the treatment). In certain embodiments, the subject having PKD is an adult transfusion independent (e.g. having no more than 3 units of RBCs transfused in the 12-month period prior to the treatment). In certain embodiments, the subject having PKD is an adult under regular transfusion (e.g. having had at least 4 transfusion episodes (e.g., at least 6 transfusion episodes) in the 12-month period prior to the treatment). In certain embodiments, the subject having PKD has a total number of at least 5 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 10 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 15 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 20 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 25 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 30 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total

number of at least 40 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 50 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 60 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD has a total number of at least 70 transfusion episodes during the subject's lifetime. In certain embodiments, the subject having PKD is not homozygous for the R479H mutation or does not have 2 non-missense mutations in the PKLR gene. In certain embodiments, the subject having PKD, under regular transfusion, has hemoglobin (Hb) $\leq$12.0 g/dL (if male) or $\leq$11.0 g/dL (if female), prior to the treatment. In certain embodiments, the subject having PKD, under regular transfusion, has transfusion occurring on average less than or equal to once every three weeks. In certain embodiments, the subject having PKD has received at least 0.8 mg (e.g. at least 1.0 mg)folic acid daily (e.g. for at least 21 days) prior to the treatment. In certain embodiments, the subject with PKD under regular transfusion achieves a reduction in transfusion burden (e.g. at least 33% reduction in the number of RBC units transfused) during the 5 weeks, 10 weeks, 15 weeks, 20 weeks, or 24 weeks, 28 weeks, or 32 weeks of treatment. In certain embodiments, the subject having PKD, not under regular transfusion (having had no more than 4 transfusion episodes in the 12-month period prior to the treatment and/or no transfusion in the 3 months prior to the treatment), has hemoglobin (Hb) $\leq$10.0 g/dL regardless of gender prior to the treatment. In certain embodiments, the subject having PKD has undergone splenectomy. In certain embodiment, the subject having PKD is a child 18 years old or younger. In certain embodiments, the child is transfusion dependent.

[00116] Exemplified conditions related to PKD include, but are not limited to, anemias, cholecystolithiasis, gallstones, tachycardia, hemochromatosis, icteric sclera, splenomegaly, leg ulcers, jaundice, fatigue, and shortness of breath. As described herein, PKD is a deficiency of PKR. In certain embodiments, the deficiency of PKR is associated with a PKR mutation.

[00117] In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 1.0 g/dL increase in Hb concentration after the treatment compared to the baseline of prior to the treatment. In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 1.5 g/dL increase in Hb concentration from baseline prior to the

treatment. In certain embodiments, the subject with PKD achieves a hemoglobin response of at least 2.0 g/dL increase in Hb concentration from baseline prior to the treatment.

[00118] In an embodiment, the mutant PKR is selected from the group consisting of A31V, A36G, G37Q, R40W, R40Q, L73P, S80P, P82H, R86P, I90N, T93I, G95R, M107T, G111R, A115P, S120F, H121Q, S130P, S130Y, V134D, R135D, A137T, G143S, I153T, A154T, L155P, G159V, R163C, R163L, T164N, G165V, L167M, G169G, E172Q, W201R, I219T, A221Y, D221N, G222A, I224T, G232C, N253D, G263R, G263W, E266K, V269F, L272V, L272P, G275R, G275R, E277K, V280G, D281N, F287V, F287L, V288L, D293N, D293V, A295I, A295V, I310N, I314T, E315K, N316K, V320L, V320M, S330R, D331N, D331G, D331E, G332S, V335M, A336S, R337W, R337P, R337Q, D339N, D339Q, G341A, G341D, I342F, K348N, A352D, I357T, G358R, G358E, R359C, R359H, C360Y, N361D, G364D, K365M, V368F, T371I, L374P, S376I, T384M, R385W, R385K, E387G, D390N, A392T, N393D, N393S, N393K, A394S, A394D, A394V, V395L, D397V, G398A, M403I, G406R, E407K, E407G, T408P, T408A, T408I, K410E, G411S, G411A, Q421K, A423A, A423A, R426W, R426Q, E427A, E427N, A431T, R449C, I457V, G458D, A459V, V460M, A468V, A468G, A470D, T477A, R479C, R479H, S485F, R486W, R486L, R488Q, R490W, I494T, A495T, A495V, R498C, R498H, A503V, R504L, Q505E, V506I, R510Q, G511R, G511E, R518S, R531C, R532W, R532Q, E538D, G540R, D550V, V552M, G557A, R559G, R559P, N566K, M568V, R569Q, R569L, Q58X, E174X, W201X, E241X, R270X, E440X, R486X, Q501X, L508X, R510X, E538X, R559X. These mutations are described in Canu et.al., Blood Cells, Molecules and Diseases **2016**, *57*, pp. 100-109. In an embodiment, the mutant PKR is selected from G332S, G364D, T384M, K410E, R479H, R479K, R486W, R532W, R510Q, and R490W. In certain embodiments, the mutant PKR is selected from A468V, A495V, I90N, T408I, and Q421K, and R498H. In certain embodiments, the mutant PKR is R532W, K410E, or R510Q. In certain embodiments, the mutant PKR is R510Q, R486W, or R479H.

[00119] In other aspects, provided are methods of treating a disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof, comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor).

Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in treating disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for treating a disease selected from hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof. In one aspect, the disease to be treated is hemolytic anemia.

[00120] Thalassemia is an inherited blood disorder in which the normal ratio of α- to β-globin production is disrupted due to a disease-causing variant in 1 or more of the globin genes. In certain embodiments, Alpha-globin aggregates (as found in β-thalassemia) readily precipitate, which disrupts the red blood cell (RBC) membrane and results in oxidative stress. In certain embodiments, Beta-globin tetramers (Hb H, found in α-thalassemia) are generally more soluble, but are still unstable and can form precipitates. The imbalance of the globin chain synthesis can lead to a net reduction in Hb concentrations and has dramatic effects on the survival of RBC precursors, ultimately resulting in their premature destruction in the bone marrow and in extramedullary sites (Cappellini et al, 2014). In certain embodiments, the disorder results in large numbers of red blood cells being destroyed, which leads to anemia. In certain embodiments, the thalassemia is alpha thalassemia. In certain embodiments, the thalassemia is beta thalassemia. In other embodiments, the thalassemia is non-transfusion-dependent thalassemia (. In other embodiments, the thalassemia is beta thalassemia intermedia. In other embodiments, the thalassemia is Hb E beta thalassemia. In other embodiments, the thalassemia is beta thalassemia with mutations of 1 or more alfa genes.

[00121] In certain embodiments, the subject is an adult subject with thalassemia. In certain embodiments, the subject has thalassemia such as β-thalassemia intermedia, Hb E β-thalassemia, α-thalassemia (Hb H disease), or β-thalassemia with mutations of 1 or more α genes. In certain embodiments, the subject has non-transfusion-dependent thalassemia. In certain embodiments, the subject has non-transfusion-dependent alpha thalassemia. In certain embodiments, the subject has beta-thalassemia or non-transfusion-dependent beta-

thalassemia. In certain embodiments, the subject is an adult male subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject is a female subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject is an adult female subject with thalassemia such as beta-thalassemia or non-transfusion-dependent thalassemia. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 6.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 7.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 8.0 g/dL. In certain embodiments, the subject has a hemoglobin concentration of less than or equal to 9.0 g/dL. In certain aspects, the subject having non-transfusion-dependent thalassemia does not have a known history (e.g., has been diagnosed in the past) of Hb S or Hb C forms of thalassemia. In certain embodiments, the term "non-transfusion dependent" thalassemia refers to subjects with thalassemia having no more than 4 (e.g. five) units of RBCs transfused during a 24-week period up to the first day of administration of mitapivat and/or no RBC transfusions in the 8 weeks prior to the first day of administration of mitapivat. In certain embodiment, the subject is an adult over 18 years old. In certain embodiment, the subject is a child 18 years old or younger.

[00122] As used herein, sickle cell disease (SCD), Hemoglobin SS disease, and sickle cell anemia are used interchangeably. Sickle cell disease (SCD) is an inherited blood disorder caused by the presence of sickle hemoglobin (HbS). In certain embodiments, subjects with SCD have abnormal hemoglobin, called hemoglobin S or sickle hemoglobin, in their red blood cells. In certain embodiments, people having SCD have at least one abnormal genes causing the body to make hemoglobin S. In certain embodiments, people having SCD have two hemoglobin S genes, Hemoglobin SS.

[00123] In other aspects, provided herein are methods for treating anemia in a subject in need thereof comprising administering to the subject an effective amount of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor). Also provided is mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), for use in treating anemia in a subject in need thereof. Further provided is the use of mitapivat or a pharmaceutically acceptable salt thereof, in combination with or in

the absence of an effective amount of a secondary drug (*e.g.* a CYP3A4/5 inducer or a CYP3A4/5 inhibitor), in the manufacture of a medicament for treating anemia. In one aspect, the anemia to be treated is dyserythropoietic anemia.

[00124] In certain embodiments, the anemia is a dyserythropoietic anemia such as congenital dyserythropoietic anemia type I, II, III, or IV. In certain embodiments, the anemia is hemolytic anemia. In certain embodiments, the hemolytic anemia is a congenital and/or hereditary form of hemolytic anemia such as PKD, sickle cell disease, thalassemias (*e.g.* alpha or beta or non-transfusion-dependent thalassemia), hereditary spherocytosis, hereditary elliptocytosis), paroxysmal nocturnal hemoglobinuria, abeta-liproteinemia (Bassen-Kornzweig syndrome). In certain embodiments, the hemolytic anemia is acquired hemolytic anemia such as autoimmune hemolytic anemia, drug-induced hemolytic anemia. In certain embodiments, the hemolytic anemia is anemia as part of a multi-system disease, such as the anemia of Congenital Erythropoietic Purpura, Fanconi, Diamond-Blackfan.

[00125] As used herein, the term "anemia" refers to a deficiency of red blood cells (RBCs) and/or hemoglobin. As used herein, anemia includes all types of clinical anemia, for example (but not limited to): microcytic anemia, iron deficiency anemia, hemoglobinopathies, heme synthesis defect, globin synthesis defect, sideroblastic defect, normocytic anemia, anemia of chronic disease, aplastic anemia, hemolytic anemia, macrocytic anemia, megaloblastic anemia, pernicious anemia, dimorphic anemia, anemia of prematurity, Fanconi anemia, hereditary spherocytosis, sickle cell disease, warm autoimmune hemolytic anemia, cold agglutinin hemolytic anemia, osteopetrosis, thalassemia, and myelodysplastic syndrome.

[00126] In certain embodiments, anemia can be diagnosed on a complete blood count. In certain embodiments, anemia can be diagnosed based on the measurement of one or more markers of hemolysis (*e.g.* RBC count, hemoglobin, reticulocytes, schistocytes, lactate Dehydrogenase (LDH), haptoglobin, bilirubin, and ferritin) and/or hemosiderinuria mean corpuscular volume (MCV) and/or red cell distribution width (RDW). In the context of the present invention, anemia is present if an individual has a hemoglobin (Hb) less than the desired level, for example, the Hb concentration of less than 14 g/dL, more preferably of less than 13 g/dL, more preferably of less than 12 g/dL, more preferably of less than 11 g/dL, or most preferably of less than 10 g/dL.