US009757384B2

(12) **United States Patent**
Cowen

(10) **Patent No.: US 9,757,384 B2**
(45) **Date of Patent: Sep. 12, 2017**

(54) **METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME**

(71) Applicant: **Essentialis, Inc.**, Carlsbad, CA (US)

(72) Inventor: **Neil M. Cowen**, Carlsbad, CA (US)

(73) Assignee: **Essentialis, Inc.**, Redwood City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/940,018**

(22) Filed: **Nov. 12, 2015**

(65) **Prior Publication Data**

US 2016/0136178 A1 May 19, 2016

Related U.S. Application Data

(60) Provisional application No. 62/080,150, filed on Nov. 14, 2014, provisional application No. 62/138,245,
(Continued)

(51) **Int. Cl.**
A61K 31/54 (2006.01)
A61K 31/549 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61K 31/549*** (2013.01); ***A61K 9/00*** (2013.01); ***A61K 9/0004*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC .. A61K 31/549; A61K 31/155; A61K 31/137; A61K 31/551; A61K 9/5026;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,986,573 A 5/1961 Topliss et al.
4,880,830 A 11/1989 Rhodes
(Continued)

FOREIGN PATENT DOCUMENTS

WO 98/10786 A2 3/1998
WO WO-2006/026469 A2 3/2006
(Continued)

OTHER PUBLICATIONS

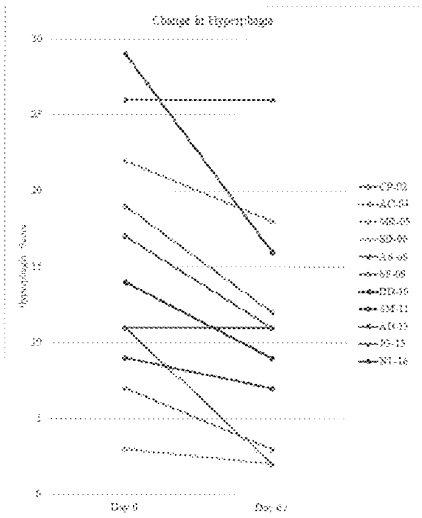
Aguilar-Bryan, et al., Toward Understanding the Assembly and Structure of KATP Channels, Physiological Review, 78(1), 227-245 (1998).
(Continued)

Primary Examiner — T. Victor Oh

(57) **ABSTRACT**

Provided are immediate or prolonged administration of certain potassium ATP (K_{ATP}) channel openers, optionally in combination with growth hormone, to a subject to achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, metabolic and compositional outcomes in the treatment of diseases or conditions involving K_{ATP} channels. Also provided are pharmaceutical formulations, methods of administration and dosing of K_{ATP} channel openers that achieve these outcomes and reduce the incidence of adverse effects in treated individuals. Further provided are methods of co-administering K_{ATP} channel openers with other drugs (e.g., in combination with growth hormone) to treat diseases of humans and animals (e.g., Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like.

14 Claims, 4 Drawing Sheets



Related U.S. Application Data

filed on Mar. 25, 2015, provisional application No. 62/170,035, filed on Jun. 2, 2015, provisional application No. 62/221,359, filed on Sep. 21, 2015.

(51) **Int. Cl.**

A61K 45/06	(2006.01)
A61K 9/00	(2006.01)
A61K 31/137	(2006.01)
A61K 31/155	(2006.01)
A61K 31/551	(2006.01)
A61K 9/20	(2006.01)
A61K 9/50	(2006.01)
A61K 38/27	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/2054*** (2013.01); ***A61K 9/5026*** (2013.01); ***A61K 9/5042*** (2013.01); ***A61K 9/5047*** (2013.01); ***A61K 31/137*** (2013.01); ***A61K 31/155*** (2013.01); ***A61K 31/551*** (2013.01); ***A61K 45/06*** (2013.01); *A61K 38/27* (2013.01)

(58) **Field of Classification Search**

CPC .. A61K 9/2054; A61K 9/0004; A61K 9/5042; A61K 9/5047; A61K 9/00; A61K 45/06; A61K 38/27

USPC 514/5.1, 11.4, 223.2, 223.5

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,284,845	A	2/1994	Paulsen	
5,399,359	A	3/1995	Baichwal	
5,415,871	A	5/1995	Pankhania et al.	
5,629,045	A	5/1997	Veech et al.	
6,022,562	A	2/2000	Autant et al.	
6,197,765	B1	3/2001	Vardi et al.	
7,572,789	B2	8/2009	Cowen et al.	
7,799,777	B2	9/2010	Cowen et al.	
9,381,202	B2	7/2016	Cowen et al.	
2002/0035106	A1	3/2002	Hansen et al.	
2003/0035106	A1	2/2003	Yeh et al.	
2003/0068366	A1	4/2003	Chungi et al.	
2003/0211123	A1	11/2003	Shukla et al.	
2004/0143213	A1	7/2004	Hunter et al.	
2004/0204472	A1	10/2004	Briggs et al.	
2006/0051418	A1	3/2006	Cowen et al.	
2006/0128673	A1	6/2006	Firnges et al.	
2009/0062264	A1	3/2009	Cowen et al.	
2009/0148525	A1	6/2009	Cowen	
2009/0149451	A1	6/2009	Cowen	
2010/0028429	A1	2/2010	Cowen et al.	
2010/0256360	A1	10/2010	Cowen et al.	
2012/0053172	A1	3/2012	De Boer	
2012/0238554	A1	9/2012	Cowen	
2013/0040942	A1	2/2013	Cowen et al.	
2013/0309301	A1	11/2013	Cowen et al.	
2014/0350001	A1	11/2014	Cowen	
2014/0364367	A1*	12/2014	Cotter	A61K 38/11 514/11.4
2014/0364425	A1	12/2014	Cowen et al.	

FOREIGN PATENT DOCUMENTS

WO	WO-2006/026469	A3	3/2006
WO	WO-2007/081521	A2	7/2007
WO	WO-2007/081521	A3	7/2007
WO	WO-2009/006483	A1	1/2009
WO	WO-2013/130411	A1	9/2013
WO	WO-2016/077629	A1	5/2016

OTHER PUBLICATIONS

Aizawa, et al., Prophylaxis of genetically determined diabetes by diazoxide: a study in rat model of naturally occurring obese diabetes. J of Pharma Exp Ther 275(1):194-199 (1995). Abstract Only.

Alemzadeh, et al., Antiobesity effect of diazoxide in obese Zucker rats. Metabolism: Clinical and Experimental, 45(3):334-341 (1996). Abstract only.

Alemzadeh, et al., Beneficial Effect of Diazoxide in Obese Hyperinsulinemic Adults, J. Clinical Endocrinology and Metabolism, 83:1911-1915 (1998).

Alemzadeh, et al., Diazoxide enhances adipose tissue protein kinase B activation and glucose transporter-4 expression in obese Zucker rats, Med Sci Monit, 2004; 10(3): BR53-60.

Alemzadeh, et al., Effect of Diazoxide on Brian Capillary Insulin Receptor Binding and Food Intake in Hyperphagic Obese Zucker Rats. Endocrinology, 140:3197-3202 (1999).

Alemzadeh, et al., Modulation of Adipoinsular Axis in Prediabetic Zucker Diabetic Fatty Rats by Diazoxide. Endocrinology 145(12):5476-5484 (2004).

Alemzadeh, R., et al., Modification of insulin resistance by diazoxide in obese Zucker rats. Endocrinology 133:705-712 (1993). Abstract Only.

Babenko, et al., Pharmaco-topology of Sulfonylurea Receptors, J. Biol. Chem., 275(2), 717-720 (2000).

Bertolino, et al., Receptors and Channels, 1, 267-278 (1993). Abstract Only.

Björk, et al., Induction of β-Cell Rest in Type 1 Diabetes: Studies on the effects of octreotide and diazoxide, Diabetes Care 21(3):427-430 (1998). Abstract Only.

Björklund, et al., Glucose-Induced Ca(2+)I Abnormalities in Human Pancreatic Islets, Important Role of Overstimulation, Diabetes, 49:1840-1848 (2000).

Butler, et al., Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects, Am. J. Med Gent A 143A(5):449-459 (2007). Abstract Only.

Cosgrove, BPDZ 154 Activates Adenosine 5'-Triphosphate-Sensitive Potassium ChannelsL In Vitro Studies Using Rodent Insulin-Secreting Cells and Islets Isolated from Patients with Hyperinsulinism, J. Clin. Endocrinol. Metab., 87, 4860-4868 (2002).

Dabrowski, The Novel Diazoxide Analog 3-Isopropylamino-7-Methoxy-H01,2,4-Benzothiadiazine 1,1-Dioxide Is a Selective Kir6.2/SUR1 Channel Opener, Diabetes, 51, 1896-1906 (2002).

De Tullio, et al., Toward Tissue-Selective Pancreatic B-Cells K(ATP) Channel Openers Belonging to 3-Alkylamino-7-halo-4*H*-1,2,4-benzothiadiazine 1, 1-Dioxides, J. Med. Chem., 46:3342-3353 (2003.) Abstract only.

Calesnick et al., Importance of Dissolution Rates in Producing Effective Diazoxide Blood Levels in Man, *J. Pharm. Sci.* 54:1277-1280 (1965). Abstract Only.

Guldstrand, et al., Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes, Diabetes and Metabolism 28:448-456 (2002). Abstract only.

Roderick, F.A., et al., "Cardiovascular and Metabolic Risk Profile and Acylation-Stimulating Protein Levels in Children with Prader-Willi Syndrome and Effects of Growth Hormone Treatment." J Clin Endocrinol Metab 95(4):1758-1766 (2010).

Marugo, et al., *Boll Spec It Biol Sper* 53:1860-1866 (1977).

Ortqvist, et al., Temporary Preservation of β-Cell Function by Diazoxide Treatment in Childhood Type 1 Diabetes, Diabetes Care, 27(9):2191-2197 (2004).

Ouedraogo, 2-Alkyl-3-Alkylamino-2H-Benzo- and Pyridothiadiazine 1,1-Dioxides: From K+ATP Channel Openers to Ca++ Channel Blockers, Biol. Chem., 383, 1759-1768 (2002). Abstract Only.

Qvigstad, et al., Nine weeks of bedtime diazoxide is well tolerated and improves β-cell function in subjects with Type 2 diabetes, Diabetic Medicine 21:73-76 (2004). Abstract Only.

Ratzmann, et al., Int J. Obesity 7(5):453-458 (1983). Abstract Only.

Reddy, et al., Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation, AAPS PharmSciTech 2003; 4(4) 1-98, 9 (2003).

(56) **References Cited**

OTHER PUBLICATIONS

Schou, et al., Synthesis and pharmacological evaluation of 4*H*-1-benzothiazine-2-carbonitrile 1,1-dioxide and *N*-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels, Bioorg. Med. Chem., 13, 141-155 (2005). Abstract Only.

Schwanstecher, et al., Potassium Channel openers require ATP to bind to and act through sulfonylurea receptors, EMBO, 17,5529-5535 (1998).

Stanridge, et al., Diazoxide down-regulates leptin and lipid metabolizing enzymes in adipose tissue of Zucker rats. FASEB J 14:455-460 (2000).

Surwit, et al., Diazoxide Restores β3-Adrenergic Receptor Function in Diet-Induced Obesity and Diabetes, Endocrinology 141:3630-3637 (2000).

Trube, et al., Opposite effects of tolbutamide and diazoxide on the ATP-dependent K+ channel in mouse pancreatic β-cells, Pfluegers Arch kEur J Physiol, 407, 493-99 (1986). Abstract Only.

Van Mil, et al., Activity related energy expenditure in children and adolescents with Prader-Willi syndrome, Int. J. Obes. 24(4), 429-434 (2000).

Wigland, et al., Downregulation of Insulin Receptors in Obese Man, Diabetes 28(4):287-291 (1979). Abstract Only.

Advisory Action dated Dec. 30, 2015, for U.S. Appl. No. 14/458,032, filed Aug. 12, 2014, 3 pages.

Ashcroft, F.M. et al. (1999). "ATP-sensitive K+ channels and insulin secretion: their role in health and disease," *Diabetologia*. 42:903-919.

Ashcroft, F.M. et al. (2000). "New windows on the mechanism of action of K(ATP) channel openers," *Trends Pharmacol*. Sci. 21:439-445.

Bay, H.E. et al. (2010). "Diazoxide choline controlled release in hyperglyceridemic subjects: Lipid and other metabolic effects," *J. American College of Cardiology* 55(10a), 1 total page.

Clinical Trials.Gov (2014). "Clinical study of diazoxide choline controlled-release tablet (DCCR) in patients with Prader-Willi syndrome," Clinical trials identifier NCT02034071, updated Jan. 10, 2014, Retrieved from https://clinicaltrials.gov/archive/nct02034071/2014_01_10, 4 total pages.

Eiholzer, U. et al. (1998). "Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance," *Eur. J. Pediatr*. 157:368-377.

Einspieler, C. et al. (2012). "Early behavioural manifestation of Smith-Magenis syndrome (del17p11.2) in a 4-month-old boy" *Dev. Neurorehab*. 15(4):313-316.

Final Office Action dated Mar. 24, 2010, for U.S. Appl. No. 11/212,130, filed Aug. 25, 2005, 15 pages.

Final Office Action dated Jun. 9, 2010, for U.S. Appl. No. 12/368,215, filed Feb. 9, 2009, 9 pages.

Final Office Action dated Oct. 17, 2014, for U.S. Appl. No. 12/370,456, filed Feb. 12, 2009, 14 pages.

Final Office Action dated Mar. 8, 2012, for U.S. Appl. No. 12/370,456, filed Feb. 12, 2009, 13 pages.

Final Office Action dated Jan. 13, 2017, for U.S. Appl. No. 14/458,032, filed Aug. 12, 2014, 14 pages.

Final Office Action dated Nov. 2, 2015, for U.S. Appl. No. 14/458,032, filed Aug. 12, 2014, 13 pages.

International Search Report dated Feb. 2, 2016, for PCT Application No. PCT/US2015/60455, filed on Nov. 12, 2015, 3 pages.

International Search Report dated Jun. 16, 2006, for PCT Application No. PCT/US2005/30481, filed on Aug. 25, 2005, 1 page.

International Search Report dated Dec. 6, 2007, for PCT Application No. PCT/US2006/48711, filed on Dec. 20, 2006, 2 pages.

International Search Report dated Sep. 30, 2008, for PCT Application No. PCT/US2008/68936, filed on Jul. 1, 2008, 2 pages.

International Search Report dated Jun. 21, 2013, for PCT Application No. PCT/US2013/027676, filed on Feb. 25, 2013, 4 pages.

Lee, P.D. (2002). "Disease management of Prader-Willi syndrome," Expert Opin. Pharmacother. 3:1451-1459.

Non-Final Office Action dated Sep. 17, 2009, for U.S. Appl. No. 11/212,130, filed Aug. 25, 2005, 14 pages.

Non-Final Office Action dated Aug. 1, 2013, for U.S. Appl. No. 12/368,215, filed Feb. 9, 2009, 12 pages.

Non-Final Office Action dated Dec. 8, 2009, for U.S. Appl. No. 12/368,215, filed Feb. 9, 2009, 8 pages.

Non-Final Office Action dated May 28, 2014, for U.S. Appl. No. 12/370,456, filed Feb. 12, 2009, 17 pages.

Non-Final Office Action dated Sep. 8, 2011, for U.S. Appl. No. 12/370,456, filed Feb. 12, 2009, 11 pages.

Non-Final Office Action dated Jun. 30, 2016, for U.S. Appl. No. 14/458,032, filed Aug. 12, 2014, 12 pages.

Non-Final Office Action dated Jul. 31, 2015, for U.S. Appl. No. 14/458,032, filed Aug. 12, 2014, 16 pages.

Proglycem® (2003). Pharmaceutical Information, Diazoxide Hyperglycemic Agent, 5 total pages.

Written Opinion of the International Searching Authority dated Feb. 2, 2016, for PCT Application No. PCT/US2015/60455, filed on Nov. 12, 2015, 8 pages.

Written Opinion of the International Searching Authority dated Jun. 16, 2006, for PCT Application No. PCT/US2005/30481, filed on Aug. 25, 2005, 3 pages.

Written Opinion of the International Searching Authority dated Dec. 6, 2007, for PCT Application No. PCT/US2006/48711, filed on Dec. 20, 2006, 8 pages.

Written Opinion of the International Searching Authority dated Sep. 30, 2008, for PCT Application No. PCT/US2008/68936, filed on Jul. 1, 2008, 7 pages.

Written Opinion of the International Searching Authority dated Jun. 21, 2013, for PCT Application No. PCT/US2013/027676, filed on Feb. 25, 2013, 6 pages.

* cited by examiner

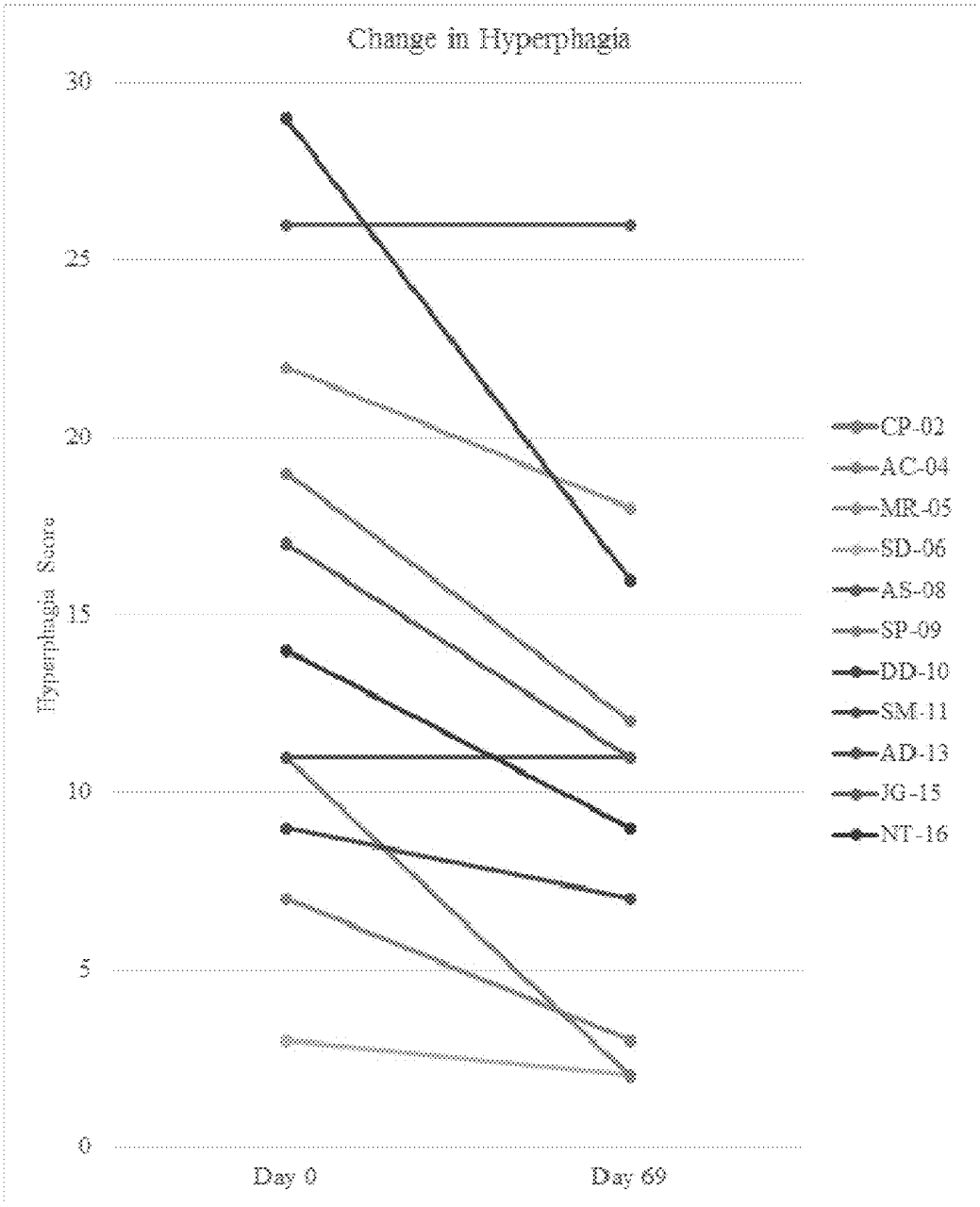

Change in Hyperphagia
Hyperphagia Score
30
25
20
15
10
5
0
Day 0
Day 69
CP-02
AC-04
MR-05
SD-06
AS-08
SP-09
DD-10
SM-11
AD-13
JG-15
NT-16

Figure 1

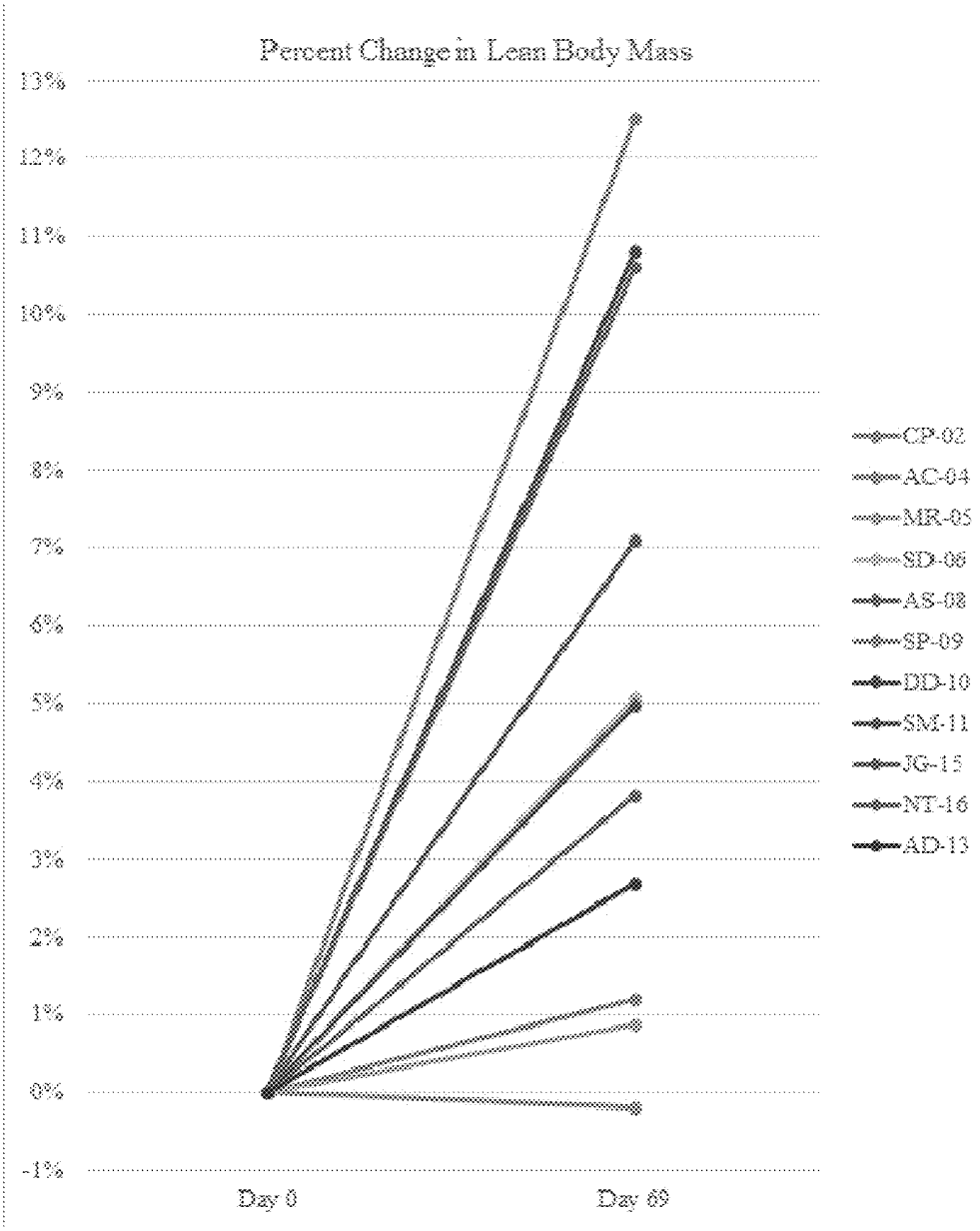

Percent Change in Lean Body Mass
13%
12%
11%
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
-1%
Day 0
Day 69
CP-02
AC-04
MR-05
SD-06
AS-08
SP-09
DD-10
SM-11
JG-15
NT-16
AD-13

Figure 2

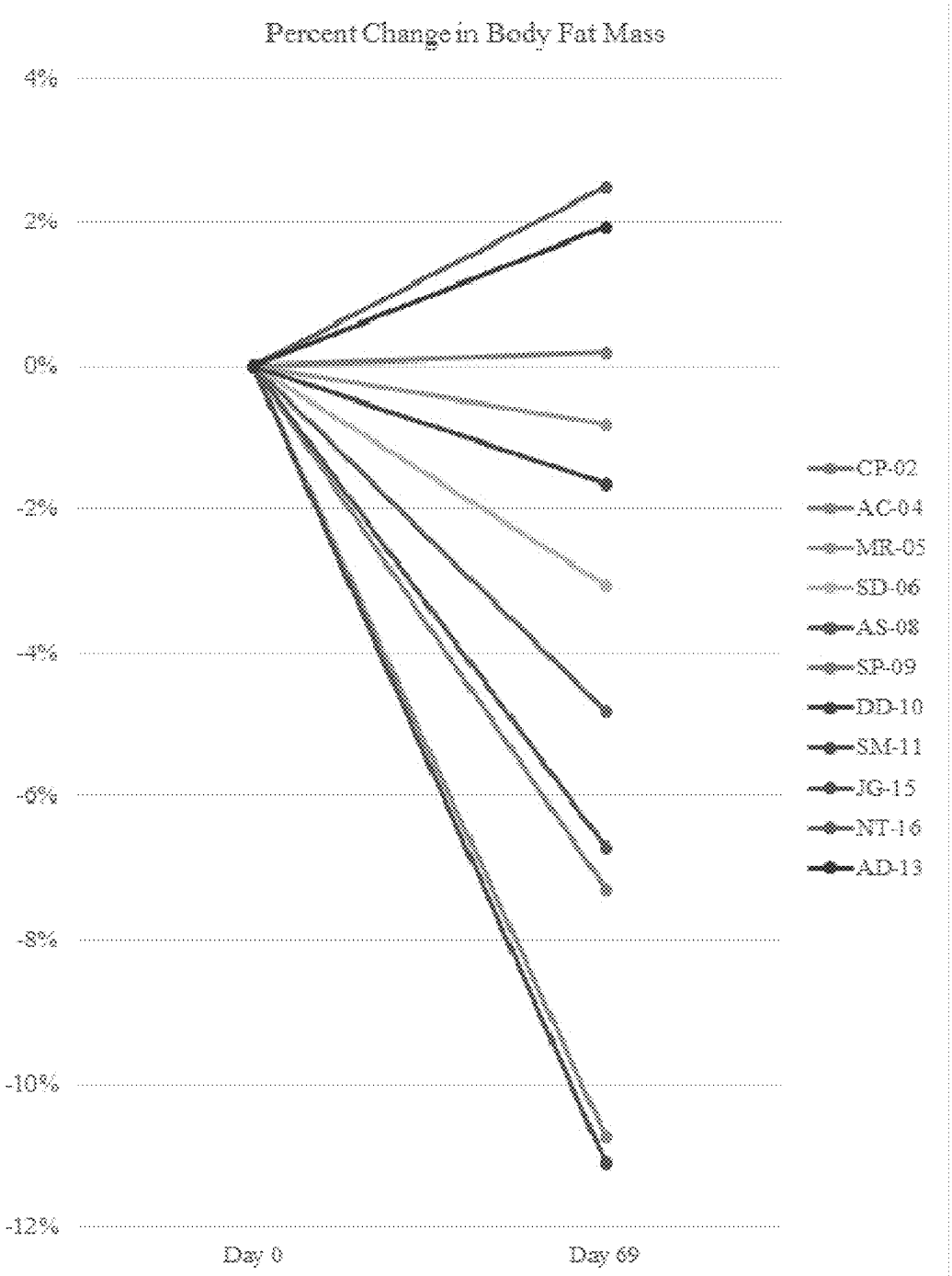

Percent Change in Body Fat Mass
4%
2%
0%
-2%
-4%
-6%
-8%
-10%
-12%
Day 0
Day 69
CP-02
AC-04
MR-05
SD-06
AS-08
SP-09
DD-10
SM-11
JG-15
NT-16
AD-13

Figure 3

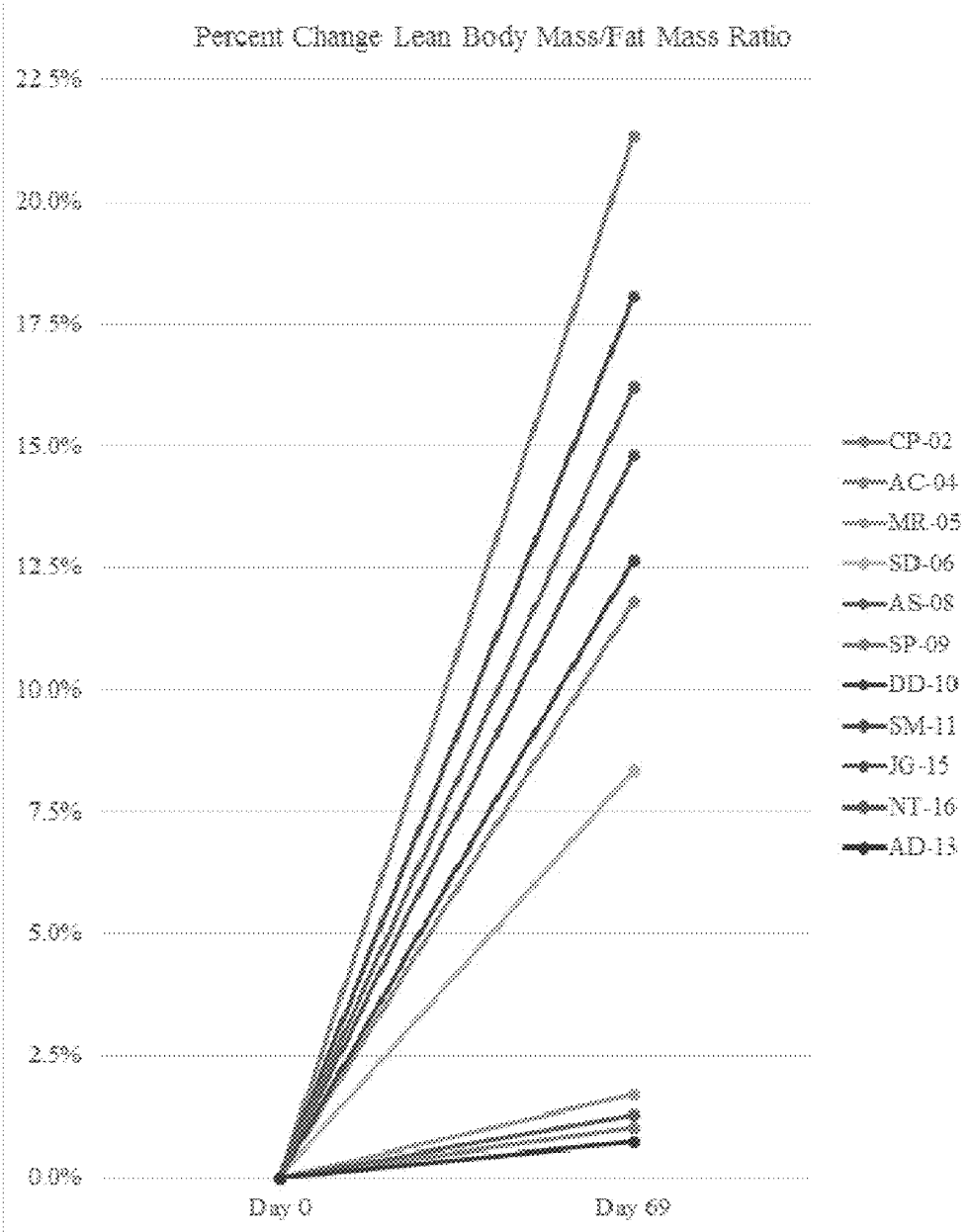

Percent Change Lean Body Mass/Fat Mass Ratio
22.5%
20.0%
17.5%
15.0%
12.5%
10.0%
7.5%
5.0%
2.5%
0.0%
Day 0
Day 69
CP-02
AC-04
MR-05
SD-06
AS-08
SP-09
DD-10
SM-11
JG-15
NT-16
AD-13

Figure 4

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Ser. No. 62/080,150, filed Nov. 14, 2014, U.S. Ser. No. 62/138,245, filed Mar. 25, 2015, U.S. Ser. No. 62/170,035, filed Jun. 2, 2015, and U.S. Ser. No. 62/221,359, filed Sep. 21, 2015, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations of potassium ATP (K_{ATP}) channel openers and their use for treatment of various diseases and conditions such as Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like.

BACKGROUND OF THE INVENTION

The following description of the background of the invention is provided simply as an aid in understanding the invention and is not admitted to describe or constitute prior art to the invention.

ATP-sensitive potassium (K_{ATP}) channels play important roles in a variety of tissues by coupling cellular metabolism to electrical activity. The K_{ATP} channel has been identified as an octameric complex of two unrelated proteins, which assemble in a 4:4 stoichiometry. The first is a pore forming subunit, Kir6.x, which forms an inwardly rectifying K^+ channel; the second is an ABC (ATP binding cassette) transporter, also known as the sulfonylurea receptor (SURx) (Babenko, et al., *Annu. Rev. Physiol.,* 60:667-687 (1998)). The Kir6.x pore forming subunit is common for many types of K_{ATP} channels, and has two putative transmembrane domains (identified as TM1 and TM2), which are linked by a pore loop (H5). The subunit that comprises the SUR receptor includes multiple membrane-spanning domains and two nucleotide-binding folds.

According to their tissue localization, K_{ATP} channels exist in different isoforms or subspecies resulting from the assembly of the SUR and Kir subunits in multiple combinations. The combination of the SUR1 with the Kir6.2 subunits (SUR1/Kir6.2) typically forms the adipocyte and pancreatic B-cell type K_{ATP} channels, whereas the SUR2A/Kir6.2 and the SUR2B/Kir6.2 or Kir6.1 combinations typically form the cardiac type and the smooth muscle type K_{ATP} channels, respectively (Babenko, et al., *Annu. Rev. Physiol.,* 60:667-687 (1998)). There is also evidence that the channel may include Kir2.x subunits. This class of potassium channels are inhibited by intracellular ATP and activated by intracellular nucleoside diphosphates. Such K_{ATP} channels link the metabolic status of the cells to the plasma membrane potential and in this way play a key role in regulating cellular activity. In most excitatory cells, K_{ATP} channels are closed under normal physiological conditions and open when the tissue is metabolically compromised (e.g. when the (ATP: ADP) ratio falls). This promotes K+ efflux and cell hyperpolarization, thereby preventing voltage-operated Ca2+ channels (VOCs) from opening. (*Prog Res Research,* (2001) 31:77-80).

Potassium channel openers (PCOs or KCOs) (also referred to as channel activators or channel agonists), are a structurally diverse group of compounds with no apparent common pharmacophore linking their ability to antagonize the inhibition of K_{ATP} channels by intracellular nucleotides. Diazoxide is a PCO that stimulates K_{ATP} channels in pancreatic β-cells (see Trube, et al., *Pfluegers Arch kEur J Physiol,* 407, 493-99 (1986)). Pinacidil and chromakalim are PCOs that activate sarcolemmal potassium channels (see Escande, et al., *Biochem Biophys Res Commun,* 154, 620-625 (1988); Babenko, et al., *J Biol Chem,* 275(2), 717-720 (2000)). Responsiveness to diazoxide has been shown to reside in the 6^{th} through 11^{th} predicted transmembrane domains (TMD6-11) and the first nucleotide-binding fold (NBF1) of the SUR1 subunit.

Diazoxide, which is a nondiuretic benzothiadiazine derivative having the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1.1-dioxide (empirical formula $C_8H_7ClN_2O_2S$), is commercialized in three distinct formulations to treat two different disease indications: 1) hypertensive emergencies and 2) hyperinsulinemic hypoglycemic conditions. Hypertensive emergencies are treated with Hyperstat IV, an aqueous formulation of diazoxide for intravenous use, adjusted to pH 11.6 with sodium hydroxide. Hyperstat IV is administered as a bolus dose into a peripheral vein to treat malignant hypertension or sulfonylurea overdose. In this use, diazoxide acts to open potassium channels in vascular smooth muscle, stabilizing the membrane potential at the resting level, and preventing vascular smooth muscle contraction.

Hyperinsulinemic hypoglycemic conditions are treated with Proglycem, an oral pharmaceutical version of diazoxide useful for administration to infants, children and adults. It is available as a chocolate mint flavored oral suspension, which includes 7.25% alcohol, sorbitol, chocolate cream flavor, propylene glycol, magnesium aluminum silicate, carboxymethylcellulose sodium, mint flavor, sodium benzoate, methylparaben, hydrochloric acid to adjust the pH, poloxamer 188, propylparaben and water. Diazoxide is also available as a capsule with 50 or 100 mg of diazoxide including lactose and magnesium stearate.

Several experimental formulations of diazoxide have been tested in humans and animals. These include an oral solution tested in pharmacodynamic and pharmacokinetic studies and a tablet formulation under development as an anti-hypertensive, but never commercialized (see Calesnick, et al., *J. Pharm. Sci.* 54:1277-1280 (1965); Reddy, et al., *AAPS Pharm Sci Tech* 4(4):1-98, 9 (2003); U.S. Pat. No. 6,361,795).

Current oral formulations of diazoxide are labeled for dosing two or three times per day at 8 or 12 hour intervals. Most patients receiving diazoxide are dosed three times per day. Commercial and experimental formulations of diazoxide are characterized by rapid drug release following ingestion with completion of release in approximately 2 hours.

Current oral formulations of diazoxide in therapeutic use result in a range of adverse side effects including dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, and headache (see current packaging insert for the Proglycem). Oral treatment with diazoxide is used in individuals experiencing serious disease where failing to treat results in significant morbidity and mortality. The adverse side effects from oral administration are tolerated because the benefits of treatment are substantial. The adverse side effects profile of oral diazoxide limit the utility of the drug in treating obese patients at doses within the labeled range of 3 to 8 mg/kg per day.

The effect of diazoxide in animal models of diabetes and obesity (e.g. obese and lean Zucker rats) has been reported. See e.g. Alemzadeh et al. (*Endocrinology* 133:705-712 (1993), Alemzadeh et al. (*Metabolism* 45:334-341 (1996)), Alemzadeh et al. (*Endocrinology* 140:3197-3202 (1999)), Stanridge et al. (FASEB J 14:455-460 (2000)), Alemzadeh et al. (Med Sci Monit 10(3): BR53-60 (2004)), Alemzadeh and Tushaus (*Endocrinology* 145(12):3476-3484 (2004)), Aizawa et al. (*J of Pharma Exp Ther* 275(1): 194-199 (1995)), and Surwit et al. (*Endocrinology* 141:3630-3637 (2000)).

The effect of diazoxide in humans with obesity or diabetes has been reported. See e.g., Wigand and Blackard (*Diabetes* 28(4):287-291 (1979); evaluation of diazoxide on insulin receptors), Ratzmann et al. (*Int J Obesity* 7(5):453-458 (1983); glucose tolerance and insulin sensitivity in moderately obese patients), Marugo et al. (*Boll Spec It Biol Sper* 53:1860-1866 (1977); moderate dose diazoxide treatment on weight loss in obese patients), Alemzadeh et al. (*J Clin Endocr Metab* 83:1911-1915 (1998); low dose diazoxide treatment on weight loss in obese hyperinsulinemic patients), Guldstrand et al. (*Diabetes and Metabolism* 28:448-456 (2002); diazoxide in obese type II diabetic patients), Ortqvist et al. (*Diabetes Care* 27(9):2191-2197 (2004); beta-cell function measured by circulating C-peptide in children at clinical onset of type 1 diabetes), Bjork et al. (*Diabetes Care* 21(3):427-430 (1998); effect of diazoxide on residual insulin secretion in adult type I diabetes patients), and Qvigstad et al., (*Diabetic Medicine* 21:73-76 (2004)).

U.S. Pat. No. 5,284,845 describes a method for normalizing blood glucose and insulin levels in an individual exhibiting normal fasting blood glucose and insulin levels and exhibiting in an oral glucose tolerance test, elevated glucose levels and at least one insulin level abnormality selected from the group consisting of a delayed insulin peak, an exaggerated insulin peak and a secondary elevated insulin peak. According to this reference, the method includes administering diazoxide in an amount from about 0.4 to about 0.8 mg/kg body weight before each meal in an amount effective to normalize the blood glucose and insulin levels.

U.S. Pat. No. 6,197,765 describes administration of diazoxide as a treatment for syndrome-X, and resulting complications, that include hyperlipidemia, hypertension, central obesity, hyperinsulinemia and impaired glucose intolerance. According to this reference, diazoxide interferes with pancreatic islet function by ablating endogenous insulin secretion resulting in a state of insulin deficiency and high blood glucose levels equivalent to that of diabetic patients that depend on exogenous insulin administration for normalization of their blood glucose levels.

U.S. Pat. No. 2,986,573 describes diazoxide and alkali metal salts for the treatment of hypertension.

U.S. Pat. No. 5,629,045 describes diazoxide for topical ophthalmic administration.

WO 98/10786 describes use of diazoxide in the treatment of X-syndrome including obesity associated therewith.

U.S. Patent publication no. 2003/0035106 describes diazoxide-containing compounds for reducing the consumption of fat-containing foods.

U.S. Patent publication no. 2004/0204472 describes the use of a Cox-2 inhibitor plus diazoxide in the treatment of obesity.

U.S. Patent publication no. 2002/0035106 describes the use of K_{ATP} channel openers including diazoxide and metal salts for reducing the consumption of fat containing food.

SUMMARY OF THE INVENTION

Provided herein are pharmaceutical formulations of K_{ATP} channel openers and their use (optionally in combination with growth hormone) for treatment of various diseases and conditions, including Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like. Such formulations are characterized as being bioavailable. A K_{ATP} channel opener as used herein has any one or more of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo. Preferably, K_{ATP} channel openers are K_{ATP} channel openers with all three properties. K_{ATP} channel openers as defined above preferably have the structure of compounds of Formulas I-VII as set forth below.

In accordance with one aspect of the present invention, it has been discovered that one or more K_{ATP} channel opener(s) (optionally in combination with growth hormone) is effective for the treatment of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, and is especially effective for increasing the lean body mass of such subjects. Therefore, in one aspect of the present invention, there are provided methods of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, said method comprising administering to said subject for at least 4 weeks an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone).

In some embodiments, the lean body mass of said subject is increased by at least 1%. In some embodiments, the lean body mass of said subject is increased by at least 2%. In some embodiments, the lean body mass of said subject is increased by at least 3%. In some embodiments, the lean body mass of said subject is increased by at least 4%. In some embodiments, the lean body mass of said subject is increased by at least 5%.

In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the hyperphagia of a subject. In some embodiments, the hyperphagia of said subject is reduced by at least 10%. In some embodiments, the hyperphagia of said subject is reduced by at least 20%. In some embodiments, the hyperphagia of said subject is reduced by at least 30%.

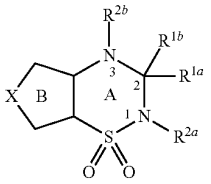
In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the body fat of a subject. In some embodiments, the body fat of said subject is reduced by at least 1%. In some embodiments, the body fat of said subject is reduced by at least 3%. In some embodiments, the body fat of said subject is reduced by at least 5%.

In another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a K_{ATP} channel opener in addition to said growth hormone.

In yet another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of an effective amount of a K_{ATP} channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said K_{ATP} channel opener.

K_{ATP} channel openers defined by Formula I are as follows:

Formula I



wherein:

R^{1a} and R^{1b}, when present, are independently selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2a} and R^{2b}, when present, are independently selected from the group consisting of hydrogen, and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

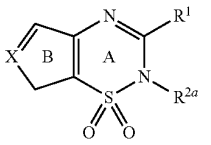
wherein rings A and B are each independently saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

In particular embodiments, compounds of Formula I may include a double bond between either positions 1 and 2 or positions 2 and 3 of Ring A. When a double bond is present between positions 1 and 2 of Ring A, R^{2a} is 1 absent and one of R^{1a} and R^{1b} are absent. When a double bond is present between positions 2 and 3 of Ring A, R^{2b} is absent and one of R^{1a} and R^{1b} are absent. In a preferred embodiment, R^{1a} and R^{1b} are not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

K_{ATP} channel openers defined by Formula II being a subgenera of Formula I are as follows:

Formula II



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2a} is selected from the group consisting of hydrogen, and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

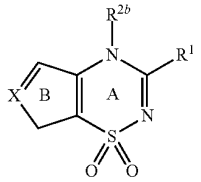
wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

In particular embodiments of Formula II, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

K_{ATP} channel openers defined by Formula III being a subgenera of Formula I are as follows:

Formula III



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2b} is selected from the group consisting of hydrogen, and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

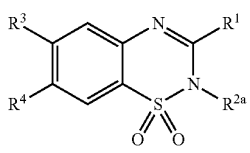
wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

In particular embodiments of Formula III, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

K_{ATP} channel openers defined by Formula IV being a subgenera of Formula I are as follows:

Formula IV



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

R^{2a} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

R^4 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

and all bioequivalents including salts, prodrugs and isomers thereof.

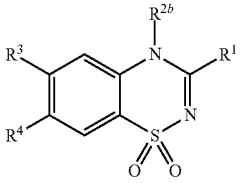
In particular embodiments of Formula IV, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2a} is hydrogen; and R^3 and R^4 are each independently halogen.

In a preferred embodiment of Formula IV, R^1 is not amino.

In another embodiment of Formula IV, R^1 is methyl; R^{2a} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

K_{ATP} channel openers defined by Formula V being a subgenera of Formula I are as follows:

Formula V



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

R^{2b} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

R^4 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

and all bioequivalents including salts, prodrugs and isomers thereof.

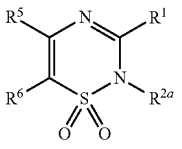
In particular embodiments of Formula V, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2b} is hydrogen; and R^3 and R^4 are each independently halogen.

In a preferred embodiment of Formula V, R^1 is not amino.

In another embodiment of Formula V, R^1 is methyl; R^{2b} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

K_{ATP} channel openers defined by Formula VI are as follows:

Formula VI



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

R^{2a} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^5 can cooperate with R^1 or R^6 to form an additional ring;

R^6 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^6 can cooperate with R^1 or R^5 to form an additional ring;

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

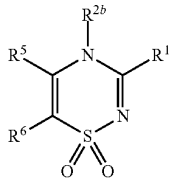
and all bioequivalents including salts, prodrugs and isomers thereof.

In a preferred embodiment, R^1 is not an amino substituent.

In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

K_{ATP} channel openers defined by Formula VII are as follows:

Formula VII



wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

R^{2b} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^5 can cooperate with R^1 or R^6 to form an additional ring;

R^6 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^6 can cooperate with R^1 or R^5 to form an additional ring;

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

and all bioequivalents including salts, prodrugs and isomers thereof.

In a preferred embodiment, R^1 is not an amino substituent.

In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

Unless otherwise indicated, reference in this application to K_{ATP} channel openers should be understood to refer to K_{ATP} channel opener(s) having one or more and preferably all three of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo. Such K_{ATP} channel openers preferably have the structure of any of the compounds of Formulae I-VII, or more preferably Formulae I-VII where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, any of the compounds of Formulae II or III, or more preferably, any of the compounds of Formulae II or III where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, the structure is diazoxide. Structural variants or bioequivalents of the compounds of any of Formulae I-VII such as derivatives, salts, prodrugs or isomers are also contemplated. Other K_{ATP} channel openers that are contemplated for use herein include BPDZ62, BPDZ 73, NN414, BPDZ 154.

In vitro analysis of glucose induced release of insulin via K_{ATP} channel openers can be determined using rat islets as provided by De Tullio, et al., *J. Med. Chem.,* 46:3342-3353 (2003) or by using human islets as provided by Björklund, et al., *Diabetes,* 49:1840-1848 (2000).

Provided herein are formulations, such as controlled release pharmaceutical formulations, of K_{ATP} channel openers and bioquivalents thereof. In one embodiment, the controlled release formulations are formulated for oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the K_{ATP} channel openers. In certain embodiments, the dosage of the K_{ATP} channel openers contained in a formulation may be determined based on the weight of the patient for which it is to be administered, i.e., the formulation may contain in a single administration dosage between 0.1-20 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 0.1-0.5 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 0.5-1 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 1-2 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 2-5 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 5-10 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 10-15 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 15-20 mg of the K_{ATP} channel opener per kg of the patient's body weight.

Also provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers obtained by at least one of the following: (a) particle size reduction involving comminution, spray drying, or other micronising techniques, (b) use of a pharmaceutical salt of the K_{ATP} channel opener, (c) use of an ion exchange resin, (d) use of inclusion complexes, for example cyclodextrin, (e) compaction of the K_{ATP} channel opener with a solubilizing agent including a low viscosity hypromellose, low viscosity metylcellulose or similarly functioning excipient or combinations thereof, (f) associating the K_{ATP} channel opener with a salt prior to formulation, (g) use of a solid dispersion of the K_{ATP} channel opener, (h) use of a self emulsifying system, (i) addition of one or more surfactants to the formulation, (j) use of nanoparticles, or (k) combinations of these approaches.

Further provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers which include at least one component that substantially inhibits release of the K_{ATP} channel activator from the formulation until after gastric transit. As used herein, "substantially inhibits" means less than 15% release, more preferably at least less than 10% release, or more preferably at least less than 5% release of the drug from the formulation during gastric transport. Release can be measured in a standard USP based in-vitro gastric dissolution assay in a calibrated dissolution apparatus (see, for example, U.S. Pharmacopeia, Chapter 711 (2005)).

Also provided are oral pharmaceutical formulations of K_{ATP} channel openers which include at least one component that substantially inhibits release of the K_{ATP} channel opener from the formulation until after gastric transit. Substantial inhibition of drug release during gastric transit is achieved by inclusion of a component in the formulation selected from the group consisting of: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet, (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet, (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system, (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or co-polymer applied as a compression coating on a tablet, (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet, (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system, (h) a non-aqueous soluble polymer applied to microparticles, (i) incorporation of the formulation in an osmotic pump system, (j) use of systems controlled by ion exchange resins, and (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

Also provided herein are controlled release pharmaceutical formulations of K_{ATP} channel openers, wherein the formulation includes at least one component that contributes to sustained release of a K_{ATP} channel opener over a period of 2-4 hours following administration, or over a period of 4-8 hours following administration, or over a period of more than 8-24 hours following administration. These formulations are characterized in having one of the following components: (a) a pH sensitive polymeric coating, (b) a hydrogel coating, (c) a film coating that controls the rate of diffusion of the drug from a coated matrix, (d) an erodable matrix that controls rate of drug release, (e) polymer coated pellets, granules or microparticles of drug which can be further encapsulated or compressed into a tablet, (f) an

osmotic pump system containing the drug, (g) a compression coated tablet form of the drug, or (h) combinations of these approaches.

As used herein, an erodable matrix is the core of a tablet formulation that, upon exposure to an aqueous environment, begins a process of disintegration which facilitates the release of drug from the matrix. The rate of release of drug from the tablet is controlled both by the solubility of the drug and the rate of disintegration of the matrix.

The above formulations may further comprise one or more additional pharmaceutically active agents (other than K_{ATP} channel openers) useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, other obesity associated comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, or other psychotic diseases.

Further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

Still further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener which upon administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener that upon administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

Provided herein is a method of treating hypoglycemia, the method comprising orally administering a controlled release formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

Further provided herein is a method of treating obesity associated co-morbidities in an obese, overweight or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener, or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Yet further provided herein is a method of achieving weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. The daily dosage administered is preferably between 50 and 180 mg. In certain embodiments, the obese individual has a body mass index greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

Also provided is a method of maintaining a weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. It is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Further provided is a method of elevating energy expenditure in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

Additionally provided is a method of elevating beta oxidation of fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

Yet further provided is a method of reducing visceral fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Still further provided is a method of delaying or preventing the transition to diabetes of a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Additionally provided is a method of restoring normal glucose tolerance in a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP}

channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Further provided is a method of restoring normal glucose tolerance in a diabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Still further provided is a method of delaying or preventing progression of diabetes in an individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Also provided is a method to prevent or treat weight gain, impaired glucose tolerance or dyslipidemia associated with the use of anti-psychotics to treat patients comprising the co-administration of an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Further provided is a method to increase lean body mass in a Prader-Willi Syndrome patient, in a Smith-Magenis syndrome patient, in a Froelich's Syndrome patient, in a Cohen Syndrome patient, in a Summit Syndrome patient, in an Alstrom Syndrome patient, in a Borjeson Syndrome patient or in a Bardet-Biedl Syndrome patient comprising the administration of an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone) or a controlled release pharmaceutical formulation of a K_{ATP} channel opener (optionally in combination with growth hormone). In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Still further provided is a method to treat obesity or elevated triglycerides in a patient suffering hyperlipoproteinemia type I, type II, type III or type IV comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

Also provided is a method of reducing the incidence of adverse effects from administration of a K_{ATP} channel opener in the treatment of diseases of a subject achieved by any of the following: (a) use of a dosage form that on administration reduces C_{max} relative to the current Proglycem oral suspension or capsule products in order to reduce the incidence of adverse side effects that are associated with peak drug levels, (b) use of a dosage form that delays release until gastric transit is complete in order to reduce the incidence of adverse side effects that are associated with the release of drug in the stomach, (c) initiating dosing at subtherapeutic levels and in a stepwise manner increasing dose daily until the therapeutic dose is achieved wherein the number of steps is 2 to 10 to reduce the incidence of adverse side effects that occur transiently at the initiation of treatment, (d) use of the lowest effective dose to achieve the desired therapeutic effect in order to reduce the incidence of adverse side effects that are dose dependent, or (e) optimizing the timing of administration of dose within the day and relative to meals.

Further provided is a method of preventing weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

Yet further provided is a method of treating weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

Also provided is a method of treating diseases characterized by obesity, hyperphagia, dyslipidemia, or decreased energy expenditure including (a) Prader Willi Syndrome, (b) Froelich's syndrome, (c) Cohen syndrome, (d) Summit Syndrome, (e) Alstrom, Syndrome, (f) Borjesen Syndrome, (g) Bardet-Biedl Syndrome, (h) hyperlipoproteinemia type I, II, III, and IV, or (i) Smith-Magenis syndrome (SMS), said method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

Further provided is a pharmaceutical formulation of a K_{ATP} channel opener further comprising a pharmaceutically active agent other than the K_{ATP} channel opener. In this formulation, the other pharmaceutically active agent is an agent useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, or other obesity associated comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, and other psychotic condition.

The formulations containing K_{ATP} channel openers described herein provide for improved compliance, efficacy and safety, and for co-formulations with other agents. Included are co-formulations of K_{ATP} channel openers with one or more additional pharmaceutically active agents that have complementary or similar activities or targets. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity or to maintain weight loss in an obesity prone individual include, but are not limited to: sibutramine, orlistat, phentermine, rimonabant, a diuretic, an antiepileptic, or other pharmaceutical active whose therapeutic utility includes weight loss. It is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. Other pharmaceutically active agents that may be combined with K_{ATP} channel openers to treat type II diabetes, or prediabetes include acarbose, miglitol, metformin, repaglinide, nateglinide, rosiglitizone, proglitizone, ramipril, metaglidasen, or any other pharmaceutical active that improves insulin sensitivity or glucose utilization or glycemic control where the mode of action is not enhanced insulin secretion. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity associated co-morbidities include a drug active used to lower cholesterol, a drug active used to lower blood pressure, an anti-inflammatory drug that is not a cox-2 inhibitor, a drug that is an antidepressant, a drug used to treat urinary incontinence, or other drug routinely used to treat disease conditions the incidence of which is elevated in overweight or obese patients as compared to normal weight individuals including, but not limited to, drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrium, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity, infertility, and the like.

In the present context, the term "therapeutically effective" or "effective amount" indicates that the materials or amount

of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

The term "pharmaceutically acceptable" indicates that the identified material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes; exemplary formulations contain at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient. Other terms as used herein are defined below.

Adipocyte: An animal connective tissue cell specialized for the synthesis and storage of fat.

Agonist: A chemical compound that has affinity for and stimulates physiological activity at cell receptors normally stimulated by naturally occurring substances, triggering a biochemical response. An agonist of a receptor can also be considered an activator of the receptor.

About: is used herein to mean in quantitative terms plus or minus 10%.

Adipose tissue: Tissue comprised principally of adipocytes.

Adolescent: A person between 10 and 19 years of age.

Adiponectin: A protein hormone produced and secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose. Adiponectin influences the body's response to insulin. Adiponectin also has anti-inflammatory effects on the cells lining the walls of blood vessels.

Amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition: refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

Analog: a compound that resembles another in structure but differs by at least one atom.

Antagonist: A substance that tends to nullify the action of another, as a drug that binds to a cell receptor without eliciting a biological response.

Atherosclerotic Plaque: A buildup of cholesterol and fatty material within a blood vessel due to the effects of atherosclerosis

Bariatric Surgery: a range of surgical procedures which are designed to aid in the management or treatment of obesity and allied diseases.

Beta cell rest: Temporarily placing beta cells in a condition in which there is reduced metabolic stress due to suppressed secretion of insulin.

Bilaminate: A component of a pharmaceutical dosage form that consists of the lamination of two distinct materials.

Bioavailability: Refers to the amount or extent of therapeutically active substance that is released from the drug product and becomes available in the body at the intended site of drug action. The amount or extent of drug released can be established by the pharmacokinetic-parameters, such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (C_{max}) of the drug.

Bioequivalent: Two formulations of the same active substance are bioequivalent when there is no significant difference in the rate and extent to which the active substance becomes available at the site of drug action when administered at the same molar dose under similar conditions. "Formulation" in this definition may include the free base of the active substance or different salts of the active substance. Bioequivalence may be demonstrated through several in vivo and in vitro methods. These methods, in descending order of preference, include pharmacokinetic, pharmacodynamic, clinical and in vitro studies. In particular, bioequivalence is demonstrated using pharmacokinetic measures such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (Cmax) of the drug, using statistical criteria.

Cannabinoid Receptor: Receptors in the endocannabinoid (EC) system associated with the intake of food and tobacco dependency. Blocking the cannabinoid receptor may reduce dependence on tobacco and the craving for food.

Combination: refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two collections. It can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

Composition: refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

Compression tablet: Tablet formed by the exertion of pressure to a volume of tablet matrix in a die.

Compression coated tablet: A tablet formed by the addition of a coating by compression to a compressed core containing the pharmaceutical active.

Derivative: a chemical substance derived from another substance by modification or substitution.

Daily dosage: the total amount of a drug taken in a 24 hour period whether taken as a single dose or taken in multiple doses.

Diazoxide: 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.

Encapsulation system: a structural feature that contains drug within such as a pharmaceutical capsule. A gel into which drug is incorporated also is considered an encapsulation system.

Equivalent amount: an amount of a derivative of a drug that in assays or upon administration to a subject produces an equal effect to a defined amount of the non-derivatized drug.

Fatty acid synthase: The central enzyme of a multienzyme complex that catalyses the formation of palmitate from acetylcoenzyme A, malonylcoenzyme A, and NADPH.

Gastric Lipase: An enzyme secreted into the gastrointestinal tract that catalyzes the hydrolysis of dietary triglycerides.

Glidant: An inactive component of a pharmaceutical formulation that prevents caking of the matrix during processing steps.

Growth hormone: also known as somatotropin or somatropin, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans and other animals. It is a type of mitogen which is specific only to certain kinds of cells. Growth hormone is a 191-amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotropic cells within the lateral wings of the anterior pituitary gland. GH is a stress hormone that raises the concentration of glucose and free fatty acids. It also stimulates production of IGF-1.

Hyperinsulemia: Excessively high blood insulin levels, which is differentiated from hyperinsulinism, excessive

secretion of insulin by the pancreatic islets. Hyperinsulinemia may be the result of a variety of conditions, such as obesity and pregnancy.

Hyperinsulinism: Excessive secretion of insulin by the pancreatic islets.

Hyperlipidemia: A general term for elevated concentrations of any or all of the lipids in the plasma, such as cholesterol, triglycerides and lipoproteins.

Hyperphagia: Ingestion of a greater than optimal quantity of food.

Ingredient of a pharmaceutical composition: refers to one or more materials used in the manufacture of a pharmaceutical composition. Ingredient can refer to an active ingredient (an agent) or to other materials in the compositions. Ingredients can include water and other solvents, salts, buffers, surfactants, water, non-aqueous solvents, and flavorings.

IGF-1, also called somatomedin C, is a protein that in humans is encoded by the IGF1 gene. IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges, and has a molecular weight of 7,649 daltons.

Insulin resistance: A condition in which the tissues of the body are diminished in their response to insulin.

Ischemic injury: injury to tissue that results from a low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

Ketoacidosis: Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissue and fluids, as in diabetic acidosis.

Kit: refers to a packaged combination. A packaged combination can optionally include a label or labels, instructions and/or reagents for use with the combination.

Kir: Pore forming subunit of the K_{ATP} channel. Also known as the inwardly rectifying subunit of the K_{ATP} channel. Typically existing as Kir6.x and infrequently as Kir2.x subspecies.

K_{ATP} channel: An ATP sensitive potassium ion channel across the cell membrane formed by the association of 4 copies of a sulfonylurea receptor and 4 copies of a pore forming subunit Kir. Agonizing the channel can lead to membrane hyperpolarization.

Lean body mass: Lean Body Mass is a component of body composition, calculated by subtracting body fat weight from total body weight: total body weight is lean plus fat. In equations:

Lean Body Mass equals Body Weight minus Body Fat (LBM=BW−BF)

Lean Body Mass plus Body Fat equals Body Weight (LBM+BF=BW)

The percentage of total body mass that is lean is usually not quoted—it would typically be 60-90%. Instead, the body fat percentage, which is the complement, is computed, and is typically 10-40%. The Lean body mass (LBM) has been described as an index superior to total body weight for prescribing proper levels of medications and for assessing metabolic disorders, as body fat is less relevant for metabolism.

Leptin: Product (16 kD) of the ob (obesity) locus. It is found in plasma of mammals and exerts a hormonal action, which reduces food uptake and increases energy expenditure.

Lipogenesis: The generation of new lipids, primarily triacylglycerides. It is dependent on the action of multiple distinct enzymes and transport molecules.

Lipolysis: The breakdown of fat by the coordinated action of multiple enzymes.

Lipoprotein lipase: An enzyme of the hydrolase class that catalyses the reaction of triacyglycerol and water to yield diacylglyerol and a fatty acid anion. The enzyme hydrolyses triacylglycerols in chylomicrons, very-low-density lipoproteins, low-density lipoproteins, and diacylglycerols.

Lubricant: An inactive component of a pharmaceutical formulation that provides for the flow of materials in various processing steps, particularly tableting.

Microparticle: A small particulate formed in the process of developing pharmaceutical formulations that may be coated prior to producing the final dosage from.

Obesity: An increase in body weight beyond the limitation of skeletal and physical requirement, as the result of an excessive accumulation of fat in the body. Formally defined as having a body mass index greater than 30 kg/m^2.

Obesity Prone: Individuals who because of genetic predisposition or prior history of obesity are at above average risk of becoming obese.

Obesity related co-morbidities: any disease or condition of animals or humans that are increased incidence in obese or overweight individuals. Examples of such conditions include hypertension, prediabetes, type 2 diabetes, osteoarthritis and cardiovascular conditions.

Osmotically controlled release: A pharmaceutical dosage form in which the release of the active drug is principally achieved by the hydration of a swellable component of the formulation.

Overweight: an individual whose weight is above that which is ideal for their height but who fails to meet the criteria for classification as obese. In humans using Body Mass Index (kg/m^2) an overweight individual has a BMI between 25 and 30.

Oxidation of Fat: A series of reactions involving acylcoenzyme A compounds, whereby these undergo beta oxidation and thioclastic cleavage, with the formation of acetylcoenzyme A; the major pathway of fatty acid catabolism in living tissue.

Pharmaceutical composition: refers a composition that contains an agent and one or more other ingredients that is formulated for administration to a subject. An agent refers to an active ingredient of a pharmaceutical composition. Typically active ingredients are active for treatment of a disease or condition. For example, agents that can be included in pharmaceutical compositions include agents for treating obesity or diabetes. The pharmaceutically active agent can be referred to as "a pharmaceutical active."

Pharmaceutical effect: refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

Pharmacodynamic: An effect mediated by drug action.

Pharmacokinetic: Relating to the absorption, distribution, metabolism and elimination of the drug in the body.

Polymorph: A compound that shares the same chemistry but a different crystal structure.

Prader-Willi syndrome (PWS): A complex neurobehavioral/metabolic disorder which is due to the absence of normally active, paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with 70-75% of the cases due to a de novo deletion in the paternally inherited chromosome 15 11-q13 region, 20-30% from maternal uniparental disomy 15 (UPD), and the

remaining 2-5% from either microdeletions or epimutations of the imprinting center (i.e., imprinting defects) (Bittel and Butler, Expert Rev Mol Med 7(14):1-20 (2005); Cassidy and Driscoll, Eur J Hum Genet 17(1):3-13(2009)).

The clinical manifestations of the condition begin in utero with diminished fetal activity (Miller Am J Med Genet A 155A(5):1-10 (2011)). Low lean body mass and hypotonia are universal in PWS and present throughout life (Brambilla Am J Clin Nutr 65(5):1369-1374 (1997), Lloret-lineras Int J Obes 37:1198-1203 (2013)). Mental retardation occurs to varying degrees with the average IQ being 70 (PWSUSA). PWS patients present with a range of behavioral complications including autistic-spectrum-disorder-like behaviors, compulsive behaviors, self-injurious behaviors, and aggressive, threatening and destructive behaviors. About 80% of PWS patients are growth hormone deficient (Goldstone, Trends Endocrinol Metab 15:12-120 (2004); Davies et al., Front Neuroendocrinol 29:413-427 (2008); Cassidy and Driscoll, 2009, supra). Nearly all PWS patients are hypogonadal, requiring sex hormone supplementation (Goldstone, 2004, supra; Davies et al., 2008, supra; Cassidy and Driscoll, 2009, supra). These patients have hypothalamic insufficiency/dysfunction (Goldstone Am J Clin Nutr 75(3):468-475 (2002)).

The accumulation of excess body fat may begin about age 2 and can continue into adulthood (Miller 2011, supra). The vast majority of body fat in PWS is subcutaneous (Brambilla 1997, supra; Sode-Carlson, Growth hormone and IGF research 20:179-184 (2010), Bedogni J Endocrinol Invest DOI 10.1007/s40618-015-0266-y (2015)). Obesity is not universal in PWS, unlike the universality of low lean body mass and hypotonia. For example, Sode-Carlson et al. (2010), supra, evaluated 46 adult PWS patients, 25 women and 21 men. The average BMI in these adult PWS patients was 27.2 kg/m^2. Thus, on average, these patients were overweight rather than obese, suggesting that more than half are not, in fact, obese by the best metric. Similarly, Brambilla et al. Nutr Metab Cardiovasc Dis 21(4):269-276 (2011) studied a population of 109 children with PWS. They found that 54% were not classified as obese by the best metric. Thus, both in adults and in children with PWS, obesity is not only not universal, but may, in fact, occur in less than half of the population. Subcutaneous fat makes up a greater percentage of total fat in PWS than it does in obese controls at all ages (Sode-Carlson 2010, supra).

Hyperphagia with the associated problematic food related behaviors begins on average about age 8 (Miller 2011, supra). These patients sense they are starving when they are not. Upon the onset of hyperphagia, PWS patients will eat any food in the line of sight, get up at night to eat, dig through the trash for food, steal food, consume frozen food, pet food, spoiled food and even consume non-food items (Miller 2011, supra). They will become angry or throw tantrums if denied food. At this stage and thereafter throughout life, access to food is strictly limited, with cabinets and refrigerators being locked. To limit food related anxiety, meal times and meal composition are strictly regimented.

The mortality rate for PWS patients is three times that of the general population at all ages (Cassidy Genet Med 14(1):10-26 (2012)), with the average age at death being about 29 years (PWSUSA mortality database, n=488). In contrast, being obese, but not morbidly obese has little impact on life expectancy (Anon (2011) National Research Council Panel on Understanding Divergent Trends in Longevity in High-Income Countries; Crimmons, E M, Preston, S H, Cohen, B, editors. National Academies Press).

Prader-Willi patients expend less energy and are more sedentary than either the general population, obese controls or patients with similar intellectual disabilities. Butler et al. Am J Med Gent A 143A(5):449-459 (2007)) compared the energy expenditure and total work of a group of 48 PWS patients with a group of 24 obese controls. Compared to the controls, PWS patients had significantly decreased total energy expenditure (−20%), resting energy expenditure (−16%) and mechanical work (−35%). After adjusting for group differences in lean body mass, the difference remained significant for mechanical work.

In a study by van Mil et al., Int J Obes Relat Metab Disord 24(4):429-434 (2000), the authors measured basal metabolic rate (BMR), average daily metabolic rate (ADMR), activity induced energy expenditure (AEE), and ADMR/BMR (PAL) in a group of PWS patients and matched controls. ADMR, AEE and PAL were significantly lower ($P<0.01$) in the PWS group compared with the control group −28.2%, −58.2%, and −14.2%, respectively).

De Lind van Wijngaarden et al., J Clin Endocrinol Metab 95(4):1758-1766 (2010) evaluated cardiovascular and metabolic risk factors in children with PWS. They showed that 63% of infants and 73% of pre-pubertal children with PWS have at least one cardiovascular risk factor, defined as dyslipidemia or hypertension. Thus, the cardiometabolic risk in PWS is elevated even in younger children.

Preadipocyte: A progenitor cell to adipocytes.

Prediabetic: A condition that precedes diagnosis of type II diabetes. Type II diabetes is a form of diabetes mellitus which is characterized by insulin insensitivity or resistance.

Prodrug: refers to a compound which, when metabolized, yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

Prolonged Administration (prolonged basis): Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).

Quick dissolving formulation: a pharmaceutical formulation which upon oral administration may release substantially all of the drug active from the formulation within 10 minutes.

Release formulation (sustained), (or "sustained release formulation"): A formulation of pharmaceutical product that, upon administration to animals, provides for release of the active pharmaceutical over an extended period of time than provided by formulations of the same pharmaceutical active that result in rapid uptake. Similar terms are extended-release, prolonged-release, and slow-release. In all cases, the preparation, by definition, has a reduced rate of release of active substance.

Release formulation (delayed), (or "delayed release formulation"): Delayed-release products are modified-release, but are not extended-release. They involve the release of discrete amount(s) of drug some time after drug administration, e.g. enteric-coated products, and exhibit a lag time during which little or no absorption occurs.

Release formulation (controlled), (or "controlled release formulation"): A formulation of pharmaceutical product that may include both delay of release of pharmaceutical active upon administration and control of release in the manner described for sustained release.

Salt: the neutral, basic or acid compound formed by the union of an acid or an acid radical and a base or basic radical.

Smith-Magenis syndrome (SMS; OMIM #182290, *607642): A complex, generally sporadic, genetic disorder

caused by haploinsufficiency of the retinoic acid induced 1 (RAI1) gene. caused by either a 17p11.2 deletion encompassing the retinoic acid-induced 1 (RAI1) gene or a mutation of RAI1. (see, for example, Burns et al., in Human Molecular Genetics, 2010, Vol. 19, No. 20, pp. 4026-4042).

Smith-Magenis syndrome is characterized by a clinically recognizable phenotype that includes physical, developmental, neurological, and behavioral features. Short stature (<5th percentile) was observed in ~67% of young patients. Short stature resolves over time with most individuals reaching the 10-25th percentile by adulthood (see, for example, Burns et al. supra). A majority of children with SMS also have significant early-onset obesity (see, for example, European Journal of Human Genetics (2008) 16, 412-421). Obesity in teens and adults is common, typically with broad chests and truncal obesity. RAI1 haploinsufficiency represents a single-gene model of obesity with hyperphagia, abnormal fat distribution and altered hypothalamic gene expression associated with satiety, food intake, behavior and obesity.

Hearing loss is variable and is often associated with chronic ear infections. Ophthalmologic features are present in >60% of SMS patients and include myopia, iris anomalies, strabismus, microcornea, and, rarely, retinal detachment (often resulting from violent behaviors).

Prenatal history of SMS is notable for significantly decreased fetal movement in 50% of pregnancies. Early infancy is complicated by feeding difficulties leading to failure to thrive, marked oral sensory motor dysfunction with poor suckling reflex, gastroesophageal reflux, and hypotonia.

Most SMS individuals have mild-to-moderate mental retardation. IQ decreases as the child ages, ultimately placing the individual in the mild mental retardation range by adulthood. Delayed speech with or without hearing loss occurs in 96% of SMS patients. In addition, delayed fine/gross motor skills, problems with sensory integration, and poor adaptive function are seen. Other neurological features include pes cavus or pes planus, an abnormal 'festinating' gait, balance problems, and a decreased sensitivity to pain, which is often observed in association with self-injury in this disorder.

Sleep disturbance has been reported in 75-100% of SMS cases. Infants typically experience hypersomnolence during the first year of life. Sleep disturbances in older children include difficulties falling asleep, diminished REM sleep, reduced 24-h and night sleep, fragmented and shortened sleep cycles with frequent nocturnal and early-morning awakenings, and excessive daytime sleepiness.

Behavioral issues are one of the unique characteristic features of SMS. Maladaptive behaviors are a cause of major concern and include frequent outbursts/temper tantrums, attention seeking, aggression, disobedience, distraction, and self-injurious behaviors. Self-injurious behaviors include head banging, skin picking, wrist biting, onychotillomania and polyembolokoilamania. The behavioral phenotype of SMS escalates with age, typically with the onset of puberty. Age, degree of developmental delay, severity of any associated systemic disorder, and degree of sleep disturbance have a strong influence on maladaptive behaviors. Individuals also have a lack of respect for personal space during a conversation and are emotionally volatile.

SMS patients share many characteristics in common with PWS patients. These include: (1) diminished fetal activity; (2) hypotonia; (3) feeding difficulties in early infancy; (4) short stature: (5) early onset obesity which may include hyperphagia; (6) developmental delays; (7) mental retardation; (8) temper outbursts; (9) aggressive behavior; (10) self-injurious behavior; (11) hypersomnolence in infancy and similar sleep disturbances in older children and adults; (12) frequent ear infections; (13) scoliosis; and (14) strabismus. While the underlying genetic basis for these disorders is quite distinct, the presentation and natural history of the disease is very similar.

Solid oral dosage form: pharmaceutical formulations designed for oral administration including capsules and tablets.

Subject: refers to animals, including mammals, such as human beings.

Sulfonylurea receptor: A component of the K_{ATP} channel responsible for interaction with sulfonylurea, other K_{ATP} channel antagonists, diazoxide and other K_{ATP} channel agonists.

Tablet: Pharmaceutical dosage form that is produced by forming a volume of a matrix containing pharmaceutical active and excipients into a size and shape suitable for oral administration.

Thermogenesis: The physiological process of heat production in the body.

Threshold Concentration: The minimum circulating concentration of a drug required to exert a specific metabolic, physiological or compositional change in the body of a treated human or animal.

Treatment: means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

Triglyceride: Storage fats of animal and human adipose tissue principally consisting of glycerol esters of saturated fatty acids.

Type I diabetes: A chronic condition in which the pancreas makes little or no insulin because the beta cells have been destroyed.

Uncoupling protein: A family of proteins that allow oxidation in mitochondria to proceed without the usual concomitant phosphorylation to produce ATP.

Visceral fat: Human adipose tissues principally found below the subcutaneous fat and muscle layer in the body.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** summarizes the change in hyperphagia score for all subjects who participated in clinical study PC025.

FIG. **2** summarizes the percent change in lean body mass for all subjects who participated in clinical study PC025.

FIG. **3** summarizes the percent change in body fat mass for all subjects who participated in clinical study PC025.

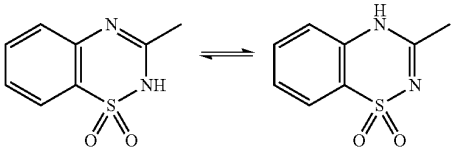
FIG. **4** summarizes the percent change of the lean body mass/fat mass ratio for all subjects who participated in clinical study PC025.

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are pharmaceutical formulations of particular K_{ATP} channel openers that when administered to subjects achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, and metabolic outcomes. Also provided are pharmaceutical formulations, methods of administration and dosing of particular K_{ATP} channel openers, optionally in combination with growth hormone, that achieve therapeutic outcomes while reducing the incidence of adverse effects.

In particular, pharmaceutical formulations formulated for oral administration exhibit advantageous properties including: facilitating consistency of absorption, pharmacokinetic and pharmacodynamic responses across treated patients, contributing to patient compliance and improving the safety profile of the product, such as by reducing the frequency of serious adverse effects. Method of treatment of metabolic and other diseases of humans and animals by administering the formulations are also provided.

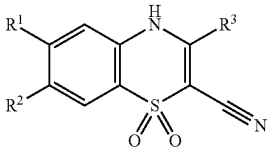
Compounds of formulas II and III, formulas IV and V, and formulas VI and VII, such as for example, diazoxide (shown below) can be proton tautomers. Proton tautomers are isomers that differ from each other only in the location of a hydrogen atom and a double bond. The hydrogen atom and double bond switch locations between a carbon atom and a heteroatom, such as for example N. Thus, when the nitrogen substituent is hydrogen, the two isomeric chemical structures may be used interchangeably.



The particular K_{ATP} channel openers that can be used in the invention formulations include any of those within formulae I to VII. Exemplary such compounds include diazoxide, BPDZ62, BPDZ 73, NN414 and BPDZ 154 (see, for example, Schou, et al., *Bioorg. Med. Chem.,* 13, 141-155 (2005)). Compound BPDZ 154 also is an effective K_{ATP} channel activator in patients with hyperinsulinism and in patients with pancreatic insulinoma. The synthesis of BPDZ compound is provided in Cosgrove, et al., *J. Clin. Endocrinol. Metab.,* 87, 4860-4868 (2002).

Analogs of diazoxide include 3-isopropylamino-7-methoxy-4H-1,2,4, -benzothiadiazine 1,1-dioxide, which is a selective Kir6.2/SUR1 channel opener (see Dabrowski, et al., *Diabetes,* 51, 1896-1906 (2002)). 2-alkyl substituted diazoxides are included (see, for example, Ouedraogo, et al., *Biol. Chem.,* 383, 1759-1768 (2002)); these channel openers show decreased activity in the inhibition of insulin release and increased activity in vascular smooth muscle tissue. Furthermore, 2-alkyl substituted diazoxides generally do not function as traditional potassium channel activators, but instead show potential as Ca^{2+} blockers.

Other diazoxide analogs are described in Schou, et al., *Bioorg. Med. Chem.,* 13, 141-155 (2005), and are shown below.



R^1, R^2 and R^3 are:

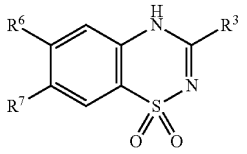
a) H, Cl, $NHCH(CH_3)_2$

b) CF_3, H, $NHCH(CH_3)_2$

c) H, Cl, $NHCH_2CH_2CH(CH_3)_2$

d) H, Cl, NH-cyclobutyl

Diazoxide analogs having different alkyl substituents at the 3 position of the molecule (identified as R^3 shown below) are described in Bertolino, et al., Receptors and Channels, 1, 267-278 (1993).



R^3, R^6 and R^7 are:

a) H, H, CH_3

b) H, H, Cl

c) CH_3, Cl, H

d) CH_2Cl, H, Cl

e) NH_2, H, H

f) CH_2CH_2Cl, H, Cl

g) nC_4H_9, H, Cl

h) nC_5H_{11}, H, Cl

i) nC_7H_{15}, H, Cl

j) nC_3H_7, Cl, H

k) nC_4H_7, Cl, H

l) nC_5H_{11}, Cl, H

m) nC_7H_{15}, Cl, H

n) nC_3H_7, Cl, Cl

o) nC_4H_9, Cl, Cl

p) nC_5H_{11}, Cl, Cl

q) nC_7H_{15}, Cl, Cl

r) H, Cl, H

K_{ATP} channel activity of formulae I-VII and related compounds can be measured by membrane potential studies as described in Schou, et al., *Bioorg. Med. Chem.,* 13, 141-155 (2005) and Dabrowski, et al., *Diabetes,* 51, 1896-1906 (2002).

Measurement of the inhibition of glucose-stimulated insulin release from βTC6 cells is described in Schou, et al., *Bioorg. Med. Chem.,* 13, 141-155 (2005). The ability of particular K_{ATP} channel openers to inhibit release of insulin from incubated rat pancreatic islets can be performed as described by Ouedraogo, et al., *Biol. Chem.,* 383, 1759-1768 (2002).

Activation of recombinant K_{ATP} channels by K_{ATP} channel openers can be examined by monitoring macroscopic currents of inside-out membrane patches from *Xenopus* oocytes coexpressing Kir6.2 and either SUR1, SUR2A or SUR2B. SUR expressing membranes can be prepared by known methods. See, for example, Dabrowski, et al., *Diabetes,* 51, 1896-1906 (2002).

Binding experiments can be used to determine the ability of K_{ATP} channel openers to bind SUR1, SUR2A and SUR2B. See, for example, Schwanstecher, et al., *EMBO J.,* 17, 5529-5535 (1998).

Preparation of SUR1 and SUR2A chimeras, as described by Babenko et al., allows for comparison of pharmacologic profiles (i.e. sulfonyl sensitivity and responsiveness to diazoxide or other potassium channel openers) of the SUR1/Kir6.2 and SUR2A/Kir6.2 potassium channels. See Babenko, et al., *J. Biol. Chem.,* 275(2), 717-720 (2000). The cloning of a sulfonylurea receptor and an inwardly rectifying K^+ channel is described by Isomoto, et al., *J. Biol. Chem.,* 271 (40), 24321-24324 (1996); D'hahan, et al., PNAS, 96(21), 12162-12167 (1999).

Differences between the human SUR1 and human SUR2 genes are described and shown in Aguilar-Bryan, et al., *Physiological Review,* 78(1), 227-245 (1998).

"Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

"Hydroxyl" and "hydroxy" refer to the group —OH.

"Substituted oxy" refers to the group —OR^f, where R^f is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

"Substituted thiol" refers to the group —SR, where R is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substi-

tuted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

"Alkyl" refers to an alkane-derived radical containing from 1 to 10, preferably 1 to 6, carbon atoms. Alkyl includes straight chain alkyl, branched alkyl and cycloalkyl, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. Straight chain or branched alkyl groups contain from 1-10, preferably 1 to 6, more preferably 1-4, yet more preferably 1-2, carbon atoms. The alkyl group is attached at any available point to produce a stable compound.

A "substituted alkyl" is an alkyl group independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halo, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, alkylsulfonylamino, carboxyl, heterocycle, substituted heterocycle, nitro, cyano, thiol, sulfonylamino or the like attached at any available point to produce a stable compound. In particular, "fluro substituted" refers to substitution by 1 or more, e.g., 1, 2, or 3 fluorine atoms. "Optionally fluro substituted" means that substitution, if present, is fluoro.

"Lower alkyl" refers to an alkyl group having 1-6 carbon atoms.

A "substituted lower alkyl" is a lower alkyl which is substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents as defined above, attached at any available point to produce a stable compound.

"Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. "Cycloalkylene" is a divalent cycloalkyl.

"Alkoxy" denotes the group —OR^f, where R^f is lower alkyl.

"Substituted alkoxy" denotes the group —OR^f, where R^f is substituted lower alkyl.

"Alkylthio" or "thioalkoxy" refers to the group —S—R, where R is lower alkyl.

"Substituted alkylthio" or "substituted thioalkoxy" refers to the group —S—R, where R is substituted lower alkyl.

"Sulfinyl" denotes the group —S(O)—.

"Sulfonyl" denotes the group —$S(O)_2$—.

"Substituted sulfinyl" denotes the group —S(O)—R, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted hetereocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

"Substituted sulfonyl" denotes the group —$S(O)_2$—R, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted hetereocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

"Sulfonylamino" denotes the group —$NRS(O)_2$—where R is hydrogen or lower alkyl.

"Substituted sulfonylamino" denotes the group —$NR^aS(O)_2$—R^b, where R^a is hydrogen or lower alkyl and R^b is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

"Amino" or "amine" denotes the group —NH_2. A "divalent amine" denotes the group —NH—. A "substituted divalent amine" denotes the group —NR— wherein R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl or substituted sulfonyl.

"Substituted amino" or "substituted amine" denotes the group —NR^iR^j, wherein R^i and R^j are independently hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl provided, however, that at least one of R^i and R^j is not hydrogen. R^iR^j in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

"Alkylsulfinyl" denotes the group —$S(O)R^p$, wherein R^p is optionally substituted alkyl.

"Alkylsulfonyl" denotes the group —$S(O)_2R^p$, wherein R^p is optionally substituted alkyl.

"Alkylsulfonylamino" denotes the group —$NR^qS(O)_2R^p$, wherein R^p is optionally substituted alkyl, and R^q is hydrogen or lower alkyl.

Pharmaceutical formulations containing K_{ATP} channel openers include the free base of the drug or a salt of the drug. Such salts may have one or more of the following characteristics: (1) stability in solution during synthesis and formulation, (2) stability in a solid state, (3) compatibility with excipients used in the manufacture of tablet formulations, (4) quantitatively yield the K_{ATP} channel opener upon exposure to simulated or actual gastric and duodenal conditions, (5) release K_{ATP} channel opener from sufficiently small particles that are readily dissolved and absorbed, (6) provide, when incorporated into a pharmaceutical formulation, for absorption of greater than 80% of the administered dose, (7) present no elevated toxicological risk as compared to the free base of the K_{ATP} channel opener, (8) can be formulated into acceptable pharmaceutical formulations to treat obesity and other diseases of humans, (9) are acceptable to the FDA as the basis of a drug product, (10) can be recrystallized to improve purity, (11) can be used to form co-crystals of two or more salts of the K_{ATP} channel opener, (12) have limited hygroscopicity to improve stability, or (13) synthetic and crystallization conditions under which the salt is formed can be varied resulting in different crystal structures (polymorphs) can be controlled in the synthesis of the salt.

K_{ATP} channel openers can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering lower effective doses of the drug.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methane-

sulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see *Remington's Pharmaceutical Sciences,* 19th ed., Mack Publishing Co., Easton, Pa., Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

Pharmaceutically acceptable salts can be prepared, for example, by dissolving the free-base form of a compound in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent.

The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, e.g., dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Salts of K_{ATP} channel openers, and particular salts of diazoxide, may include, but are not limited to acetate, acetonide, acetyl, adipate, aspartate, besylate, biacetate, bitartrate, bromide, butoxide, butyrate, calcium, camsylate, caproate, carbonate, citrate, cyprionate, decaroate, diacetate, dimegulumine, dinitrate, dipotassium, dipropionate, disodium, disulfide, edisylate, enanthate, estolate, etabonate, ethylsuccinate, fumarate, furoate, gluceptate, gluconate, hexacetonide, hippurate, hyclate, hydrobromide, hydrochloride, isethionate, lactobionate, malate, maleate, meglumine, methylbromide, methylsulfate, metrizoate, nafate, napsylate, nitrate, oleate, palmitate, pamoate, phenpropionate, phosphate, pivalate, polistirex, polygalacturonate, probutate, propionate, saccharate, sodium glycinate, sodium phosphate, podium succinate, state, succinate, sulfate, sulfonate, sulfosalicylate, tartrate, tebutate, terephalate, terephthalate, tosylate, triflutate, trihydrate, trisilicate, tromethamine, valerate, xinafolate, or the like.

Formulations provided herein exhibit some or all the following characteristics: (1) they are stable at ambient temperatures for a minimum of one year; (2) they provide for ease of oral administration; (3) they facilitate patient compliance with dosing; (4) upon administration, they consistently facilitate high levels of absorption of the pharmaceutical active; (5) upon once or twice daily oral administration they allow release of the K_{ATP} channel opener over a sustained time frame such that the circulating concentration of the K_{ATP} channel opener or its metabolically active metabolites does not fall below a therapeutically effective concentration; (6) they achieve these results independent of the pH of the gastrointestinal tract of treated individuals, and (7) they delay release until gastric transit is complete or nearly complete.

Formulations designed for oral administration can be provided, for example, as capsules or tablets. Capsule or tablet formulations include a number of distinguishing components. One is a component to improve absorption of the K_{ATP} channel opener. Another sustains release of the drug over more than 2 hours. A third delays substantial release of the drug until gastric transit is completed.

The formulations disclosed herein exhibit improved solubility and absorption of the K_{ATP} channel opener compared to previous formulations of these drugs. These advantageous properties are achieved by any one or more of the following approaches: (1) reducing particle size of the formulation by comminution, spray drying, or other micronising techniques, (2) using a pharmaceutical salt of the K_{ATP} channel opener, (3) using an ion exchange resin in the formulation, (4) using inclusion complexes, for example using a cyclodextrin, (5) compaction of the K_{ATP} channel opener with a solubilizing agent including low viscosity hypromellose, low viscosity metylcellulose or similarly functioning excipient and combinations thereof, (6) associating the K_{ATP} channel opener with a salt prior to formulation, (7) using a solid dispersion of the K_{ATP} channel opener, (8) using a self emulsifying system, (9) adding one or more surfactants to the formulation, (10) using nanoparticles in the formulation, or (11) combinations of these approaches. Preferably, when the K_{ATP} channel opener is a salt of diazoxide, the salt is not a sodium salt.

Release of K_{ATP} channel opener over a sustained period of time (2-24 hours) is achieved by the use of one or more approaches including, but not limited to: (1) the use of pH sensitive polymeric coatings, (2) the use of a hydrogel, (3) the use of a film coating that controls the rate of diffusion of the drug from a coated matrix, (4) the use of an erodable matrix that controls rate of drug release, (5) the use of polymer coated pellets, granules, or microparticles which can be further encapsulated or compressed into a tablet, (6) the use of an osmotic pump system, or (7) the use of a compression coated tablet, or (8) combinations of these approaches.

Delay of release of K_{ATP} channel openers from the formulation until gastric transit is complete is achieved in the formulations provided herein by any of several mechanisms. A pH sensitive polymer or co-polymer is used which when applied around the drug matrix functions as an effective barrier to release of active at pH 3.0 or lower and is unstable at pH 5.5 and above. This provides for control of release of the active compound in the stomach but rapidly allows release once the dosage form has passed into the small intestine. An alternative to a pH sensitive polymer or co-polymer is a polymer or co-polymer that is non-aqueous-soluble. The extent of resistance to release in the gastric environment can be controlled by coating with a blend of the non-aqueous-soluble and a aqueous soluble polymer. In this approach neither of the blended polymers or co-polymers are pH sensitive. One example of a pH sensitive co-polymer is the Eudragit methacrylic co-polymers, including Eudragit L100, S100 or L100-55 solids, L30 D-55 or FS 30D dispersions, or the L12,5 or S12,5 organic solutions.

Polymers that delay release can be applied to a tablet either by spray coating (as a thin film) or by compression coating. If a capsule is used, then the polymer(s) may be applied over the surface of the capsule or applied to microparticles of the drug, which may then be encapsulated such as in a capsule or gel. If the capsule is coated, then it will resist disintegration until after gastric transit. If microparticles are coated, then the capsule may disintegrate in the stomach but little to no drug will be released until after the free microparticles complete gastric transit. Finally, an osmotic pump system that uses e.g., a swellable hydrogel can be used to delay drug release in the stomach. The swellable hydrogel takes up moisture after administration. Swelling of the gel results in displacement of the drug from the system for absorption. The timing and rate of release of the drug depend on the gel used, and the rate at which

moisture reaches the gel, which can be controlled by the size of the opening in the system through which fluid enters. See Drug Delivery Technologies online article Dong et al. "L-OROS® SOFTCAP™ for Controlled Release of Non-Aqueous Liquid Formulations."

Accordingly, delay of release of K_{ATP} channel openers from the invention formulations until after gastric transit is complete is achieved in the formulations provided herein by any of several mechanisms, including, but not limited to: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet; (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet; (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system; (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or co-polymer applied as a compression coating on a tablet; (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet; (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system; (h) a non-aqueous soluble polymer applied to microparticles; (i) incorporation of the formulation in an osmotic pump system, or (j) use of systems controlled by ion exchange resins, or (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

Formulations are provided that are designed for administration once daily (per 24 hours). These can contain between 25 and 500 mg of K_{ATP} channel openers. Formulations intended for administration twice daily (per 24 hours) are also provided. These can contain between 25 and 250 mg of K_{ATP} channel openers.

The formulations provided herein exhibit improved safety of the administered drug product. This improvement in safety occurs by at least two mechanisms. First, delay of release of active drug until gastric transit is complete can reduce the incidence of a range of gastrointestinal adverse side effects including nausea, vomiting, dyspepsia, abdominal pain, diarrhea and ileus. Second, by sustaining release of the active drug over 2 or more hours to as long as 24 hours, peak drug levels are reduced relative to the peak drug levels observed for the same administered dose using any oral formulation that does not have sustained or controlled release. This reduction in peak drug levels can contribute to reductions in adverse effects that are partially or completely determined by peak drug levels. These adverse effects include: fluid retention with the associated reduced rates of excretion of sodium, chloride and uric acid, edema, hyperglycemia and the associated potential for progression to ketoacidosis, cataracts and non-ketotic hyperosmolar coma, headaches, tachycardia and palpitations.

Also provided herein are controlled release formulations of K_{ATP} channel openers, which have one feature from each of A-D as shown in Table 1.

Table 1: Controlled Release Formulation Characteristics and Properties

A. Unit Form: Tablet or Capsule
B. Dosage/unit: 10-100 mg
100-200 mg
200-300 mg
300-500 mg
500-2000 mg
C. Dosing Once daily (24 hours)
Twice daily (24 hours)
D. Release time: 2-4 hrs
4-8 hrs
8-24 hours

For example, a controlled release composition can be a tablet containing 25-100 mg of a K_{ATP} channel opener, such tablet administered once daily to achieve a controlled release time of 2-4 hours. All of these formulations can further include the feature of substantially delaying pharmaceutical active release until after gastric transit is complete.

In addition, any of the above formulations from Table 1 can include at least one feature that improves the solubility or absorption of the K_{ATP} channel opener.

The controlled release formulations provided herein comprise the active compound (e.g., K_{ATP} channel opener, optionally in combination with growth hormone) and a matrix which comprises a gelling agent that swells upon contact with aqueous fluid. The active compound(s) entrapped within the gel is(are) slowly released into the body upon dissolution of the gel. The active compound(s) can be evenly dispersed within the matrix or can be present as pockets of drug in the matrix. For example, the drug can be formulated into small granules which are dispersed within the matrix. In addition, the granules of drug also can include a matrix, thus, providing a primary and a secondary matrix as described in U.S. Pat. No. 4,880,830 to Rhodes.

The gelling agent preferably is a polymeric material, which can include, for example, any pharmaceutically acceptable water soluble or water insoluble slow releasing polymer such as xantham gum, gelatin, cellulose ethers, gum arabic, locust bean gum, guar gum, carboxyvinyl polymer, agar, acacia gum, tragacanth, veegum, sodium alginate or alginic acid, polyvinylpyrrolidone, polyvinyl alcohol, or film forming polymers such as methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose, hyroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), ethylcellulose (EC), acrylic resins or mixtures of the above (see e.g., U.S. Pat. No. 5,415,871).

The gelling agent of the matrix also can be a heterodisperse gum comprising a heteropolysaccharide component and a homopolysaccharide component which produces a fast-forming and rigid gel as described in U.S. Pat. No. 5,399,359. The matrix also can include a crosslinking agent such as monovalent or multivalent metal cations to further add rigidity and decrease dissolution of the matrix, thus further slowing release of drug. The amount of crosslinking agent to add can be determined using methods routine to the ordinary skilled artisan.

The matrix of the controlled release composition also can include one or more pharmaceutically acceptable excipients recognized by those skilled in the art, i.e. formulation excipients. Such excipients include, for example, binders: polyvinylpyrrolidone, gelatin, starch paste, microcrystalline cellulose; diluents (or fillers): starch, sucrose, dextrose, lactose, fructose, xylitol, sorbitol, sodium chloride, dextrins, calcium phosphate, calcium sulphate; and lubricants: stearic acid, magnesium stearate, calcium stearate, Precirol™ and flow aids for example talc or colloidal silicon dioxide.

The matrix of the controlled release composition can further include a hydrophobic material which slows the hydration of the gelling agent without disrupting the hydrophilic nature of the matrix, as described in U.S. Pat. No. 5,399,359. The hydrophobic polymer can include, for example, alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or co-polymers derived from acrylic or methacrylic acid esters, co-polymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, waxes and waxy substances such as carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, ceresin, paraffin,

myristyl alcohol, stearyl alcohol, cetylalcohol and stearic acid. and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art.

The amount of hydrophobic material incorporated into the controlled release composition is that which is effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments, the hydrophobic material is included in the matrix in an amount from about 1 to about 20 percent by weight and replaces a corresponding amount of the formulation excipient. A solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC) and Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds).

The controlled release composition also can be coated to retard access of liquids to the active compound and/or retard release of the active compound through the film-coating. The film-coating can provide characteristics of gastroresistance and enterosolubility by resisting rapid dissolution of the composition in the digestive tract. The film-coating generally represents about 5-15% by weight of the controlled release composition. Preferably, the core by weight represents about 90% of the composition with the remaining 10% provided by the coating. Such coating can be a film-coating as is well known in the art and include gels, waxes, fats, emulsifiers, combination of fats and emulsifiers, polymers, starch, and the like.

Polymers and co-polymers are useful as thin film coatings. Solution coatings and dispersion coatings can be used to coat the active compound, either alone or combined with a matrix. The coating is preferably applied to the drug or drug and matrix combination as a solid core of material as is well known in the art.

A solution for coating can include polymers in both organic solvent and aqueous solvent systems, and typically further including one or more compounds that act as a plasticizer. Polymers useful for coating compositions include, for example, methylcellulose (Methocel® A; Dow Chemical Co.), hydroxypropylmethylcellulose with a molecular weight between 1,000 and 4,000,000 (Methocel® E; Dow Chemical Co. or Pharmacoat®; Shin Etsu), hydroxypropyl cellulose with a molecular weight between 2,000 and 2,000,000, ethyl cellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate (Eastman Kodak), carboxymethylethyl cellulose (Duodcel®), hydroxypropyl methylcellulose phthalate, ethylcellulose, methylcellulose and, in general, cellulosic derivatives, olymethacrylic acid-methacrylic acid co-polymer (Type A 1:1 Eudragit L100; Type B 1:2 Eudragit S100; and Type C 1:1 Eudragit L100-55, aqueous dispersion 30% solids, Eudragit L30D), poly (meth)acryl ester: poly(ethyl acrylate, methyl methacrylate 2:1), Eudragit NE30D aqueous dispersion 30% solids, polyaminomethacrylate Eudragit E100, poly(trimethylammonioethyl methacrylate chloride)ammoniomethacrylate co-polymer, Eudragit RL30D and Eudragit RS30D, carboxyvinyl polymers, polyvinylalcohols, glucans scleroglucans, mannans, and xanthans.

Aqueous polymeric dispersions include Eudragit L30D and RS/RL30D, and NE30D, Aquacoat brand ethyl cellulose, Surelease brand ethyl cellulose, EC brand N-10F ethyl cellulose, Aquateric brand cellulose acetate phthalate, Coateric brand Poly(vinyl acetate phthalate), and Aqacoat brand hydroxypropyl methylcellulose acetate succinate. Most of these dispersions are latex, pseudolatex powder or micronized powder mediums.

A plasticizing agent may be included in the coating to improve the elasticity and the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes may affect the drug release rate. Suitable conventional plasticizing agents include, for example, diethyl phthalate, glycerol triacetate, acetylated monoglycerides, acetyltributylcitrate, acetyltriethyl citrate, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate, diethyloxalate, diethyl malate, diethylfumarate, diethylphthalate, diethylsuccinate, diethylmalonate, diethyltartarate, dimethylphthalate, glycerin, glycerol, glyceryl triacetate, glyceryltributyrate, mineral oil and lanolin alcohols, petrolatum and lanolin alcohols, phthalic acid esters, polyethylene glycols, propylene glycol, rape oil, sesame oil, triacetin, tributyl citrate, triethyl citrate, and triethyl acetyl citrate, or a mixture of any two or more of the foregoing. Plasticizers which can be used for aqueous coatings include, for example, propylene glycol, polyethylene glycol (PEG 400), triacetin, polysorbate 80, triethyl citrate, and diethyl d-tartrate.

A coating solution comprising a mixture of hydroxypropylmethylcellulose and aqueous ethylcellulose (e.g. Aquacoat brand) as the polymer and dibutyl sebacate as plasticizer can be used for coating microparticles. (Aquacoat is an aqueous polymeric dispersion of ethylcellulose and contains sodium lauryl sulfate and cetyl alcohol). Preferably, the plasticizer represents about 1-2% of the composition.

In addition to the polymers, the coating layer can include an excipient to assist in formulation of the coating solution. Such excipients may include a lubricant or a wetting agent. Suitable lubricants as excipients for the film coating include, for example, talc, calcium stearate, colloidal silicon dioxide, glycerin, magnesium stearate, mineral oil, polyethylene glycol, and zinc stearate, aluminum stearate or a mixture of any two or more of the foregoing. Suitable wetting agents include, for example, sodium lauryl sulfate, acacia, benzalkonium chloride, cetomacrogol emulsifying wax, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, docusate sodium, sodium stearate, emulsifying wax, glyceryl monostearate, hydroxypropyl cellulose, lanolin alcohols, lecithin, mineral oil, onoethanolamine, poloxamer, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, propylene glycol alginate, sorbitan esters, stearyl alcohol and triethanolamine, or a mixture of any two or more of the foregoing.

The specified tablet or capsule formulations of Table 1 may include co-formulation with an obesity treating drug (in addition to the K_{ATP} channel opener). Obesity treating drugs that may be used include, but are not limited to, sibutramine hydrochloride (5-30 mg/unit), orlistat (50-360 mg/unit), phentermine hydrochloride or resin complex (15 to 40 mg/unit), zonisamide (100 to 600 mg/unit) topiramate (64 to 400 mg/unit), naltrexone hydrochloride (50 to 600 mg/unit), rimonabant (5 to 20 mg/unit), ADP356 (5 to 25 mg/unit), ATL962 (20 to 400 mg/unit), or A0D9604 (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is one half the amount included in the once daily formulation

and the coformulated obesity treating drug is half of the amount specified. Alternative obesity treating drugs may include: selective serotonin 2c receptor agonists, dopamine antagonists, cannabinoid-1 receptor antagonists, leptin analogues, leptin transport and/or leptin receptor promoters, neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin and cocaine and amphetamine regulated transcript promoters, melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor- receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin, gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues, agents that may increase resting metabolic rate ("selective" β-3 stimulators/agonist, uncoupling protein homologues, and thyroid receptor agonists), melanin concentrating hormone antagonists, phytostanol analogues, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11 Bhydroxysteroid dehydrogenase type 1 activity, corticotropin releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a diabetes treating drug (in addition to the K_{ATP} channel opener). Diabetes treating drugs that may be used include, but are not limited to acarbose (50 to 300 mg/unit), miglitol (25 to 300 mg/unit), metformin hydrochloride (300 to 2000 mg/unit), repaglinide (1-16 mg/unit), nateglinide (200 to 400 mg/unit), rosiglitizone (5 to 50 mg/unit), metaglidasen (100 to 400 mg/unit) or any drug that improves insulin sensitivity, or improves glucose utilization and uptake. These formulations are preferably used once daily. For a twice daily dosing, the amount of the the K_{ATP} channel opener is half the amount included in the once daily formulation and the co-formulated diabetes treating drug is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a cholesterol lowering drug. Cholesterol lowering drugs that may be used include, but are not limited to pravastatin or simvastatin or atorvastatin or fluvastatin or rosuvastatin or lovastatin (all at 10 to 80 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably 25 to 200 mg/unit and the coformulated cholesterol lowering drug is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a depression treating drug. Depression treating drugs that may be used include, but are not limited to citalopram hydrobromide (10 to 80 mg/unit), escitalopram hydrobromide (5 to 40 mg/unit), fluvoxamine maleate (25 to 300 mg/unit), paroxetine hydrochloride (12.5 to 75 mg/unit), fluoxetine hydrochloride (30 to 100 mg/unit), setraline hydrochloride (25 to 200 mg/unit), amitriptyline hydrochloride (10 to 200 mg/unit), desipramine hydrochloride (10 to 300 mg/unit), nortriptyline hydrochloride (10 to 150 mg/unit), duloxetine hydrochloride (20 to 210 mg/unit), venlafaxine hydrochloride (37.5 to 150 mg/unit), phenelzine sulfate (10 to 30 mg/unit), bupropion hydrochloride (200 to 400 mg/unit), or mirtazapine (7.5 to 90 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated depression treating drug is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a hypertension treating drug. Hypertension treating drugs that may be used include, but are not limited to enalapril maleate (2.5 to 40 mg/unit), captopril (2.5 to 150 mg/unit), lisinopril (10 to 40 mg/unit), benzaepril hydrochloride (10 to 80 mg/unit), quinapril hydrochloride (10 to 80 mg/unit), peridopril erbumine (4 to 8 mg/unit), ramipril (1.25 to 20 mg/unit), trandolapril (1 to 8 mg/unit), fosinopril sodium (10 to 80 mg/unit), moexipril hydrochloride (5 to 20 mg/unit), losartan potassium (25 to 200 mg/unit), irbesartan (75 to 600 mg/unit), valsartan (40 to 600 mg/unit), candesartan cilexetil (4 to 64 mg/unit), olmesartan medoxamil (5 to 80 mg/unit), telmisartan (20 to 160 mg/unit), eprosartan mesylate (75 to 600 mg/unit), atenolol (25 to 200 mg/unit), propranolol hydrochloride (10 to 180 mg/unit), metoprolol tartrate, succinate or fumarate (all at 25 to 400 mg/unit), nadolol (20 to 160 mg/unit), betaxolol hydrochloride (10 to 40 mg/unit), acebutolol hydrochloride (200 to 800 mg/unit), pindolol (5 to 20 mg/unit), bisoprolol fumarate (5 to 20 mg/unit), nifedipine (15 to 100 mg/unit), felodipine (2.5 to 20 mg/unit), amlodipine besylate (2.5 to 20 mg/unit), nicardipine (10 to 40 mg/unit), nisoldipine (10 to 80 mg/unit), terazosin hydrochloride (1 to 20 mg/unit), doxasoxin mesylate (4 to 16 mg/unit), prazosin hydrochloride (2.5 to 10 mg/unit), or alfuzosin hydrochloride (10 to 20 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated hypertension treating drug is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a diuretic to treat edema. Diuretics that may be used include, but are not limited to amiloride hydrochloride (1 to 10 mg/unit), spironolactone (10 to 100 mg/unit), triamterene (25 to 200 mg/unit), bumetanide (0.5 to 4 mg/unit), furosemide (10 to 160 mg/unit), ethacrynic acid or ethacrynate sodium (all at 10 to 50 mg/unit), tosemide (5 to 100 mg/unit), chlorthalidone (10 to 200 mg/unit), indapamide (1 to 5 mg/unit), hydrochlorothiazide (10 to 100 mg/unit), chlorothiazide (50 to 500 mg/unit), bendroflumethiazide (5 to 25 mg/unit), hydroflumethiazide (10 to 50 mg/unit), mythyclothiazide (1 to 5 mg/unit), or polythiazide (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat inflammation or pain. Drugs for treating inflammation or pain that may be used include, but are not limited to aspirin (100 to 1000 mg/unit), tramadol hydrochloride (25 to 150 mg/unit), gabapentin (100 to 800 mg/unit), acetominophen (100 to 1000 mg/unit), carbamazepine (100 to 400 mg/unit), ibuprofen (100 to 1600 mg/unit), ketoprofen (12 to 200 mg/unit), fenprofen sodium (100 to 600 mg/unit), flurbiprofen sodium or flurbiprofen (both at 50 to 200 mg/unit), or combinations of any of these with a steroid or aspirin. These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat obesity associated comorbidities include those specified above for treating diabetes, cholesterol, depression, hypertension and edema, or drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrial, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity and infertility.

The specified tablet or capsule formulations of Table 1 may include co-formulation with an anti-psychotic drug the combination used to treat the psychotic condition and to treat or prevent weight gain, dyslipidemia or impaired glucose tolerance in the treated individual. Drugs for treating various psychotic conditions that may be used include, but are not limited to, lithium or a salt thereof (250 to 2500 mg/unit), carbamazepine or a salt thereof (50 to 1200 mg/unit), valproate, valproic acid, or divalproex (125 to 2500 mg/unit), lamotrigine (12.5 to 200 mg/unit), olanzapine (5 to 20 mg/unit), clozapine (12.5 to 450 mg/unit), or risperidone (0.25 to 4 mg/unit). These coformulations are preferably intended for once per day administration. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated anti-psychotic is half of the amount specified.

The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat or prevent ischemic or reperfusion injury. Drugs for treating or preventing ischemic or reperfusion injury that may be used include, but are not limited to: low molecular weight heparins (dalteparin, enoxaparin, nadroparin, tinzaparin or danaparoid), ancrd, pentoxifylline, nimodipine, flunarizine, ebselen, tirilazad, clomethiazole, an AMPA agonist (GYKI 52466, NBQX, YM90K, zonampanel, or MPQX), SYM 2081, selfotel, Cerestat, CP-101,606, dextrophan, dextromethorphan, MK-801, NPS 1502, remacemide, ACEA 1021, GV150526, eliprodil ifenprodil, lubeluzole, naloxone, nalfemene citicoline, acetyl-l-carnitine, nifedipine, resveratrol, a nitrone derivative, clopidogrel, dabigatram, prasugrel, troxoprodil, AGY-94806, or KAI-9803.

Provided are formulations administered once or twice daily to an obese or overweight subject continuously to result in a circulating concentration of K_{ATP} channel opener sufficient to induce weight loss. Weight loss occurs by the preferential loss of body fat. Additional weight loss can occur when the formulation is administered in combination with a reduced calorie diet.

Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the inhibition of fasting or glucose stimulated insulin secretion for about 24 hours or for about 18 hours.

Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of energy expenditure for about 24 hours or for about 18 hours.

Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of beta oxidation of fat for about 24 hours or for about 18 hours.

Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.

Provided are formulations administered once or twice daily (per 24 hours) to a subject continuously result in a circulating concentration of K_{ATP} channel opener sufficient to induce either beta-cell rest or improved insulin sensitivity or both. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective treatment of type I diabetes, type II diabetes and prediabetes. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective restoration of normal glucose tolerance in type II diabetic and prediabetic subjects.

The various pharmaceutical K_{ATP} channel opener formulations have a variety of applications, including, but not limited to: (1) treatment of obesity; (2) prevention of weight gain in individuals who are predisposed to obesity; (3) treatment of hyperinsulemia or hyperinsulinism; (4) treatment of hypoglycemia; (5) treatment of hyperlipidemia, (6) treatment of type II diabetes, (7) preservation of pancreatic function in type I diabetics; (8) treatment of metabolic syndrome (or syndrome X); (9) prevention of the transition from prediabetes to diabetes, (10) correction of the defects in insulin secretion and insulin sensitivity contributing to prediabetes and type II diabetes, (11) treatment of polycystic ovary syndrome, (12) prevention of ischemic or reperfusion injury, (13) treat weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs, (14) prevent weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs and (15) treatment of any disease where hyperlipidemia, hyperinsulemia, hyperinsulinism, hyperlipidemia, hyperphagia or obesity are contributing factors to the severity or progression of the disease, including but not limited to, Prader-Willi Syndrome, Smith-Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, hyperlipoproteinemia type I, II, III, and IV, and the like.

In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage once per 24 hours, optionally in combination with growth hormone, to induce weight loss. In further embodiments, the individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not experiencing chronic, recurrent or drug-induced hypoglycemia, (d) does not have metabolic syndrome, or (e) is not experiencing malignant hypertension.

In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage twice per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese individual (a) does not have an insulin secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, (f) is not experiencing chronic recurrent or drug-induced hypoglycemia, (g) has not been treated for schizophrenia with haloperidol, or (h) is not experiencing malignant hypertension. In further embodiments, the overweight or obese adolescent (a) has not been diagnosed as being type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia, or (c) has not been diagnosed as having metabolic syndrome.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In

further embodiments, the overweight or obese individual (a) does not have an insulin-secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, or (f) is not experiencing chronic, recurrent or drug-induced hypoglycemia.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese adolescent as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese adolescent is (a) is a type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia or (c) does not have metabolic syndrome.

In another embodiment, a K_{ATP} channel opener is administered as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss to an overweight or obese adult who (a) is not simultaneously receiving glucagon injections, triiodothyroxin or furosemide, (b) is not being treated for schizophrenia with haloperidol, or (c) is not experiencing malignant hypertension.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form four times per 24 hours, optionally in combination with growth hormone, to induce weight loss.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 50 to 275 mg. In a further embodiment, the overweight or obese individual individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 130 to 275 mg. In a further embodiment, the overweight or obese individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

In another embodiment, a K_{ATP} channel opener is administered to an overweight or obesity prone individual as a solid oral dosage form one, two, three or four times per 24 hours, optionally in combination with growth hormone, to maintain a weight loss, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In a further embodiment, the administered daily dose of the K_{ATP} channel opener is 50 to 275 mg.

In other embodiments, a K_{ATP} channel opener is administered as a solid oral dosage form to an overweight, obese, or obesity prone individual, optionally in combination with growth hormone, to (a) elevate energy expenditure, (b) elevate beta oxidation of fat, or (c) reduce circulating triglyceride concentrations.

In other embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof to induce the loss of 25%, 50%, or 75% of initial body fat.

In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof, optionally in combination with growth hormone, to induce (a) the preferential loss of body fat or (b) the preferential loss of visceral body fat.

In additional embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis one, two or three times per 24 hours at daily doses of 50 to 275 mg to an individual, optionally in combination with growth hormone, to (a) induce the loss of 25%, 50% or 75% of initial body fat, (b) induce the preferential loss of body fat, or (c) induce the preferential loss of visceral fat.

In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered to an individual, optionally in combination with growth hormone, to induce the preferential loss of body fat and to induce reduction in circulating triglycerides.

In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone.

In yet another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of sibutramine, orlistat, rimonabant, an appetite suppressant, an anti-depressant, an anti-epileptic, a diuretic that is not furosemide, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener but is not metformin, furosemide or triiodothyroxin, or a drug that lowers blood pressure, to induce weight loss and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual. In further embodiments, the overweight, obese, or obesity prone individual (a) is a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

In another embodiment a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of an anti-depressant, a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to an overweight, obese, or obesity prone individual to induce weight loss and/or treat obesity associated comorbidities. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to maintain weight and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

In additional embodiments, a tablet formulation of a K_{ATP} channel opener is used to administer a therapeutically effective dose of a K_{ATP} channel opener to an obese, overweight or obesity prone individual in need thereof to treat obesity, to (a) provide beta cell rest, (b) treat type I or type II diabetes, or (c) prevent the occurrence of diabetes.

In additional embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to an obese adult or adolescent to induce weight loss and/or treat obesity and obesity-associated co-morbidities. In further embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with Phentermine or a derivative, optionally in combination with growth hormone, thereof to an obese adult or adolescent to treat metabolic syndrome in a patient in need thereof.

In further embodiments, a pharmaceutically acceptable formulation of a K_{ATP} channel opener at doses of 50 to 275 mg/day is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof at daily doses of 15 to 37.5 mg to an overweight or obese individual to induce weight loss, to treat metabolic syndrome, or to induce weight loss and treat obesity-associated co-morbidities. In another embodiment, a tablet formulation is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to treat metabolic syndrome in a patient.

In another embodiment, a quick dissolving formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is used to provide a therapeutically effective dose to a patient in need thereof.

In further embodiments, a K_{ATP} channel opener is administered, optionally in combination with growth hormone, once per 24 hours at doses of 125 mg to 275 mg to an overweight or obese individual who is not type II diabetic and is not being treated for nighttime hypoglycemia.

In further embodiments, a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration. The tablet or capsule may be co-formulated with metformin. In another embodiment, a K_{ATP} channel opener is formulated as an oral suspension, and the oral suspension may be further encapsulated in another embodiment.

In another embodiment, a pharmaceutical salt of a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration, or as an oral suspension or as an oral solution, or as an oral solution that is encapsulated. If the opener is diazoxide, the salt, is preferably not a sodium salt.

In another embodiment a K_{ATP} channel opener is co-formulated with hydrochlorothiazide, chlorothiazide, cyclothiazide, benzthiazide, metyclothiazide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, or polythiazide in a pharmaceutical formulation suitable for oral administration.

Upon administration of the formulations provided herein to humans or animals, some or all of the following effects are observed: (1) the production of lipoprotein lipase by adipocytes is reduced; (2) enhanced lipolysis by adipocytes; (3) expression of fatty acid synthase by adipocytes is reduced; (4) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (5) little or no new triglycerides are synthesized and stored by adipocytes; (6) enhanced expression of β_3 Adrenergic Receptor (β_3AR) an improvement in the adrenergic function in adipocytes; (7) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (8) decreased insulinemia; (9) enhanced blood glucose levels; (10) increased expression of Uncoupling Protein 1 in adipocytes; (11) enhanced thermogenesis in white and brown adipose tissue; (12) reduction of plasma triglyceride concentration; (13) decrease in circulating leptin concentrations; (14) up-regulation of insulin receptors; (15) enhanced glucose uptake; (16) reduced adipocyte hyperplasia; (17) reduced adipocyte hypertrophy; (18) reduced rates of conversion of preadipocytes to adipocytes; (19) reduced rates of hyperphagia, (20) increased protection of CNS, cardiac and other tissues from ischemic or reperfusion injury, (21) improved insulin sensitivity, (22) elevated CSF insulin concentrations, (23) elevated circulating adiponectin concentrations, (25) reduced circulating triglyceride concentrations, (26) enhancement of beta-cell rest, and/or (27) increase in lean body mass.

Threshold concentrations of the current invention include those circulating concentrations of K_{ATP} channel openers, optionally in combination with growth hormone, resulting from the administration of the drug as an i.v. formulation, an immediate release oral formulation, a controlled release formulation, a transdermal formulation, or an intranasal formulation to an overweight or obese individual which results in (1) measurable suppression of fasting insulin levels, (2) suppression of fasting insulin levels by at least 20% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (3) suppression of fasting insulin levels by at least 30% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (4) suppression of fasting insulin levels by at least 40% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (5) suppression of fasting insulin levels by at least 50% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (6) suppression of fasting insulin levels by at least 60% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (7) suppression of fasting insulin levels by at least 70% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (8) suppression of fasting insulin levels by at least 80% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (9) loss of weight, (10) elevation of resting energy expenditure, or (11) elevation of the oxidation of fat or fatty acids.

Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to an obesity prone individual which result in (1) the loss of weight, and (2) the maintenance of weight.

Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a prediabetic individual which result in prevention of the transition to diabetes.

Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a individual with type 1 diabetes which result in beta cell rest.

The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to overweight, obese or obesity prone individuals as provided herein includes, but is not limited to one or more of (1) enhanced energy expenditure, (2) enhanced oxidation

of fat and fatty acids, (3) the enhancement of lipolysis in adipose tissue, (4) enhanced glucose uptake by tissues, enhanced insulin sensitivity, (5) improved beta adrenergic response, and (6) increase in lean body mass. The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to obese or obesity prone individuals as provided herein may also include the suppression of appetite.

Prolonged administration of pharmaceutical formulations of K_{ATP} channel openers to overweight or obese humans or animals, optionally in combination with growth hormone, results in substantial and sustained weight loss including some or all of the following effects: (1) preferential loss of body fat; (2) loss of greater than 25% of initial body fat mass; (3) loss of greater than 50% of initial body fat mass; (4) loss of greater than 75% of initial body fat mass; (5) significant increase in resting energy expenditure; (6) increase in the oxidation of fat and fatty acids; (7) reduction in blood pressure; (8) production of lipoprotein lipase by adipocytes is reduced; (9) enhanced lipolysis by adipocytes; (10) expression of fatty acid synthase by adipocytes is reduced; (11) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (12) little or no new triglycerides are synthesized and stored by adipocytes; (13) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and an improvement in the adrenergic function in adipocytes; (14) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (15) decreased insulinemia; (16) enhanced blood glucose levels; (17) increased expression of Uncoupling Protein 1 in adipocytes; (18) enhanced thermogenesis in white and brown adipose tissue; (19) reduction of plasma triglyceride concentration; (20) decrease in circulating leptin concentrations; (21) up-regulation of insulin receptors; (22) enhanced glucose uptake; (23) reduced adipocyte hyperplasia; (24) reduced adipocyte hypertrophy; (25) reduced rates of conversion of preadipocytes to adipocytes; (26) reduced rates of hyperphagia; (27) the sequential loss first of the metabolically most active adipose tissue (visceral), followed by the loss of less metabolically active adipose tissue, (28) elevation of circulating adiponectin concentrations, (29) elevation of cerebrospinal fluid insulin levels, (30) enhanced islet insulin mRNA and insulin content, (31) enhanced metabolic efficiency of insulin, or (32) increase in lean body mass.

Prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to obesity prone humans or animals, including individuals who have undergone various types of bariatric surgery, results in sustained maintenance of weight including some or all of the following effects: (1) increased resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentration; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; and (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentration, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to prediabetic or type I diabetic humans or animals results in the prevention of beta cell failure, improved glycemic control, and prevention of the transition from prediabetes to diabetes including some or all of the following effects: (1) increase in resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and an improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentrations; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentrations, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to humans or animals that are at risk for myocardial infarct, or stroke or undergoing a surgical procedure that restores blood flow to heart or brain results in improved therapeutic outcomes post-surgically, or following the occurrence of myocardial infarct or stroke by improving the survival of tissue after blood flow is restored, reduced stunning of tissue, and altering the nature of the inflammatory responses.

Pharmaceutical formulations as provided herein are designed to be used in the treatment of obesity, hyperlipidemia, hypertension, weight maintenance, type I diabetes, prediabetes, type II diabetes, or any condition where weight loss, reduction in circulating triglycerides or beta cell rest contributes to therapeutic outcomes provide for a range of critical changes in pharmacodynamic and pharmacokinetic responses to administered doses of K_{ATP} channel openers, optionally in combination with growth hormone, which changes include one or more of the following: (1) extending the pharmacodynamic effect of an administered dose to greater than 24 hours as measured by the suppression of insulin secretion, (2) providing for substantial uptake of the active pharmaceutical ingredient in the small intestine, (3) providing for substantial uptake of the active pharmaceutical ingredient in the large intestine, (4) result in lowered Cmax versus current oral suspension or capsule products for the same administered dose of active pharmaceutical ingredient, (5) provide for circulating concentrations of unbound active pharmaceutical ingredient above threshold concentrations

for 24 or more hours from a single administered dose, and (6) provide for more consistent drug absorption by treated individuals as compared to existing capsule formulations.

Pharmaceutical co-formulations of the current invention designed to treat a range of conditions in humans and animals include the combination of K_{ATP} channel openers with growth hormone and optionally one or more of: (1) a diuretic, (2) a drug that lowers blood pressure, (3) a drug that suppresses appetite, (4) a cannabinoid receptor antagonist, (5) a drug that suppresses that action of gastric lipases, (6) any drug that is used to induce weight loss, (7) a drug that lowers cholesterol, (8) a drug that lowers LDL bound cholesterol, (9) a drug that improves insulin sensitivity, (10) a drug that improves glucose utilization or uptake, (11) a drug that reduces incidence of atherosclerotic plaque, (12) a drug that reduces inflammation, (13) a drug that is antidepressant, (14) a drug that is an anti-epileptic, or (15) a drug that is an anti-psychotic.

Treatment of humans or animals of the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in reduced incidence of adverse side effects including but not limited to edema, fluid retention, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, ketoacidosis, nausea, vomiting, dyspepsia, ileus and headaches. These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of individuals at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved where the number of days over which the step up in dose is effected is 2 to 10, (2) use of the lowest effective dose to achieve the desired therapeutic effect, (3) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (4) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (5) use of a pharmaceutical formulation that results in lower circulating peak drug levels as compared to an immediate release oral suspension or capsule formulation for the same administered dose, and (6) optimizing the timing of administration of dose within the day and relative to meals.

Treatment of patients suffering from Prader-Willi Syndrome, Smith-Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, and hyperlipoproteinemia type I, II, III, and IV with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) reduced rates of weight gain, (3) inhibition of hyperphagia, (4) reduced incidence of impaired glucose tolerance, prediabetes or diabetes, (5) reduced incidence of congestive heart failure, (6) reduced hypertension, and (7) reduced rates of all cause mortality.

Treatment of prediabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression to diabetes, (4) reduced hypertension, and (5) reduced rates of all cause mortality.

Treatment of diabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression of diabetes, (4) improvements in glucose tolerance, (5) reduced hypertension, and (6) reduced rates of all cause mortality.

Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment of diseases of overweight, obese or obesity prone human and animal subjects involves the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with an acceptable formulation of growth hormone and optionally one or more of: (1) Sibutramine, (2) orlistat, (3) Rimonabant, (4) a drug that is an appetite suppressant, (5) any drug used to induce weight loss in an obese or overweight individual, (6) a non-thiazide diuretic, (7) a drug that lowers cholesterol, (8) a drug that raises HDL cholesterol, (9) a drug that lowers LDL cholesterol, (10) a drug that lowers blood pressure, (11) a drug that is an anti-depressant, (12) a drug that improves insulin sensitivity, (13) a drug that improves glucose utilization and uptake (14) a drug that is an anti-epileptic, (15) a drug that is an anti-inflammatory, or (16) a drug that lowers circulating triglycerides.

Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment or prevention of weight gain, dyslipidemia, or impaired glucose tolerance in subjects treated with antipsychotics drugs involve the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with growth hormone and optionally one or more of an acceptable formulation of: lithium, carbamazepine, valproic acid and divalproex, and lamotrigine, antidepressants generally classified as monoamine oxidase inhibitors including isocarboxazid, phenelzine sulfate and tranylcypromine sulfate, tricyclic antidepressants including doxepin, clomipramine, amitriptyline, maproiline, desipromine, nortryptyline, desipramine, doxepin, trimipramine, imipramine and protryptyline, tetracyclic antidepressants including mianserin, mirtazapine, maprotiline, oxaprotline, delequamine, levoprotline, triflucarbine, setiptiline, lortalaline, azipramine, aptazapine maleate and pirlindole, and major tranquilizers and atypical antipsychotics including paloproxidol, perphenazine, thioridazine, risperidone, clozapine, olanzapine and chlorpromazine.

In one embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to measurably reduce fasting insulin levels for a prolonged period. Preferably the K_{ATP} channel opener formulation reduces fasting insulin levels by at least 20%, more preferably by at least 30%, more preferably by at least by 40%, more preferably by at least 50%, more preferably by at least by 60% more preferably by at least by 70%, and more preferably by at least 80%. Fasting insulin levels are commonly measured using the glucose tolerance test (OGTT). After an overnight fast, a patient ingests a known amount of glucose. Initial glucose levels are determined by measuring pre-test glucose levels in blood and urine. Blood insulin levels are measured by a blood is draw every hour after the glucose is consumed for up to three hours. In a fasting glucose assay individuals with plasma glucose values greater than 200 mg/dl at 2 hours post-glucose load indicate an impaired glucose tolerance.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal

formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate resting energy expenditure for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate fat and fatty acid oxidation for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to maintain weight for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to reduce body fat by more than 25%, more preferably by at least 50%, and more preferably by at least 75%.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to preferentially reduce visceral fat deposits.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to reduce visceral fat depots and other fat deposits.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a normoinsulemic overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a prediabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to prevent the transition to diabetes for a prolonged period.

In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a type 1 diabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce beta cell rest for a prolonged period.

In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to diminish the secretion of insulin for 24 or more hours.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to diminish the secretion of insulin on a continuous basis.

In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation for 24 or more hours.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation on a continuous basis.

In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to treat hypoglycemia in circulation for 24 or more hours.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to treat hypoglycemia on a continuous basis.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to induce weight loss on a continuous basis.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combi-

nation with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to maintain weight on a continuous basis, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to reduce circulating triglyceride levels on a continuous basis.

In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to reduce or prevent ischemic or reperfusion injury in circulation for 24 or more hours.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient reduce or prevent ischemic or reperfusion injury on a continuous basis.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete and in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with sibutramine to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with orlistat to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with rimonabant to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an appetite suppressant to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an anti-depressant to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with antiepileptic to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a non-thiazide diuretic to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that induces weight loss by a mechanism that is distinct from diazoxide to an overweight or obese individual to induce weight loss.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers blood pressure to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that raises HDL associated cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combi-

nation with growth hormone, is co-administered with a drug that improves insulin sensitivity to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an anti-inflammatory to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers circulating triglycerides to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with sibutramine in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with orlistat or other active that suppresses the action of gastric lipases in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with a non-thiazide diuretic in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an appetite suppressant in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with a cannabinoid receptor antagonist in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-cholesteremic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an antihypertensive active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an insulin sensitizing active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-inflammatory active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-depressant active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-epileptic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an active that reduces the incidence of atherosclerotic plaque in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an active that lowers circulating concentrations of triglycerides in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

The reduction of circulating triglycerides in an overweight, obese or obesity prone individual is achieved by the administration of an effective amount of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

A solid oral dosage form of K_{ATP} channel opener can be used to administer a therapeutically effective dose of K_{ATP} channel opener to an overweight or obesity prone individual in need thereof to maintain weight, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

A method of inducing loss of greater than 25% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

A method of inducing loss of greater than 50% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

A method of inducing loss of greater than 75% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

A method of inducing preferential loss of visceral fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

A method of inducing loss of body fat and reductions in circulating triglycerides in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

The invention will now be described with reference to the following non-limiting examples.

EXAMPLES

Example 1

Potassium ATP Channel Activator Containing Formulations

1. Compressed Tablet Formulations

Diazoxide or a derivative thereof at about 15-30% by weight is mixed with hydroxypropyl methylcellulose at about 55-80% by weight, ethylcellulose at about 3-10 wt/vol % and magnesium stearate (as lubricant) and talc (as glidant) each at less than 3% by weight. The mixture is used to produce a compressed tablet as described in Reddy et al., *AAPS Pharm Sci Tech* 4(4):1-9 (2003). The tablet may be coated with a thin film as discussed below for microparticles.

A tablet containing 100 mg of diazoxide or a derivative thereof will also contain approximately 400 mg of hydroxypropyl cellulose and 10 mg of ethylcellulose. A tablet containing 50 mg of diazoxide or a derivative thereof will also contain approximately 200 mg of hydroxypropyl cellulose and 5 mg of ethylcellulose. A tablet containing 25 mg of diazoxide or a derivative thereof will also contain approximately 100 mg of hydroxypropyl cellulose and 2.5 mg of ethylcellulose.

2. Encapsulated Coated Microparticle Formulation of Diazoxide

Diazoxide or a derivative thereof is encapsulated into microparticles in accordance with well known methods (see, e.g. U.S. Pat. No. 6,022,562). Microparticles of between 100 and 500 microns in diameter containing diazoxide or derivative, alone or in combination with one or more suitable excipient, is formed with the assistance of a granulator and then sieved to separate microparticles having the appropriate size. Micriparticles are coated with a thin film by spray drying using commercial instrumentation (e.g. Uniglatt Spray Coating Machine). The thin film comprises ethylcellulose, cellulose acetate, polyvinylpyrrolidone and/or polyacrylamide. The coating solution for the thin film may include a plasticizer which may be castor oil, diethyl phthalate, triethyl citrate and salicylic acid. The coating solution may also include a lubricating agent which may be magnesium stearate, sodium oleate, or polyoxyethylenated sorbitan laurate. The coating solution may further include an excipient such as talc, colloidal silica or of a mixture of the two added at 1.5 to 3% by weight to prevent caking of the film coated particles.

3. Formulation of a Tableted Form of Diazoxide or a Derivative for Controlled Release

Prior to mixing, both the active ingredient and hydroxypropyl methylcellulose (Dow Methocel K4M P) are passed through an ASTM 80 mesh sieve. A mixture is formed from 1 part diazoxide or a derivative thereof to 4 parts hydroxypropyl methylcellulose. After thorough mixing, a sufficient volume of an ethanolic solution of ethylcellulose as a granulating agent is added slowly. The quantity of ethylcellulose per tablet in the final formulation is about 1/10th part. The mass resulting from mixing the granulating agent is sieved through 22/44 mesh. Resulting granules are dried at 40° C. for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry the granules retained on 44 mesh are mixed with 15% fines (granules that passed through 44 mesh). Talc and magnesium stearate are added as glidant and lubricant at 2% of weight each. A colorant is also added. The tablets are compressed using a single punch tablet compression machine.

4. Formulation of a Compression Tableted Form of Diazoxide or a Derivative Thereof that Provides for Controlled Release

Diazoxide or a derivative thereof at 20-40% weight is mixed with 30% weight hydroxypropyl methylcellulose (Dow Methocel K100LV P) and 20-40% weight impalpable lactose. The mixture is granulated with the addition of water. The granulated mixture is wet milled and then dried 12 hours at 110° C. The dried mixture is dry milled. Following milling, 25% weight ethylcellulose resin is added (Dow Ethocel 10FP or Ethocel 100FP) followed by 0.5% weight magnesium stearate. A colorant is also added. The tablets are compressed using a single punch tablet compression machine (Dasbach, et al, Poster at AAPS Annual Meeting November 10-14 (2002)).

5. Formulation of a Compression Coated Tableted Form of Diazoxide or a Derivative Thereof that Provides for Controlled Release.

The core tablet is formulated by mixing either 100 mg of diazoxide or a derivative thereof with 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 75 mg of diazoxide or a derivative thereof with 25 mg lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 50 mg of diazoxide or a derivative thereof with 50 mg of lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP). The core tablets are formed on an automated press with concave tooling. The compression coating consisting of 400 mg of ethylene oxide (Union Carbide POLYOX WSR Coagulant) is applied and compressed to 3000 psi (Dasbach, et al., Poster at AAPS Annual Meeting Oct 26-30 (2003)).

6. A Controlled Release Dosage Form of Diazoxide or a Derivative Thereof Using an Osmotically Controlled Release System

Diazoxide or a derivative thereof is formulated as an osmotically regulated release system. In general, two components, and expandable hydrogel that drives release of the active drug is assembled with diazoxide or a derivative thereof into a semipermeable bilaminate shell. Upon assembly a hole is drilled in the shell to facilitate release of active upon hydration of the hydrogel.

A dosage form adapted, designed and shaped as an osmotic delivery system is manufactured as follows: first, a diazoxide or a derivative thereof composition is provided by blending together into a homogeneous blend of polyethylene oxide, of diazoxide or a derivative thereof and hydroxypropyl methylcellulose. Then, a volume of denatured anhydrous ethanol weighing 70% of the dry mass is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 0.5% weight of magnesium stearate for 5 minutes.

A hydrogel composition is prepared as follows: first, 69% weight of polyethylene oxide weight, 25% weight of sodium chloride and 1% weight ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 5% weight of hydroxypropyl methylcellulose to produce a homogeneous blend. Next, a volume of denatured anhydrous alcohol equal to 50% of the dry mass is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh

screen. The screened granulation is mixed with 0.5% weight of magnesium stearate 5 minutes (see U.S. Pat. No. 6,361,795 by Kuczynski, et al.).

The diazoxide or a derivative thereof composition and the hydrogel composition are compressed into bilaminate tablets. First the diazoxide or a derivative thereof composition is added and tamped, then, the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

The bilaminate arrangements are coated with a semipermeable wall (i.e. thin film). The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol. The wall forming composition is sprayed onto and around the bilaminate.

Finally an exit passageway is drilled through the semipermeable wall to connect the diazoxide or a derivative thereof drug lamina with the exterior of the dosage system. The residual solvent is removed by drying at 50° C. and 50% humidity. Next, the osmotic systems are dried at 50° C. to remove excess moisture (see U.S. Pat. No. 6,361,795 by Kuczynski, et al.).

7. Preparation of a Salt of Diazoxide

A hydrochloride salt of diazoxide is prepared by dissolving one mole of diazoxide (230.7 g) in 500 ml of Et_2O. Dry HCl is passed into the solution until the weight of the container is increased by 36 g. During the addition of the HCl, the HCl salt of diazoxide precipitates as a powder. The salt is filtered off and washed with dry Et_2O.

Example 2

In Vivo Obesity Testing

1. Obesity Animal Model

Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in an animal model of obesity as described by Surwit et al. (*Endocrinology* 141:3630-3637 (2000)). Briefly, 4-week-old B6 male mice are housed 5/cage in a temperature-controlled (22° C.) room with a 12-h light, 12-h dark cycle. The high fat (HF) and low fat (LF) experimental diets contain 58% and 11% of calories from fat, respectively. A group of mice are fed the HF diet for the first 4 weeks of the study; the remaining 15 mice are fed the LF diet. The mice assigned to the LF diet are maintained on this diet throughout the study as a reference group of lean control mice. At week 4, all HF-fed mice a reassigned to 2 groups of mice. The first group remains on the HF diet throughout the study as the obese control group. The remaining 3 groups of mice are fed the HF diet and administered the controlled release formulation of diazoxide or derivative at about 150 mg of active per kg per day as a single dose administered by oral gavage. Animals are weighed weekly, and food consumption is measured per cage twice weekly until the diets are changed at week 4, whereupon body weight and food intake are determined daily. The feed efficiency (grams of body weight gained per Cal consumed) is calculated on a per cage basis. Samples for analysis of insulin, glucose, and leptin are collected on day 24 (4 days before the diets are changed), on day 32 (4 days after the change), and biweekly thereafter. In all cases food is removed 8 h before samples are collected. Glucose is analyzed by the glucose oxidase method. Insulin and leptin concentrations are determined by double antibody RIA. The insulin assay is based on a rat standard, and the leptin assay uses a mouse standard. At the termination of the study, a postprandial plasma sample is collected and analyzed for triglyceride and nonesterified fatty acid concentrations. After 4 weeks of drug treatment, a subset of 10 animals from each group is killed. The epididymal white adipose tissue (EWAT), retroperitoneal (RP) fat, interscapular brown adipose tissue (IBAT) fat pads, and gastrocnemius muscle are removed, trimmed, and weighed. The percent body fat is estimated from the weight of the epididymal fat pad. A subset of five animals from each group is injected ip with 0.5 g/kg glucose. At 30 min postinjection, a plasma sample is collected and analyzed for glucose content by the glucose oxidase method.

2. Treatment of Obesity in Humans

Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in obese humans. The study is conducted as described by Alemzadeh (Alemzadeh, et al., *J Clin Endocr Metab* 83:1911-1915 (1998)). Subjects consist of moderate-to-morbidly obese adults with a body mass index (BMI) greater than or equal to 30 kg/m^2. Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 50 patients are tested at each dosage of drug. Daily dosage is set at 100, 200, and 300 mg/day. The daily dose is divided into 2 doses for administration. The dose is administered as either one, two or three 50 mg capsules or tablets at each time of administration. Individual patients are dosed daily for up to 12 months. Patients are reviewed weekly, weighed, and asked about any side effects or concurrent illnesses.

Twenty-four-hour dietary recall is obtained from each patient. The dietary recalls are analyzed using a standard computer software program. All patients are placed on a hypocaloric diet and encouraged to participate in regular exercise.

Before commencing, and after completion of the study, the following laboratory tests are obtained: blood pressure fasting plasma glucose, insulin, cholesterol, triglycerides, free fatty acids (FFA), and glycohemoglobin and measures of rate of appearance and oxidation of plasma derived fatty acids. Additionally, routine chemistry profiles and fasting plasma glucose are obtained weekly to identify those subjects with evidence of glucose intolerance and/or electrolyte abnormalities. Glucose is analyzed in plasma, by the glucose oxidase method.

Insulin concentration is determined by RIA using a double-antibody kit. Cholesterol and triglycerides concentrations are measured by an enzymatic method. Plasma FFA is determined by an enzymatic colorimetric method. SI was assessed by an iv glucose tolerance test (IVGTT) using the modified minimal model. After an overnight fast, a glucose bolus (300 mg/kg) was administered iv, followed (20 min later) by a bolus of insulin. Blood for determination of glucose and insulin is obtained from a contra lateral vein at −30, −15, 0, 2, 3, 4, 5, 6, 8, 10, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. SI and glucose effectiveness (SG) are calculated using Bergman's modified minimal-model computer program before and after the completion of the study. Acute insulin response to glucose is determined over the first 19 min of the IVGTT, and the glucose disappearance rate (Kg) is determined from 8-19 min of the IVGTT. Body composition is measured by bioelectrical impedance before and at the completion of the study. Resting energy expenditure (REE) is measured by indirect calorimetry after an

overnight 12-h fast, with subjects lying supine for a period of 30 min. Urine is collected over the corresponding 24 h, for measurement of total nitrogen and determination of substrate use, before and after the study.

3. Treatment of Obesity in Humans by Coadministering Diazoxide and Phentermine

Evaluation of a prolonged co-administration of solid oral dosage form of diazoxide or a derivative thereof and phentermine in obese humans with a moderate-to-morbidly and a body mass index (BMI) greater than or equal to 30 kg/m^2. Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 100 patients are tested. Daily dosage of diazoxide is set at 200 mg. The daily dose is divided into 2 doses for administration. The dose is administered as either a 100 mg capsule or a 100 mg tablet at each time of administration. Individual patients are dosed daily for up to 12 months. Phentermine is administered as a single daily dose of 15 mg. Patients are reviewed every two weeks, weighed, and asked about any side effects or concurrent illnesses.

All patients are continued on a hypocaloric diet and encouraged to participate in regular exercise. Before commencing, and after completion of the study, laboratory tests as described in the example above are obtained.

4. Prevention of Diabetes in Prediabetic Humans

The example describes use of diazoxide in a prediabetic individual to prevent the occurrence of diabetes. Individuals included in the study all have elevated risk of developing diabetes as measured by one of two methods. In a fasting glucose assay they have plasma glucose values between 100 and 125 mg/dl indicating impaired fasting glucose, or in an oral glucose tolerance test they have plasma glucose values between 140 and 199 mg/dl at 2 hours post-glucose load indicating they have impaired glucose tolerance. Treatment is initiated in any individual meeting either criteria. Treated individuals receive either 200 mg diazoxide per day as a 100 mg capsule or tablet twice per day or as two 100 mg capsules or tablets once per day. Placebo treated individuals receive either one placebo capsule or tablet twice per day or two placebo capsules or tablets once per day.

Treatment is continued for one year with OGTT or fasting glucose measured monthly.

5. A Sustained Release Coformulation of Diazoxide HCl and Metformin HCl Use to Treat Diabetic Patients

A sustained release co-formulation of diazoxide HCl and metformin HCl is produced by forming a compressed tablet matrix that includes 750 mg of metformin HCl and 100 mg of diazoxide HCl. These active ingredients are blended with sodium carboxymethyl cellulose (about 5% (w/w)), hypromellose (about 25% (w/w), and magnesium stearate (<2% (w/w)). The compressed tablet is further coated with a combination of ethylcellulose (80% (w/w)) and methyl cellulose (20% (w/w)) as a thin film to control rate of hydration and drug release.

Type II diabetic patients are treated with the oral dosage form by administration of two tablets once per day or one tablet every 12 hours. Treatment of the patient with the drug is continued until one of two therapeutic endpoints is reached, or for so long as the patient derives therapeutic benefit from administration. The two therapeutic endpoints that would serve as the basis for the decision to cease treatment include the patient reaching a Body Mass Index (BMI (kg/m^2)) between 18 and 25 or the re-establishment of normal glucose tolerance in the absence of treatment. The patient is monitored periodically for (a) glucose tolerance using an oral glucose tolerance test, (b) glycemic control using a standard blood glucose assay, (c) weight gain or loss, (d) progression of diabetic complications, and (e) adverse effects associated with the use of these active ingredients.

6. Prevention or Treatment of Weight Gain in a Patient Treated with Olanzapine

Pharmacotherapy for schizophrenia is initiated for a patient meeting DSM III-R criteria for schizophrenia. The patient is administered 10 mg of olanzapine (Zyprexa, Lilly) once per day. Adjunctive therapy to the patient for schizophrenia includes 250 mg equivalent of valproic acid as divalproex sodium (Depakote, Abbott Labs). Weight gain, dyslipidemia and impaired glucose tolerance, and metabolic syndrome are high frequency adverse events in patients treated with this combination of anti-psychotics. Weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome are treated by the co-administration of a therapeutically effective dose of a K_{ATP} channel opener. The patient is treated with administration of 200 mg/day of diazoxide as a once daily tablet formulation. Diazoxide administration continues until the weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome is corrected or until treatment of the patient with olanzapine is discontinued. Dyslipidemia is detected by measuring circulating concentrations of total, HDL, and LDL cholesterol, triglycerides and non-esterified fatty acids. Impaired glucose tolerance is detected through the use of oral or IV glucose tolerance tests. Metabolic syndrome is detected by measuring its key risk factors including central obesity, dyslipidemia, impaired glucose tolerance, and circulating concentrations of key proinflammatory cytokines.

Example 3

Clinical Study in Obese Pediatric and Adult PWS Patients

A single-center, open-label, single-arm clinical study (PC025) with a double-blind, placebo-controlled, randomized withdrawal extension has been carried out. Patients were initiated on a DCCR dose of about 1.5 mg/kg (maximum starting dose of 145 mg) and were titrated every 14 days to about 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg (maximum dose of 507.5 mg). These DCCR doses are equivalent to diazoxide doses of 1.03, 1.66, 2.28, and 2.9 mg/kg, respectively. Patients were up-titrated at each visit at the discretion of the investigator. Any patient who showed an increase in resting energy expenditure and/or a reduction in hyperphagia from Baseline through Day 27 or Day 55 was designated a Responder and eligible to be randomized in the double-blind phase. Everyone who completed the open-label phase was a Responder and was randomized in and completed the double-blind phase. During the double-blind, placebo-controlled, randomized withdrawal phase, Responders were randomized in a 1:1 ratio either to continue on active treatment at the dose they were treated with on Day 55 or to the placebo equivalent of that dose for an additional 4 weeks (29 days). Non-responders continued open label treatment with DCCR at the dose they were treated with on Day 55 for an additional 29 days. A total of 12 patients were enrolled in the study.

Schematic Screening (28 Days)*	Open Label Treatment Period (69 days)						Double-Blind, Placebo-Controlled, Randomized Withdrawal Extension
Day −28 to Day −1	Baseline Day 0	Day 13	Day 27	Day 41	Day 55	Day 69	(29 days) Day 97
	1.5 mg/kg	2.4 mg/kg	3.3 mg/kg	4.2 mg/kg	5.1 mg/kg	Day 55 dose or Placebo Equivalent for Responders and Day 55 dose for Non-Responders	

*All screening procedures must be completed by Day −14

Inclusion Criteria: Basic Requirements

Ability to follow verbal and written instructions with or without assistance from caregiver

Informed consent form signed by the subject or their legal guardian

Completed the screening process between 2 and 4 weeks prior to Baseline Visit

General Demographic Characteristics

Male and female patients 10 to 22 years of age, inclusive at the time of dosing

Genetically confirmed Prader-Willi syndrome

BMI exceeds the 95th percentile of the age specific BMI value on the CDC BMI charts or percent body fat ≥35%

(The body fat criteria will only be used if there were a measurement made within 12 months of the Screening Visit, and the patient has not lost weight since the measurement. Under all other circumstances, the BMI criteria will apply.)

Generally healthy as documented by the medical history, physical examination, vital sign assessments, 12-lead electrocardiogram (ECG), and clinical laboratory assessments

Specific Laboratory Test Results

fasting glucose≤126 mg/dL

HbA1c≤6.5%

Endpoints and Statistical Analysis

Every endpoint is measured in two timeframes: (1) during the open label treatment phase as change (or percent change) from Baseline to Day 69; and (2) during the double-blind, placebo-controlled, randomized withdrawal phase as change (or percent change) from Day 69 to Day 97.

Endpoints measured during the open label treatment phase were analyzed by paired t-test while those measured during the double-blind, placebo-controlled treatment phase are subjected to ANOVA and paired t-tests.

Efficacy endpoints include: hyperphagia (measured using parent/caregiver responses on a modified Dykens hyperphagia questionnaire—converted to a numeric score between 0 and 34); weight; body fat (measured by DEXA); lean body mass (measured by DEXA); resting energy expenditure (measured by indirect calorimetry); respiratory quotient (measured by indirect calorimetry); waist circumference; BMI; ghrelin; leptin; triglycerides; total cholesterol; HDL cholesterol; non-HDL cholesterol and LDL cholesterol. Additional information was collected in a behavioral questionnaire. Tables 2 and 3 summarize the visits at which each efficacy parameter was measured.

TABLE 2

Time points for assessment of efficacy parameters during open-label phase

Parameter	Screening	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	End of Open label treatment
Hyperphagia	+	+	+	+	+	+	+
Body fat	Either at screening or baseline						+
Lean body mass							+
Weight	+	+	+	+	+	+	+
REE & RQ		+		+		+	+
Waist circumference	+	+	+	+	+	+	+
Ghrelin, leptin		+					+
Lipids		+					+
Behavioral questionnaire		+					+

TABLE 3

Time points for assessment of efficacy parameters during double-blind treatment

Parameter	Screening	Baseline	Day 69 End of Open label treatment	Day 97 End of double blind treatment
Hyperphagia	+	+	+	+
Body fat	Either at screening or baseline		+	
Lean body mass			+	
Weight	+	+	+	+
REE & RQ		+	+	+
Waist circumference	+	+	+	+
Ghrelin, leptin		+	+	
Lipids		+	+	+
Behavioral questionnaire		+	+	

Patients in the Study

Demographic information and relevant medical history for each patient are shown in Table 4. Eleven of the thirteen

subjects enrolled in clinical study PC025 completed the open-label phase. All were identified as Responders and were, therefore, randomized in the double-blind phase of the study. All subjects randomized in the double-blind phase of the study completed the phase.

Baseline characteristics of patients enrolled in the study are provided in Table 5.

were evaluated separately for subjects who were growth hormone treated and growth hormone naïve. These results are shown in Table 6.

Weight by DEXA was calculated as the sum of body fat and lean body mass. The ratio of lean body mass to body fat was also calculated.

TABLE 4

Demographic information and relevant medical history for patients enrolled in PC025

Patient	Sex	Age	PWS sub-type	Age at diagnosis	GH trt*	Relevant medical history
BN-01	M	11.6	Deletion	4 wk	No	acanthosis nigricans, obesity @ 3 yr, asthma, undescended testes, fatty liver, sleep apnea
CP-02	M	16.5	Deletion	3 wk	Yes	cerebral palsy, obesity @ 2 yr, type 2 diabetes, gynecomastia, undescended testicle, sleep apnea, asthma @ 1 yr
TJ-03	M	18.6	Deletion	6 wk	No	obesity @ 3 yr with hyperphagia, psychiatric illness @ 2 yr, undescended testicle, osteopenia
AC-04	F	17.0	Deletion	15 yr	No	scoliosis, short stature, osteopenia
MR-05	F	17.8	Deletion	5.7 yr	No	scoliosis, strabismus, amenorrhea
SD-06	M	16.7	Deletion	3 yr	Yes	morbid obesity @ 6 yr, sleep apnea, scoliosis, pulmonary hypertension, undescended testes, strabismus
AS-08	M	11.9	Deletion	10 wk	Yes	hyperphagia @ 3 yr, dyslipidemia, opthalmoplegia, osteopenia, scoliosis
SP-09	F	21.6	Deletion	6 wk	No	scoliosis, sleep apnea, osteopenia, amenorrhea
DD-10	M	12.5	UPD	16 wk	Yes	osteopenia
SM-11	F	15.4	Deletion	1 wk	Yes	psychiatric disease, osteopenia, scoliosis
AD-13	F	14.7	Deletion	4 wk	No	obesity @ 5 yr, osteopenia
JG-15	M	14.4	Deletion	2 wk	Yes	obesity @ 5 yr
NT-16	M	19.3	Deletion	2 wk	No	Scoliosis, strabismus, sleep apnea

TABLE 5

Baseline characteristics of subjects who were randomized in the double-blind phase of clinical study PC025.

Subject	Weight (kg)	Height (cm)	Percent body fat	BMI	Hyper-phagia score	REE % RDA	RQ
CP-02	97.2	166	52.0	35.3	18.5	83%	0.86
AC-04	56.9	151	46.8	25.0	7	84%	0.78
MR-05	113.1	145	59.1	53.8	20.5	83%	0.87
SD-06	133.6	145	53.5	51.5	3	102%	0.84
AS-08	60.9	140	53.4	31.0	25.5	86%	1.03
SP-09	106.8	148	60.7	48.8	10.5	84%	0.72
DD-10	70.8	155	49.3	29.5	32	101%	0.97
SM-11	62.2	140	48.8	31.7	8	97%	0.81
AD-13	103.5	149	56.6	46.6	10	94%	0.85
JG-15	106.3	161	53.7	41.0	16	71%	0.79
NT-16	80.8	177	36.4	25.7	14	100%	0.78
Average	90.4	152.5	51.8	38.2	14.95	89.6%	0.85

TABLE 6

Changes in body composition by DEXA from Baseline through Day 69

Parameter	n	Percent Change	p-value
All subjects randomized in the double blind phase			
Body fat	11	−3.8%	0.011
Lean body mass	11	5.41%	0.001
Lean body mass/fat mass ratio	11	9.82%	0.002
Weight	11	0.67%	0.150
Growth hormone treated subjects			
Body fat	6	−3.31%	0.056
Lean body mass	6	5.50%	0.005
Lean body mass/fat mass ratio	6	9.37%	0.014
Weight	6	0.90%	0.189
Growth hormone naive subjects			
Body fat	5	−4.34%	0.083
Lean body mass	5	5.30%	0.055
Lean body mass/fat mass ratio	5	10.36%	0.043
Weight	5	0.39%	0.301

Dosing

One subject, a treated type 2 diabetic, finished the open-label treatment period on a dose of 1.5 mg/kg. Of the remaining 10 subjects, 1 finished the open-label treatment period at a dose of 2.4 mg/kg, and 3 at 3.3 mg/kg. The last 6 subjects enrolled in the study finished the open-label treatment phase at a dose 4.2 mg/kg.

Changes in Body Composition, Waist Circumference and Weight

Body fat and lean body mass were measured by DEXA at baseline and again at the end of the open label treatment. Since DEXA was not run on Day 97, the only body composition measurements made on the subjects randomized in the double-blind phase occurred in the period from Baseline to Day 69. The body composition changes are outlined in Table 6. Changes in body composition by DEXA

Treatment with DCCR for 10 weeks had a highly significant and clinically relevant impact on body composition including reductions in body fat, increases in lean body mass and a very marked increase in lean body mass to body fat ratio. Because these patients had almost equal lean body mass and fat mass at Baseline, parallel increases in lean body mass and reductions in body fat result in almost no net change in weight. In general, the changes in body composition were of similar magnitude in both growth hormone treated and growth hormone naïve subjects.

The changes in body composition were dose dependent. Those subjects who completed the open-label treatment phase at a dose of 4.2 mg/kg experienced a 6.3% decrease in fat mass, a 9.2% increase in lean body mass and a 16.6% increase in the lean body mass to fat mass ratio.

Three subjects in the study showed greater than 10% increase in lean body mass. Every subject showed an increase in lean body mass/fat mass ratio. More than half of the subjects in the study showed a >10% increase in the lean body mass/fat mass ratio, and one showed more than a 20% increase.

FIGS. **1-4** summarize the percent change in body fat, lean body mass and lean body mass/fat mass ratio from Baseline through Day 69.

Weight and waist circumference were measured during the physical exam at each visit. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 7. The results from the period covering Day 69 through Day 97 are shown in Table 8. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 9.

TABLE 7

Changes in weight and waist circumference from Baseline through Day 69

Parameter	n	Change/Percent change	p-value
Weight	11	0.53%	0.317
Waist circumference	11	−3.5 cm	0.003

TABLE 8

Changes in weight and waist circumference from Day 69 through Day 97

Parameter	Arm	n	Change/Percent change	p-value comparing arms
Weight	DCCR	5	−1.7%	0.723
Weight	Placebo	6	−1.1%	
Waist circumference	DCCR	5	−2.9 cm	0.047
Waist circumference	Placebo	5	0.25 cm	

TABLE 9

Changes in weight and waist circumference from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	n	Change Through Day 97	p-value
Weight	5	0.4%	0.828
Waist circumference	5	−3.7 cm	0.039

Interestingly, the change in weight from Baseline through day 69 by DEXA and by the standard weight measurement produces almost identical results (an increase of 0.67% by DEXA and 0.53% by the standard approach). In contrast to the lack of change in weight, there was a statistically significant reduction in waist circumference through Day 69 in all subjects randomized in the double-blind phase; through Day 97 for those who continued on DCCR. The comparison of change in waist circumference between arms between Day 69 and Day 97, during which the placebo treated patients showed an incremental increase in waist circumference, while those who continued on DCCR, showed a notable reduction. The reduction in waist circumference is consistent with the explanation that DCCR treated subjects are losing visceral fat.

Changes in Hyperphagia

The hyperphagia questionnaire was administered at all visits. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 10. The results from the period covering Day 69 through Day 97 are shown in Table 11. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 12.

TABLE 10

Changes in hyperphagia from Baseline through Day 69

Parameter	n	Percent change	p-value
Hyperphagia	11	−31.6%	0.003

TABLE 11

Changes in hyperphagia from Day 69 through Day 97

Parameter	Arm	n	Change	p-value comparing arms
Hyperphagia	DCCR	5	2.0	0.389
Hyperphagia	Placebo	6	0.33	

TABLE 12

Changes in hyperphagia from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	n	Percent change through Day 97	p-value
Hyperphagia	5	−29.2%	0.006

There was a statistically significant reduction in hyperphagia in all subjects randomized in the double-blind phase from Baseline through Day 69 and in those who continued on DCCR through the double-blind phase from Baseline through Day 97.

DCCR treated patients at the end of 97 days of treatment showed an improvement in hyperphagia of 29.2% while those that were treated with DCCR for 69 days followed by 28 days of placebo treatment showed only a 13.9% improvement in hyperphagia on Day 97. Thus, at the end of the double-blind phase, DCCR treated patients showed more than twice the improvement in hyperphagia as did those who were randomized to placebo in the double-blind phase. Once patients discontinue from DCCR treatment, given the long half-life of DCCR (28-32 hours) it takes about 7-10 days to completely clear from circulation. Verbatim statements were obtained from parents of subjects in the study suggesting that they had seen their children's food related behavior deteriorate only in the last couple of weeks of the study, suggesting a longer double-blind phase might have resulted in further separation of the arms. In general, the magnitude of impact on how upset subjects became when denied food,

how easy it was to get them to think about something else if once denied food, and the impact on the frequency of stealing food, digging through the trash for food and bargaining for food were of equivalent or greater magnitude as the overall impact on the hyperphagia score. DCCR appeared to have lesser impact on how sneaky or quick subjects were with respect to food and on how often they got up at night to seek food.

Improvements in hyperphagia were observed in subjects with baseline hyperphagia ranging from 29 (−45%) to less than 5 (−33%) on a 0 to 34 point scale.

About 25% of the subjects ended the open-label phase with very low levels of hyperphagia (2 or 3 on a 0 to 34 scale). These subjects tended to be able to lose more body fat than the average. Two such subjects, both females, one growth hormone treated and one growth hormone naïve, lost more than 10% of their initial body fat mass through 10 weeks.

FIG. **1** shows the change in hyperphagia from Baseline through Day 69.

Changes in Lipids

A lipid panel was evaluated at Baseline, and again on Day 69 and Day 97. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 13. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 14.

TABLE 13

Changes in Lipids from Baseline through Day 69

Parameter	n	Percent change	p-value
Total cholesterol	8	−4.0%	0.044
Triglycerides	7	−21.0%	0.084
HDL-C	8	10.8%	0.244
LDL-C	8	−7.0%	0.030
Non-HDL-C	8	−6.5%	0.019

TABLE 14

Median Percent Change in lipids from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	Median Percent change from Baseline through Day 97
Total Cholesterol	−11.0%
Triglycerides	−41.8%
HDL-C	25.2%
LDL-C	−7.9%
Non-HDL-C	−13.4%

Consistent with previous studies involving DCCR, treatment of subjects randomized in the double-blind phase with DCCR from Baseline through Day 69 resulted in a number of statistically significant changes in lipids including reductions in total cholesterol, LDL cholesterol and non-HDL cholesterol. Even though the impact on triglycerides was of larger magnitude, it did not reach significance because of the smaller n and greater variability in the population. In general, greater reductions in triglycerides were seen in those with significant elevations in triglycerides at Baseline. A similar pattern was observed in those who were treated with DCCR through the end of the double-blind treatment. The decreases in total cholesterol, triglycerides, LDL-C and non-HDL-C were all larger in those who were treated with DCCR longer.

Changes in Leptin and Ghrelin

Leptin and ghrelin were measured at Baseline and again on Day 69. The results from Baseline through Day 69 for leptin and ghrelin are provided in Table 15.

TABLE 15

Leptin and ghrelin changes from Baseline through Day 69

Parameter	n	Percent change	p-value
Leptin	6	−22.0%	0.061
Ghrelin	6	−15.0%	0.052

Further evidence for loss of body fat comes from the analysis of leptin, the results of which are consistent with the DEXA data and the data on waist circumference. Although not quite reaching statistical significance, leptin is down more than 20% from Baseline.

While ghrelin may or may not contribute substantially to hyperphagia in PWS, reductions in ghrelin are beneficial in PWS patients.

Behavioral Changes

A questionnaire, adapted from the PWS natural history study, was used to document the presence or absence of 23 PWS-associated behaviors at Baseline and again on Day 69. These behaviors generally fell into 4 categories:

(1) aggressive, threatening and destructive behaviors;
(2) self-injurious behaviors;
(3) compulsive behaviors; and
(4) other behaviors.

The questionnaire was administered at Baseline and again on Day 69. Discontinuation rates for aggressive, threatening, destructive behaviors and for all other behaviors are shown in Table 16.

TABLE 16

Discontinuation rates for various classes of behavior in clinical study PC025

Behaviors	Discontinuation rate	p-value
Aggressive, threatening, destructive	−62.5%	0.01
All other PWS associated behaviors	−29.8%	

The impact on aggressive, threatening and destructive behaviors was independent of an impact on hyperphagia.

Changes in Resting Energy Expenditure and Respiratory Quotient

The measurements for resting energy expenditure and respiratory quotient were quite variable from visit to visit. Despite the variability, resting energy expenditure and respiratory quotient appeared to be unchanged from Baseline through Day 69.

Changes in Insulin Sensitivity

Treatment with DCCR in other clinical studies was associated with improvements in insulin resistance as measured by changes in homeostatic model assessment of insulin resistance (HOMA-IR). Improvements in insulin sensitivity are well documented in the literature on diazoxide. The subjects enrolled in the double-blind phase of this study were quite insulin sensitive at Baseline, which is typical of PWS patients in this age range. Consistent with prior DCCR clinical studies and the historic diazoxide literature, treat-

ment with DCCR for 10 weeks resulted in an improvement in HOMA-IR from 2.61±1.85 at Baseline to 1.46±1.36 on Day 69. The difference did not reach statistical significance (p=0.095).

Example 4

Clinical Studies with Smith-Magenis Syndrome Patients

In a first example, a Smith-Magenis syndrome patient is treated with an oral suspension of diazoxide. The initial dose is approximately 1 mg/kg administered in divided doses. After the patient has been stably treated with 1 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 1.5 mg/kg. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.0 mg/kg. This process of increasing the dose by about 0.5 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior, and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

In a second example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.1 mg/kg. After the patient has been stably treated with 2.1 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.7 mg/kg. This process of increasing the dose by about 0.6 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

In a third example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.2 mg/kg. After the patient has been stably treated with 2.2 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.9 mg/kg. This process of increasing the dose by about 0.7 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment or a maximal dose of 5 mg/kg is reached. In parallel, the patient may also be treated with beloranib. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

In a fourth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.3 mg/kg. After the patient has been stably treated with 2.3 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.0 mg/kg. This process of increasing the dose by about 0.8 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. In parallel, the patient may also be treated with an unacylated ghrelin analog. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

In a fifth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose would be titrated to about 2.4 mg/kg. After the patient has been stably treated with 2.4 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.3 mg/kg. This process of increasing the dose by about 0.9 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg was reached. In parallel, the patient may also be treated with an MC4 agonist. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

In a sixth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.5 mg/kg. After the patient has been stably treated with 2.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.5 mg/kg. This process of increasing the dose by about 1.0 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg was reached. In parallel, the patient may also be treated with an MC4 agonist. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

Definitions provided herein are not intended to be limiting from the meaning commonly understood by one of skill in the art unless indicated otherwise.

The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

That which is claimed is:

1. A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of diazoxide or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.

2. The method of claim **1** wherein the pharmaceutically acceptable salt is diazoxide choline.

3. The method of claim **1** wherein said pharmaceutical formulation is administered orally.

4. The method of claim **1** wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof.

5. The method of claim **4** wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof.

6. The method of claim **1** wherein the pharmaceutical formulation further comprises at least one other active ingredient.

7. The method of claim **1** further comprising administering human growth hormone to the subject.

8. The method of claim **7** wherein said human growth hormone is administered by injection.

9. The method of claim **1** wherein said administering is carried out for one or more years.

10. The method of claim **1**, wherein the circulating concentration of IGF-1 is not increased.

11. The method of claim **1** in which a second therapeutic product is administered, wherein the second product is intended to further reduce the one or more aggressive behaviors.

12. The method of claim **1** wherein the pharmaceutical formulation is administered twice per day.

13. The method of claim **1** wherein the pharmaceutical formulation is administered once per day.

14. A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a formulation consisting essentially of diazoxide or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.

* * * * *

EXHIBIT 2

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT3616164

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
NEIL M COWEN	11/13/2015

RECEIVING PARTY DATA

Name:	ESSENTIALIS, INC.
Street Address:	7915 CORTE CARDO
City:	CARLSBAD
State/Country:	CALIFORNIA
Postal Code:	92009

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	14940018

CORRESPONDENCE DATA

Fax Number: (858)350-6111

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 858-350-6100
Email: wgorman@kilpatricktownsend.com, ipefiling@kilpatricktownsend.com
Correspondent Name: KILPATRICK TOWNSEND & STOCKTON LLP
Address Line 1: TWO EMBARCADERO CENTER, EIGHTH FLOOR
Address Line 4: SAN FRANCISCO, CALIFORNIA 94111

ATTORNEY DOCKET NUMBER:	096593-001000US-0955615
NAME OF SUBMITTER:	WILLIAM H. GORMAN
SIGNATURE:	/WILLIAM H. GORMAN/
DATE SIGNED:	11/13/2015

Total Attachments: 2
source=2015-11-13_Assignment_096593-001000US-0955615#page1.tif
source=2015-11-13_Assignment_096593-001000US-0955615#page2.tif

ASSIGNMENT
(Patent Application)

I, the undersigned, have invented certain inventions and improvements disclosed in a utility (provisional or non-provisional) or design patent application entitled

"METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME,"

filed with the U.S. Patent & Trademark Office on November 12, 2015

and assigned serial no. 14/940,018

For good and valuable consideration, the receipt and sufficiency of which I acknowledge, we I:

1. Agree to assign, transfer, convey, and sell, hereby assign, transfer, convey, and sell and have assigned, transferred, conveyed, and sold to Essentialis, Inc., a corporation having a principal place of business at 7915 Corte Cardo, Carlsbad, California 92009 ("Assignee"), the entire right, title, and interest in and to:

    (a) all intellectual property (including, without limitation, any innovation, information, invention, discovery, product, process, work or design) disclosed, embodied, shown, or claimed in the above-referenced patent application, implicitly or explicitly;

    (b) the above-referenced patent application, the right to claim priority to the above-referenced patent application, all applications based in whole or in part upon the above-referenced patent application, including, without limitation, all applications that are a provisional, non-provisional, design, divisional, continuation, continuation-in-part, registration, utility model, industrial design, reissue, renewal, substitute, extension, reexamination, post-grant review, inter partes review, supplemental examination or non-U.S. patent application or application for other rights based in whole or in part on the above-referenced patent application;

    (c) all patents (including, without limitation, all U.S. and non-U.S. patents, registrations, utility models, industrial designs, design patents, counterparts, continuations, continuations-in-part, divisionals, reissues, renewals, substitutes, extensions, reexaminations, post-grant reviews, inter partes reviews and supplemental examinations) that are granted or issued upon, or that claim priority to, any and all applications described in (b) of this paragraph or that disclose or claim intellectual property described in (a) of this paragraph, in whole or in part; and

(d) all claims for damages by reason of past infringement of any rights under the applications or patents described in (a), (b) or (c) of this paragraph (including provisional rights to reasonable royalties pursuant to 35 U.S.C. §154(d)) and the right to sue for and collect such damages and royalties for Assignee's own use.

2. Authorize and request the U.S. Patent and Trademark Office or any other U.S. or non-U.S. agency to issue to the Assignee any and all patent(s), or other rights or documents, resulting from the intellectual property, patent application(s) and patents described in paragraph 1 of this Assignment.

3. Agree to sign all papers and documents, including without limitation, applications, declarations, oaths and petitions, and, at the Assignee's expense, perform any other acts that are necessary in connection with prosecution of patent application(s) or intellectual property described in paragraph 1 of this Assignment and the enforcement of patent(s) or other rights resulting from such patent application(s) or intellectual property.

4. Agree that the terms, covenants, and conditions of this Assignment shall inure to the benefit of the Assignee, its successors, assigns and other legal representative, and shall be binding upon me, as well as my heirs, legal representatives, and assigns.

5. Promise and affirm that I have not entered, and will not enter, into any assignment, contract, or understanding that conflicts with this Assignment.

6. Authorize Kilpatrick Townsend & Stockton to insert above the application number and filing date of the above-described patent application when known.

Signed on the date indicated beside my signature.

Signature: _____ Date: 11/13/15

Neil M. Cowen

EXHIBIT 3

Delaware

The First State

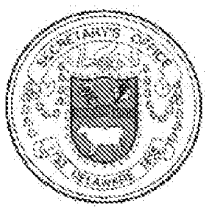
I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"COMPANY E MERGER SUB, INC.", A DELAWARE CORPORATION,

WITH AND INTO "ESSENTIALIS, INC." UNDER THE NAME OF "ESSENTIALIS, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE ON THE SEVENTH DAY OF MARCH, A.D. 2017, AT 1:25 O`CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE SUSSEX COUNTY RECORDER OF DEEDS.



3660270 8100M
SR# 20171636318

Authentication: 202153760
Date: 03-07-17

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 01:25 PM 03/07/2017
FILED 01:25 PM 03/07/2017
SR 20171636318 - File Number 3660270

CERTIFICATE OF MERGER

OF

COMPANY E MERGER SUB, INC.
(a Delaware corporation)

WITH AND INTO

ESSENTIALIS, INC.
(a Delaware corporation)

March 7, 2017

* * * * * * * * * * *

In accordance with the provisions of Section 251 of the General Corporation Law of the State of Delaware

* * * * * * * * * * *

Essentialis, Inc., a Delaware corporation (the "Corporation"), desiring to merge Company E Merger Sub, Inc., a Delaware corporation ("Merger Sub"), with and into the Corporation, pursuant to the provisions of Section 251 of the General Corporation Law of the State of Delaware, DOES HEREBY CERTIFY as follows:

FIRST: The name and state of incorporation of each constituent corporation of the merger (the "Merger") are as follows: (i) Essentialis, Inc., a Delaware corporation, and (ii) Company E Merger Sub, Inc., a Delaware corporation.

SECOND: An Agreement and Plan of Merger, dated as of December 22, 2016 (the "Merger Agreement"), by and among the Corporation, Merger Sub, Capnia, Inc., a Delaware corporation and owner of Merger Sub, and Stockholders Representative (as defined in the Merger Agreement), has been approved, adopted, certified, executed and acknowledged by each constituent corporation, in accordance with the requirements of Sections 228 and 251 of the General Corporation Law of the State of Delaware.

THIRD: The name of the surviving corporation of the Merger is Essentialis, Inc. (the "Surviving Corporation").

FOURTH: The Amended and Restated Certificate of Incorporation of the Corporation shall be amended and restated in its entirety to read as set forth on ***Exhibit A*** attached hereto and, as so amended and restated, shall constitute the Certificate of Incorporation of the Surviving Corporation until thereafter amended as provided therein or by applicable law.

FIFTH: An executed copy of the Merger Agreement is on file at the principal place of business of the Surviving Corporation, 1235 Radio Road, Suite 110, Redwood City, CA 94065, and a copy of the Merger Agreement will be furnished by the Surviving Corporation, upon request and without cost, to any stockholder of any constituent corporation.

SIXTH: The Merger shall be effective upon the filing of this Certificate of Merger with the Secretary of State of the State of Delaware.

IN WITNESS WHEREOF, the Surviving Corporation has caused this Certificate of Merger to be signed by an authorized officer as of the date first written above.

ESSENTIALIS, INC.,
a Delaware corporation

By: _____
Name: Neil Cowen
Title: President and Chief Executive Officer

[Signature Page to Certificate of Merger]

Exhibit A

SEVENTH AMENDED AND RESTATED CERTIFICATE OF INCORPORATION
OF
ESSENTIALIS, INC.

FIRST: The name of the corporation (hereinafter the "Corporation") is Essentialis, Inc.

SECOND: The address of the registered office of the Corporation in the State of Delaware is 1209 Orange Street, City of Wilmington, County of New Castle, State of Delaware 19801, and the name of the registered agent of the Corporation in the State of Delaware at such address is The Corporation Trust Company.

THIRD: The nature of the business and the purposes to be conducted and promoted by the Corporation shall be to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware (as amended from time to time, the "DGCL").

FOURTH: The total number of shares of stock which the Corporation shall have authority to issue is One Thousand (1,000) shares. The par value of each such share is $0.001. All such shares are of one class and are shares of Common Stock.

FIFTH: The Corporation is to have perpetual existence.

SIXTH:

A. The liability of the directors of the Corporation for monetary damages shall be eliminated to the fullest extent under applicable law. If the DGCL is amended to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of a director of the Corporation shall be eliminated or limited to the fullest extent permitted by the DGCL, as so amended.

B. To the fullest extent permitted by applicable law, the Corporation is authorized to provide indemnification of (and advancement of expenses to) directors, officers and agents of the Corporation (and any other persons to which applicable law permits the Corporation to provide indemnification) through provisions of the Bylaws of the Corporation, agreements with such agents or other persons, vote of stockholders or disinterested directors or otherwise in excess of the indemnification and advancement otherwise permitted by such applicable law. If applicable law is amended after approval by the stockholders of this Article SIXTH to authorize corporation action further eliminating or limiting the personal liability of directors, then the liability of a director to the Corporation shall be eliminated or limited to the fullest extent permitted by applicable law as so amended.

C. Any repeal or modification of this Article SIXTH shall only be prospective and shall not affect the rights or protections or increase the liability of any director under this Article SIXTH in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

D. The Corporation renounces any interest or expectancy of the Corporation in, or in being offered an opportunity to participate in, any Excluded Opportunity. An "Excluded Opportunity" is any matter, transaction or interest that is presented to, or acquired, created or developed by, or which otherwise comes into the possession of, any director of the

Corporation who is not an employee of the Corporation or any of its subsidiaries (collectively, "Covered Persons"), unless in either case such matter, transaction or interest is presented to, or acquired, created or developed by, or otherwise comes into the possession of, a Covered Person expressly and solely in such Covered Person's capacity as a director of the Corporation.

SEVENTH: From time to time any of the provisions of this certificate of incorporation may be amended, altered or repealed, and other provisions authorized by the laws of the State of Delaware at the time in force may be added or inserted in the manner and at the time prescribed by said laws, and all rights at any time conferred upon the stockholders of the Corporation by this certificate of incorporation are granted subject to the provisions of this Article SEVENTH.

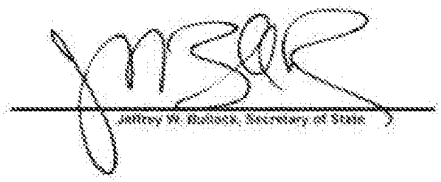
EXHIBIT 4

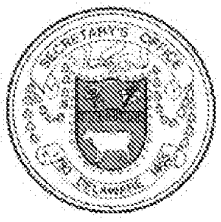
Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "CAPNIA, INC.", CHANGING ITS NAME FROM "CAPNIA, INC." TO "SOLENO THERAPEUTICS, INC.", FILED IN THIS OFFICE ON THE EIGHTH DAY OF MAY, A.D. 2017, AT 7:11 O`CLOCK P.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE EFFECTIVE DATE OF THE AFORESAID CERTIFICATE OF AMENDMENT IS THE TWELFTH DAY OF MAY, A.D. 2017 AT 12:01 O'CLOCK A.M.





3083882 8100
SR# 20173294107

Authentication: 202512838
Date: 05-09-17

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 07:11 PM 05/08/2017
FILED 07:11 PM 05/08/2017
SR 20173230761 - File Number 3083882

CAPNIA, INC.

CERTIFICATE OF AMENDMENT
OF THE
CERTIFICATE OF INCORPORATION

Capnia, Inc., a Delaware corporation (the "**Corporation**"), hereby certifies as follows:

1. The name of the Corporation is Capnia, Inc. The Corporation was originally incorporated under the name "Capnia, Inc." The original Certificate of Incorporation of the Corporation was filed with the Secretary of State of the State of Delaware on August 25, 1999.

2. Article I of the Certificate of Incorporation, as amended (the "**Certificate**") of the Corporation is hereby amended and restated to read in its entirety as follows:

"The name of this Corporation shall be Soleno Therapeutics, Inc."

3. The foregoing amendment to the Amended and Restated Certificate of Incorporation shall be effective on May 12, 2017, and the effective time shall be 12:01 a.m., Eastern Time.

4. This Amendment of the Corporation's Certificate has been duly authorized and adopted by the Corporation's Board of Directors and stockholders in accordance with the provisions of Section 242 of the Delaware General Corporation Law.

IN WITNESS WHEREOF, Capnia, Inc. has caused this Certificate of Amendment to be signed by Anish Bhatnagar, a duly authorized officer of the Corporation, on May 8, 2017.

CAPNIA, INC.

By: /s/ Anish Bhatnagar
Anish Bhatnagar,
Chief Executive Officer

EXHIBIT 5

Exhibit 5
Docket No.: SLNO-034/04US 333072-2375
PTE Application for U.S. Pat. No. 9,757,384
VYKAT™ XR
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Neil M. COWEN	Assignee:	Essentialis, Inc.
		Confirmation No.:	6992
Patent No.:	9,757,384	Unit:	Office of Patent Legal Administration
Issue Date:	September 12, 2017	Examiner:	Taylor V. OH
Application No.:	14/940,018		

For: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Commissioner of Patents and Trademarks
P.O. Box 1450
Mail Stop: Hatch-Waxman Patent Term Extension
Alexandria, VA 22313-1450

AUTHORIZATION TO RELY UPON MARKETING ACTIVITIES
IN REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Madam:

Pursuant to M.P.E.P § 2752 and 37 CFR 1.730, Soleno Therapeutics, Inc., a corporation organized and existing under the laws of the State of Delaware, having a place of business at 100 Marine Parkway, Suite 400, Redwood City, CA 94065, United States of America, hereby authorizes Essentialis, Inc. to rely upon the activities of Soleno Therapeutics, Inc. before the Food and Drug Administration during the regulatory review period for VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use, in its request for extension of patent term under 35 U.S.C. § 156 of United States Patent No. 9,757,384, which was granted September

318160431

12, 2017, and assigned to Essentialis, Inc. by virtue of assignment of U.S. Application No. 14/940,018 by the inventor, Neil M. COWEN on November 13, 2015 that was recorded with the Office on November 13, 2015 at reel/frame 037039/0755.

Essentialis, Inc. was the original sponsor of IND 73,179 and IND 132,498, which were later transferred to Soleno Therapeutics, Inc. Data generated under these INDs were included in NDA 216665. Sponsorship of IND 73,179 was transferred to Soleno Therapeutics, Inc. on July 12, 2017. Sponsorship of IND 132,498 was transferred to Capnia, Inc. on or about March 10, 2017, after which the name of the sponsor was changed to Soleno Therapeutics, Inc., and the FDA was notified of the change on May 22, 2017. Soleno Therapeutics, Inc. is the sponsor of NDA 216665, under which VYKAT™ XR was approved. Patent owner Essentialis, Inc. is a wholly owned subsidiary of Soleno Therapeutics, Inc.

Respectfully submitted,
Soleno Therapeutics, Inc.

Date: 04/28/2025

/ Anish Bhatnagar /
Anish Bhatnagar
CEO, Soleno Therapuetics, Inc.
Marketing Applicant

EXHIBIT 6

U.S. FOOD & DRUG ADMINISTRATION

NDA 216665

NDA ACKNOWLEDGMENT

Soleno Therapeutics, Inc.
Attention: Patricia C. Hirano
Senior Vice President, Regulatory Affairs
203 Redwood Shores Parkway
Suite 500
Redwood, CA 94065

Dear Patricia C. Hirano:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug: diazoxide choline

Date of Application: June 27, 2024

Date of Receipt: June 27, 2024

Our Reference Number: NDA 216665

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 26, 2024, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Cite the NDA reference number at the top of each page of any submission related to this marketing application.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Ex. 2002-1560

RESPONSIBILITIES UNDER TITLE VIII OF FDAAA AND 42 CFR PART 11

You are also responsible for complying with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) [42 U.S.C. § 282(j)], including its implementing regulations in 42 CFR part 11. Section 402(j) of the PHS Act was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Unless you have delegated your responsibilities to another entity, you are the "responsible party" and are required to submit registration and results information for each "applicable clinical trial" to the ClinicalTrials.gov data bank, as provided by section 402(j) of the PHS Act and 42 CFR part 11.

SUBMISSION REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[2]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[3]

SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

---

[2] http://www.fda.gov/ectd
[3] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

If you have any questions, contact me at Tiffanie.Taylor@fda.hhs.gov.

Sincerely,

(See appended electronic signature page)

Tiffanie Taylor, PharmD
Senior Regulatory Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANIE A TAYLOR
07/08/2024 02:34:18 PM

EXHIBIT 7

U.S. FOOD & DRUG ADMINISTRATION

NDA 216665

NDA APPROVAL

Soleno Therapeutics, Inc.
Attention: Patricia C. Hirano
Senior Vice President, Regulatory Affairs
100 Marine Parkway, Suite 400
Redwood, CA 94065

Dear Patricia C. Hirano:

Please refer to your new drug application (NDA) received June 27, 2024, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vykat XR (diazoxide choline) tablets.

We acknowledge receipt of your major amendments dated November 15, 2024, and November 19, 2024, which extended the goal date by three months.

This NDA provides for the use of Vykat XR (diazoxide choline) tablets for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Ex. 2002-1565

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216665**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Vykat XR (diazoxide choline) tablets shall be 24 months from the date of manufacture for 25 mg tablets and 36 months from the date of manufacture for 75 and 150 mg tablets when stored at 20°C and 25°C.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4793-1 Conduct a 6-month carcinogenicity study of diazoxide choline orally administered to transgenic mice, using an appropriate mouse model.

The timetable you submitted on February 11, 2025, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2025
Study Completion: 08/2026
Final Report Submission: 02/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of lower or higher drug exposure in patients with hepatic impairment, lower or higher drug exposure in patients with renal impairment, and a potential drug interaction with substrates of CYP1A2.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4793-2 Conduct a dedicated clinical study to assess the effect of hepatic impairment on the pharmacokinetics of diazoxide choline and its major metabolites.

The timetable you submitted on February 11, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Trial Completion: 12/2026
Final Report Submission: 06/2027

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Ex. 2002-1567

4793-3 Conduct a dedicated clinical study to assess the effect of renal impairment on the pharmacokinetics of diazoxide choline and its major metabolites.

The timetable you submitted on February 11, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Trial Completion: 12/2026
Final Report Submission: 06/2027

4793-4 Conduct a dedicated drug interaction study to assess the effect of diazoxide on a substrate of CYP1A2.

The timetable you submitted on February 11, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Trial Completion: 12/2026
Final Report Submission: 06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 132498 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Ex. 2002-1568

21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website.[8]

If you have any questions, contact Tiffanie Taylor, Senior Regulatory Project Manager, at 301-796-4395 or Tiffanie.Taylor@fda.hhs.gov.

Sincerely,

(See appended electronic signature page)

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[8] https://www.uspnf.com/

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYKAT XR safely and effectively. See full prescribing information for VYKAT XR.

VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use
Initial U.S. Approval: 1973

INDICATIONS AND USAGE

VYKAT XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS). (1)

DOSAGE AND ADMINISTRATION

- Prior to initiation, test fasting plasma glucose and HbA1c; optimize blood glucose in patients who have hyperglycemia. (2.1)
- Do not substitute with diazoxide oral suspension. (2.1)
- Administer orally once daily. (2.2)
- Recommended starting dosage and titration schedule is based on patient's body weight. (2.2)

Weight	Starting Dosage Weeks 1 and 2	Titration Dosage Weeks 3 and 4	Titration Dosage Weeks 5 and 6	Target Maintenance Dosage
20 to <30 kg	25 mg	50 mg	75 mg	100 mg
30 to <40 kg	75 mg	150 mg	150 mg	150 mg
40 to <65 kg	75 mg	150 mg	225 mg	225 mg
65 to <100 kg	150 mg	225 mg	300 mg	375 mg
100 to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

- The maximum recommended dosage is 5.8 mg/kg/day or 525 mg per day. (2.2)
- Interrupt VYKAT XR or reduce dosage for clinically significant elevations in fasting glucose or HbA1c; consider dosage reduction or interruption for clinically significant fluid overload. (2.3)
- See full prescribing information for VYKAT XR dosage modifications due to drug interactions (2.4)
- Following dosage interruption or a missed dose of 7 days or more, re-titrate according to Table 1 or Table 2. (2.5)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 25 mg, 75 mg, and 150 mg of diazoxide choline. (3)

CONTRAINDICATIONS

Known hypersensitivity to diazoxide, other components of VYKAT XR, or to thiazides. (4)

WARNINGS AND PRECAUTIONS

- *Hyperglycemia*: Hyperglycemia, including diabetic ketoacidosis, has been reported. During treatment, monitor fasting glucose and HbA1c. Monitor fasting glucose more frequently during first few weeks of treatment in patients with risk factors for hyperglycemia. (2.3, 5.1)
- *Risk of Fluid Overload*: Edema, including severe reactions associated with fluid overload, has been reported. Monitor for signs or symptoms of edema or fluid overload. (2.3, 5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10% and at least 2% greater than in placebo) are hypertrichosis, edema, hyperglycemia, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Soleno Therapeutics, Inc. at 1-833-765-3661 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Strong CYP1A2 Inhibitors*: Reduce VYKAT XR dosage. (2.4, 7)
- *CYP1A2 Substrates*: Concomitant use with VYKAT XR is not recommended. (7)
- See full prescribing information for additional clinically significant drug interactions. (7)

USE IN SPECIFIC POPULATIONS

- *Renal Impairment or Hepatic Impairment*: Use is not recommended. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Important Recommendations Prior to VYKAT XR Initiation
  2.2 Dosage and Administration Recommendations
  2.3 Monitoring and Dosage Modifications Due to Adverse Reactions
  2.4 Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors
  2.5 Recommendations Regarding Dosage Interruption, Missed Dose, or Discontinuation of Treatment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Hyperglycemia
  5.2 Risk of Fluid Overload
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.4 Pediatric Use
  8.5 Geriatric Use
  8.6 Renal Impairment
  8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYKAT XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to VYKAT XR Initiation

Laboratory Testing Prior to VYKAT XR Initiation

Prior to initiating treatment with VYKAT XR, test fasting plasma glucose (FPG) and HbA1c and optimize blood glucose in patients who have hyperglycemia *[see Warnings and Precautions (5.1)]*.

For fasting glucose and HbA1c monitoring recommendations during VYKAT XR treatment and for dosage modifications based on results, *see Dosage and Administration (2.3)*.

Important Information Regarding Substitution

Do not substitute VYKAT XR with diazoxide oral suspension because the pharmacokinetic profiles are different *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage and Administration Recommendations

Administer VYKAT XR orally with or without food once daily *[see Clinical Pharmacology (12.3)]*.

Swallow tablets whole. Do not split, crush, or chew the extended-release tablets because doing so may compromise the extended-release characteristics, efficacy, or safety of VYKAT XR.

The recommended oral dosage of VYKAT XR is based on body weight. The recommended starting dosage and titration schedule of VYKAT XR are shown in Table 1.

Table 1: Recommended Starting Dosage and Titration Regimen in Adults and Pediatric Patients 4 Years of Age and Older

Weight	Recommended Once Daily Dosage			
	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 kg to <30 kg	25 mg	50 mg	75 mg	100 mg
30 kg to <40 kg	75 mg	150 mg	150 mg	150 mg
40 kg to <65 kg	75 mg	150 mg	225 mg	225 mg
65 kg to <100 kg	150 mg	225 mg	300 mg	375 mg
100 kg to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

The maximum recommended dosage of VYKAT XR is 5.8 mg/kg/day or 525 mg per day. Dosages above 5.8 mg/kg/day or 525 mg per day have not been evaluated in patients with PWS.

2.3 Monitoring and Dosage Modifications Due to Adverse Reactions

Elevations in Fasting Glucose or HbA1c

After initiating treatment with VYKAT XR, monitor:

- Fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated.
- HbA1c every 3 months and as clinically indicated.

Monitor fasting glucose more frequently during the first few weeks of VYKAT XR treatment in patients with risk factors for hyperglycemia.

If clinically significant elevations in fasting glucose or HbA1c occur during treatment, temporarily interrupt VYKAT XR or reduce the dosage until glycemic parameters are appropriately managed. Consider initiation or adjustment of standard antidiabetic therapy(ies). If clinically significant glucose elevations are noted during titration, titrate over a longer duration and/or to a lower dosage *[see Warnings and Precautions (5.1)]*.

Fluid Overload

Monitor for signs or symptoms of edema or fluid overload. Consider dosage reduction or temporary dosage interruption in the event of clinically significant fluid overload. If clinically significant fluid overload is noted during titration, titrate over a longer duration and/or to a lower dosage *[see Warnings and Precautions (5.2)]*.

Titration After Resolution of Fluid Overload or Elevation in Fasting Glucose or HbA1c

If fluid overload or elevations in fasting glucose or HbA1c resolve after a dosage reduction:

- For patients weighing less than 30 kg, titrate the dosage in increments of no more than 25 mg every 2 weeks or titrate over longer duration to a maximum dosage of 5.8 mg/kg/day.
- For patients weighing greater than or equal to 30 kg, titrate the dosage in increments of no more than 75 mg every 2 weeks or titrate over longer duration to a maximum dosage of 5.8 mg/kg/day.

For recommendations on resuming VYKAT XR after dosage interruption, *see Dosage and Administration (2.5)*.

2.4 Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors

VYKAT XR dosage modifications for concomitant use with strong CYP1A2 inhibitors are shown in Table 2 *[see Drug Interactions (7)]*.

Ex. 2002-1573

Table 2: VYKAT XR Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors

Weight	VYKAT XR Recommended Once Daily Dosage			
	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 kg to <30 kg	25 mg	25 mg	50 mg	75 mg
30 kg to <40 kg	50 mg	100 mg	100 mg	100 mg
40 kg to <65 kg	50 mg	100 mg	150 mg	150 mg
65 kg to <100 kg	100 mg	150 mg	200 mg	250 mg
100 kg to <135 kg	100 mg	200 mg	250 mg	300 mg
≥135 kg	100 mg	200 mg	300 mg	325 mg

Based on clinical response, VYKAT XR may be titrated to a maximum recommended dosage of 3.6 mg/kg/day. The VYKAT XR daily dosage should not exceed 325 mg per day.

No dosage modification is recommended when VYKAT XR is concomitantly used with moderate CYP1A2 inhibitors.

2.5 Recommendations Regarding Dosage Interruption, Missed Dose, or Discontinuation of Treatment

Following a dosage interruption or missed dose of:

- Less than 7 days, resume VYKAT XR at the previous dosage
- 7 days or more, re-titrate VYKAT XR according to Table 1 or 2, as appropriate *[see Dosage and Administration (2.2, 2.4)]*

Treatment with VYKAT XR can be discontinued without tapering.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

- VYKAT XR 25 mg of diazoxide choline: white, capsule-shaped, film-coated, waxed tablets, debossed with S-25 on one side.
- VYKAT XR 75 mg of diazoxide choline: white, round, standard convex-shaped, film-coated, waxed tablets, debossed with S-75 on one side.
- VYKAT XR 150 mg of diazoxide choline: white, oval-shaped, film-coated, waxed tablets, debossed with S-150 on one side.

4 CONTRAINDICATIONS

VYKAT XR is contraindicated in patients with known hypersensitivity to diazoxide, other components of VYKAT XR, or to thiazides. Erythema multiforme has been reported with VYKAT XR *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperglycemia

VYKAT XR increases blood glucose, due primarily to an inhibition of insulin release from the pancreas. Hyperglycemia, including severe adverse reactions associated with diabetic ketoacidosis, occurred in VYKAT XR-treated patients during clinical trials *[see Adverse Reactions (6)]*.

Precipitating conditions for diabetic ketoacidosis may include reduction in the dosages of concomitant antihyperglycemic medications, increase in the dosages of concomitant growth hormone, intercurrent illness, surgery, volume depletion or alcohol abuse. Signs and symptoms of ketoacidosis include nausea, vomiting, abdominal pain, generalized malaise and shortness of breath.

Before initiating VYKAT XR, test fasting plasma glucose (FPG) and HbA1c; optimize blood glucose in patients who have hyperglycemia. After initiating treatment with VYKAT XR, regularly monitor fasting glucose (FPG or fasting blood glucose) and HbA1c *[see Dosage and Administration (2.3)]*. Monitor fasting glucose more frequently for the first few weeks of treatment with VYKAT XR in patients with risk factors for hyperglycemia, such as obesity, elevated FPG, HbA1c at the upper limit of normal or above, concomitant use of growth hormone, or concomitant use of systemic corticosteroids.

Advise patients of the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss). If a patient experiences hyperglycemia after initiating treatment with VYKAT XR, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. Consider monitoring ketones in patients with worsening hyperglycemia.

If hyperglycemia is treated with anti-hyperglycemic medication during VYKAT XR treatment, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare provider with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes. Based on the severity of the hyperglycemia, VYKAT XR may require dosage interruption, reduction, or discontinuation in order to avoid progression to ketoacidosis *[see Dosage and Administration (2.3)]*.

5.2 Risk of Fluid Overload

Edema, including general, localized, and peripheral edema, occurred in 27% of VYKAT XR-treated patients versus 12% of placebo-treated patients in the placebo-controlled trial with treatment-naïve subjects (Study 1). Severe adverse reactions associated with fluid overload, including pulmonary edema, were reported in VYKAT XR-treated patients during clinical trials *[see Adverse Reactions (6)]*.

The antidiuretic property of diazoxide may lead to significant fluid retention, which may precipitate congestive heart failure in patients with compromised cardiac reserve. VYKAT XR has not been studied in patients with compromised cardiac reserve and should be used with caution in these patients.

Monitor for signs or symptoms of edema or fluid overload and consider appropriate clinical management, which may include VYKAT XR dosage reduction or treatment interruption, if clinically significant *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hyperglycemia *[see Warnings and Precautions (5.1)]*
- Risk of Fluid Overload *[see Warnings and Precautions (5.2)]*

Adverse Reactions from Clinical Studies of VYKAT XR in Patients with PWS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the clinical study development program for treatment of hyperphagia in patients aged 4 years and older with PWS, a total of 125 patients received at least 1 dose of VYKAT XR. Patients received dosages of VYKAT XR up to 5.8 mg/kg/day (up to a maximum dosage of 525 mg/day) for up to 4.86 years (median: 3.0 years) in the following studies:

- Study 1: 13-week, randomized, double-blind, placebo-controlled, parallel-arm study in which 126 patients were randomized in a 2:1 ratio to VYKAT XR or placebo and received at least one dose of VYKAT XR.
- Study 2-OLE: A long-term, open-label, maintenance treatment period in 115 patients (mean duration 2.6 years; maximum duration 4.3 years) who had previously been enrolled in Study 1.
- Study 2-RWP: A 16-week, double-blind, placebo-controlled, randomized withdrawal treatment period, in which 77 patients who had completed Study 1 and Study 2-OLE were randomized in a 1:1 ratio to VYKAT XR or placebo *[see Clinical Trials (14)]*.
- Study 3: A long-term, open-label, maintenance study in 77 patients who had completed Study 1 and Study 2-OLE.

Adverse reactions leading to discontinuation in VYKAT XR-treated patients included aggression, diabetes mellitus, fluid retention, hirsutism, hyperglycemia, lower respiratory tract infection, peripheral edema, pulmonary edema, and papular rash.

The primary safety analyses are based on Study 1. The most common adverse reactions (10% or more and at least 2% greater than in placebo) in Study 1 were hypertrichosis, edema, hyperglycemia, and rash.

Table 3 presents adverse reactions that occurred in at least 5% of patients in Study 1 receiving VYKAT XR and 2% more frequently in VYKAT XR-treated patients than placebo.

Table 3: Adverse Reactions Occurring in ≥5% of Patients with PWS Receiving VYKAT XR and at Least 2% Greater than Placebo in Study 1

Adverse Reaction	VYKAT XR (N=84)	Placebo (N=42)
Hypertrichosis	36%	14%
Edema*	27%	12%
Hyperglycemia**	17%	5%
Rash***	12%	2%
Pyrexia	6%	0%
Arthralgia	5%	2%
Influenza	5%	2%
Nasopharyngitis	5%	2%

*Edema includes peripheral edema, periorbital edema, swelling face, pulmonary edema, and peripheral swelling.
**Hyperglycemia includes type 2 diabetes mellitus.
***Rash includes contact dermatitis, erythema multiforme, maculo-papular rash, papular rash, and urticaria.

In Study 2-RWP, the adverse reactions that occurred most frequently (at least 5%) and to a greater extent than placebo included:

Immune System Disorders: Seasonal allergy

Investigations: Increased weight

Nervous System Disorders: Hyperphagia, anxiety, affect lability, anger, compulsive hoarding, suicidal ideation

Respiratory Disorders: Streptococcal pharyngitis, upper respiratory infection

Skin and Subcutaneous Tissue Disorders: Hirsutism

Erythema multiforme was reported in one subject in Study 1. One subject in Study 3 experienced a serious adverse reaction of diabetic ketoacidosis.

Adverse Reactions from Clinical Trials or Postmarketing Experience of Diazoxide in An Unapproved Population

The following adverse reactions associated with use of diazoxide for an unapproved population have been identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity

Investigations: Increased serum uric acid, transient neutropenia, thrombocytopenia, decreased hemoglobin/hematocrit, eosinophilia

Respiratory Disorders: Pulmonary hypertension

Special Senses: Cataracts

Musculoskeletal and Connective Tissue Disorders: Abnormal facial features

7 DRUG INTERACTIONS

Table 4 displays clinically significant drug interactions with VYKAT XR.

Table 4: Clinically Significant Drug Interactions with VYKAT XR

Strong CYP1A2 Inhibitors[1]	
Prevention or Management	Reduce the dosage of VYKAT XR when concomitantly used with strong inhibitors of CYP1A2 *[see Dosage and Administration (2.4)]*.
Mechanism and Clinical Effect(s)	VYKAT XR is a CYP1A2 substrate. Concomitant use of VYKAT XR with strong CYP1A2 inhibitors increases exposure of diazoxide, which may increase the frequency and/or severity of adverse reactions from VYKAT XR *[see Clinical Pharmacology (12.3)]*.

CYP1A2 Substrates[1]	
Prevention or Management	Concomitant use of VYKAT XR with CYP1A2 substrates is not recommended.
Mechanism and Clinical Effect(s)	VYKAT XR is an inhibitor of CYP1A2. Concomitant use of VYKAT XR with CYP1A2 substrates increases exposure of these substrates. This may increase the frequency and/or severity of adverse reactions from such substrates.
Strong CYP3A4 Inhibitors[1]	
Prevention or Management	Monitor the frequency and severity of adverse reactions from VYKAT XR. A dosage reduction of VYKAT XR may be needed when used concomitantly with strong CYP3A4 inhibitors.
Mechanism and Clinical Effect(s)	Concomitant use of VYKAT XR with strong CYP3A4 inhibitors increases exposure of diazoxide, which may increase the frequency and/or severity of adverse reactions from VYKAT XR *[see Clinical Pharmacology (12.3)]*.
Dual Strong CYP3A4 / Moderate 1A2 Inducers[1]	
Prevention or Management	Concomitant use of VYKAT XR with dual strong CYP3A4/moderate CYP1A2 inducers is not recommended.
Mechanism and Clinical Effect(s)	VYKAT XR is a substrate of CYP3A4 and CYP1A2. Concomitant use of VYKAT XR with strong CYP3A4/moderate 1A2 inducers may decrease exposure of VYKAT XR. This may decrease the efficacy of VYKAT XR *[see Clinical Pharmacology (12.3)]*.
Drugs Highly Bound to Protein	
Prevention or Management	Monitor international normalized ratio (INR) in patients who use coumarin or its derivatives concomitantly with VYKAT XR. Dosage modification of coumarin or its derivatives may be needed when used concomitantly with VYKAT XR. Monitor diphenylhydantoin serum levels when VYKAT XR is used concomitantly with diphenylhydantoin. Dosage modification of diphenylhydantoin may be needed when used concomitantly with VYKAT XR.
Mechanism and Clinical Effect(s)	Diazoxide is highly bound to serum proteins. Diazoxide may displace other drugs which are also highly bound to protein resulting in higher or lower blood levels of the concomitantly used drugs. The impact of protein binding displacement is expected to be clinically important for drugs with narrow therapeutic range such as coumarin or its derivatives and diphenylhydantoin. Protein binding displacement may result in an increased risk of adverse reactions due to higher blood levels of coumarin or its derivative or loss of efficacy due to lower exposures of diphenylhydantoin.

Thiazide or Other Diuretics	
Prevention or Management	Monitor for signs and symptoms of hyperglycemia *[see Warnings and Precautions (5.1)]* and hyperuricemia when VYKAT XR is used concomitantly with thiazides or other diuretics. Dosage adjustment of VYKAT XR or diuretics may be needed when VYKAT XR is concomitantly used with diuretics.
Mechanism and Clinical Effect(s)	Both diazoxide and thiazides or other diuretics may produce hyperglycemia and hyperuricemia. The concomitant use of VYKAT XR with thiazides or other diuretics may potentiate the hyperglycemic and hyperuricemic effects of diazoxide *[see Adverse Reactions (6) and Clinical Pharmacology (12.2)]*.

[1]See www.fda.gov/CYPandTransporterInteractingDrugs for examples of strong CYP1A2 and CYP3A4 inhibitors, sensitive CYP1A2 substrates, and dual strong CYP3A4 / moderate 1A2 inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with diazoxide use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal outcomes.

Adverse reactions, including hyperglycemia, alopecia, and hypertrichosis lanuginosa, have been reported in neonates exposed to diazoxide in utero prior to delivery *(see Clinical Considerations)*.

In animal reproduction studies, oral gavage administration of diazoxide choline to pregnant rats during organogenesis at dose exposures equal to the human exposure of 525 mg resulted in no malformations. Maternal and fetal toxicities were observed at a dose approximately equal to the maximum recommended human dose (MRHD) of 525 mg based on AUC *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Diazoxide crosses the placenta and has been detected in cord blood. Based on adverse reactions reported in adults, in utero exposure of the infant prior to delivery may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions. Monitor infants who were exposed to diazoxide in utero for adverse reactions and treat accordingly.

Alopecia and hypertrichosis lanuginosa have occurred in a small number of infants whose mothers received oral diazoxide during the last 19 to 60 days of pregnancy. Abnormal hair growth was first noted at the age of one week and persisted when the infants were last seen at the ages of 5 months to one year. An infant born to a mother who was treated with oral diazoxide, 150 mg daily for 47 days prior to delivery, developed hyperglycemia which resolved after a 6-hour insulin infusion. Because there was an inappropriately low plasma insulin concentration for the degree of hyperglycemia, it was considered compatible with transplacental transfer of diazoxide causing inhibition of release of insulin from the neonatal pancreas.

Labor or Delivery

Intravenous administration of diazoxide during labor may cause cessation of uterine contractions, which may require administration of oxytocic agents to reinstate labor. However, this has not been reported with diazoxide when administered orally. Use caution in administering VYKAT XR during labor.

Data

Animal Data

Diazoxide choline was administered orally to pregnant rats during the period of organogenesis at doses of 40, 100, and 160 mg/kg/day (0.3, 0.6, and 1.2 times the MRHD of 525 mg based on AUC). No malformations were observed; however, decreased fetal body weights, delayed skeletal ossification, and increased fetal resorptions were observed at 160 mg/kg/day (a dose approximately equal to the MRHD based on AUC) which was a maternally toxic dose.

In a study in which rabbits were administered diazoxide intravenously, evidence of skeletal and cardiac teratogenic effects was noted at unknown multiples of the MRHD for diazoxide choline.

8.2 Lactation

Risk Summary

Diazoxide is present in human milk. There are no data on the effects of diazoxide on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYKAT XR and any potential adverse effects on the breastfed child from VYKAT XR or from the underlying maternal condition.

Clinical Considerations

Because of potential adverse reactions, including hyperglycemia, monitoring the infant's blood glucose may be advisable, especially during the neonatal period.

8.4 Pediatric Use

The safety and effectiveness of VYKAT XR have been established for the treatment of hyperphagia in pediatric patients 4 years of age and older with PWS. Use of VYKAT XR for this indication is supported by efficacy data from an adequate and well-controlled study that included pediatric patients with PWS *[see Clinical Studies (14)]* and safety data from additional studies that included pediatric patients with PWS *[see Adverse Reactions (6)]*, and the information on this use is described throughout the labeling.

The safety and effectiveness of VYKAT XR have not been established for the treatment of hyperphagia in pediatric patients with PWS less than 4 years of age.

Adverse Reactions in Pediatric Patients in an Unapproved Population

The following postmarketing adverse reactions have been reported with the use of other diazoxide products for the treatment of hyperinsulinemic hypoglycemia, an unapproved population *[see Adverse Reactions (6)]*:

- Pulmonary hypertension in pediatric patients less than 6 months of age, including neonates.
- Transient cataracts in association with hyperosmolar coma in a pediatric patient that subsided with correction of the hyperosmolarity.
- Development of abnormal facial features with chronic use in pediatric patients.

VYKAT XR is not approved and is not recommended for the treatment of hyperinsulinemic hypoglycemia.

Juvenile Animal Toxicity Data

Diazoxide choline was orally administered at doses of 29, 58, and 145 mg/kg/day to juvenile rats from weaning (postnatal day 21) through adulthood (postnatal day 91). Reduced body weight and body weight gains, correlated with decreased food consumption, occurred at doses ≥ 58 mg/kg/day. Delayed sexual maturation occurred in males at ≥ 58 mg/kg/day and in females at all doses. Decreased motor activity was observed in males at ≥ 58 mg/kg/day, but no effect was observed on learning and memory at any dose in both males and females. The no adverse effect level (NOAEL) was 29 mg/kg/day, which results in exposures less than the clinical exposure at the maximum recommended human dose (MRHD) of 525 mg based on AUC.

8.5 Geriatric Use

Clinical studies of VYKAT XR did not include any subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

8.6 Renal Impairment

VYKAT XR has not been studied in patients with renal impairment. VYKAT XR is not recommended in patients with renal impairment.

8.7 Hepatic Impairment

VYKAT XR has not been studied in patients with hepatic impairment. VYKAT XR is not recommended in patients with hepatic impairment.

10 OVERDOSAGE

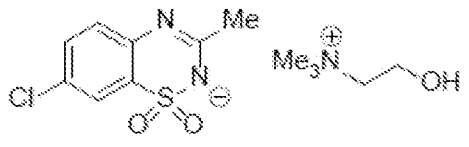
An overdosage of VYKAT XR may cause marked hyperglycemia, which may be associated with ketoacidosis *[see Warnings and Precautions (5.1)]*.

No specific antidotes for VYKAT XR are known. Monitor ketones in patients with severe hyperglycemia following overdose and consider insulin treatment if necessary. Treat severe hyperglycemia associated with ketoacidosis with prompt insulin administration and restoration of fluid and electrolyte balance. Because of VYKAT XR's long half-life (approximately 106 hours) in patients with PWS, the symptoms of overdosage (hyperglycemia, with or without ketoacidosis) require prolonged surveillance for periods up to three weeks or until blood sugar levels stabilize within the patient's normal range. Consider contacting a Poison Help line (1-800-222-1222) or a medical toxicologist for overdosage management recommendations for VYKAT XR.

11 DESCRIPTION

VYKAT XR contains diazoxide choline. Diazoxide choline is very slightly soluble to soluble in solvents dichloromethane, tetrahydrofuran, acetonitrile, and methanol and practically insoluble in solvents methyl *tert*-butyl ether. The pKa is 8.44 ± 0.01

Diazoxide choline is 7-Chloro-3-methyl-1λ6, 2,4-benzothiadiazin-2-ide 1,1-dioxide 2-hydroxyethyl(trimethyl)azanium. The empirical formula is $C_8H_6ClN_2O_2S \cdot C_5H_{14}NO$ and the molecular weight is 333.83 g/mole. The structural formula is:



VYKAT XR is for oral administration and is available as extended-release tablets in the following strengths: 25 mg tablet contains diazoxide choline 25 mg, equivalent to 17.2 mg diazoxide; 75 mg tablet contains diazoxide choline 75 mg, equivalent to 51.6 mg diazoxide; and 150 mg tablet contains diazoxide choline 150 mg, equivalent to 103.2 mg diazoxide.

Each tablet contains the following inactive ingredients: carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene oxide, silicified microcrystalline cellulose, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of diazoxide choline in the treatment of hyperphagia in patients 4 years of age and older with Prader-Willi syndrome (PWS) is unknown.

12.2 Pharmacodynamics

VYKAT XR resulted in a reduction in fasting plasma insulin from baseline through 1 year of treatment.

Diazoxide increases blood glucose, due primarily to an inhibition of insulin release from the pancreas.

Other pharmacodynamic effects of VYKAT XR include increased uric acid, renin secretion and IgG concentrations, and decreased cortisol secretion.

12.3 Pharmacokinetics

Absorption

Following oral administration, diazoxide choline is hydrolyzed to diazoxide prior to absorption. Peak diazoxide concentrations occur after 16 hours. VYKAT XR is expected to reach steady state after 7 days.

Effect of Food
Following administration of 150 mg diazoxide choline to healthy subjects, the C_{max} increased by 39% and AUC_{inf} was unchanged with a high-fat meal, compared to fasted conditions. The median T_{max} was 12 hours in the fasted state, and 8 hours in the fed state.

Distribution

The volume of distribution of diazoxide following oral administration is about 44.9 L. Diazoxide is extensively bound (91% to 93%) to plasma proteins (primarily human albumin), and crosses the blood-brain barrier.

Elimination

Metabolism

Diazoxide is mainly metabolized by CYP1A2 and to a minor extent by CYP3A4. Diazoxide is metabolized by oxidation or sulfate conjugation at the methyl group resulting in two inactive metabolites. Following long term administration in patients with PWS, only metabolite M1(3-hydroxymethyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide) is detectable in circulation.

Excretion

Diazoxide is excreted almost exclusively in urine as free or conjugated compound. In humans, following administration of radiolabeled diazoxide, 85 to 92% of the total dose was recovered in urine, with about 31% eliminated as unchanged drug. About 2% of the dose is eliminated in the feces. The terminal half-life following single-dose administration in healthy subjects was 28.7 to 32.4 hours. In patients with PWS, the estimated terminal half-life is 106 hours.

Specific Populations

Pediatric Patients

Approximately 72% of the patients with PWS were under 17 years of age at enrollment. There were no clinically relevant differences in pharmacokinetics in these participants compared to those observed in adult participants.

Male and Female Patients

No sex-related differences in pharmacokinetics have been observed in clinical trials of VYKAT XR in patients with PWS who have hyperphagia.

Patients with Renal or Hepatic Impairment

VYKAT XR has not been studied in patients with renal or hepatic impairment *[see Use in Specific Populations (8.6, 8.7)]*.

Drug Interaction Studies

Drugs That Inhibit CYP1A2

VYKAT XR is metabolized by CYP1A2 and coadministration with a strong CYP1A2 inhibitor may increase exposure of diazoxide and decrease concentrations of diazoxide metabolites. In a clinical study with fluvoxamine (a strong CYP1A2 inhibitor), coadministration with fluvoxamine at an inhibitory dose increased single dose diazoxide C_{max} by 17.5% and $AUC_{0\text{-}inf}$ by 60% compared to the same parameter measured on single dose in the absence of fluvoxamine co-administration *[see Drug Interactions (7)]*.

Strong CYP3A4 Inhibitor

Physiology-based pharmacokinetic model-based analysis suggests that concomitant use of VYKAT XR with itraconazole (a strong CYP3A4 inhibitor) may increase the AUC_{inf} of VYKAT XR by 1.1 to 2-fold, compared to VYKAT XR alone. Itraconazole did not appreciably affect the C_{max} of VYKAT XR *[see Drug Interactions (7)]*.

Strong CYP3A4 Inducers

Physiology-based pharmacokinetic model-based analysis suggests that concomitant use of VYKAT XR with rifampin (a strong CYP3A4 inducer and moderate CYP1A2 inducer) may decrease the C_{max} and AUC_{inf} of VYKAT XR by 14% to 30% and 40% to 70%, respectively, compared to VYKAT XR alone *[see Drug Interactions (7)]*.

Drugs that Alter Gastric pH

Use of VYKAT XR with gastric pH adjusting-drugs is not expected to affect the pharmacokinetics of diazoxide. Based on population pharmacokinetic modeling, use of VYKAT XR with gastric pH adjusting drugs did not significantly affect relative bioavailability or apparent clearance of diazoxide.

Protein Binding Displacement

VYKAT XR may also displace bilirubin bound to serum protein, thus resulting in higher blood levels of bilirubin.

In Vitro Studies

Enzyme systems: Diazoxide choline is an inhibitor of CYP1A2. It is not an inhibitor of CYP2B6, 2C19, 2C8, 2C9, 2D6 or 3A4. It does not an induce CYP1A2, CYP2B6 or CYP3A4 at the therapeutic dose range.

Transporter systems: Diazoxide choline is a substrate for OAT1, OAT3, and BCRP. It is an inhibitor of OAT1/3. It is not an inhibitor of P-gp, BCRP, MATE1/2-K, OATP1B1/3, OCT1/2 at the therapeutic dose range.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been performed with diazoxide choline.

Mutagenesis

Diazoxide choline was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and in the mouse lymphoma assay. Diazoxide choline was not clastogenic in the *in vivo* rat micronucleus assay.

Impairment of Fertility

Diazoxide choline was orally administered to male and female rats at doses of 58, 116, and 232 mg/kg/day (1, 2, and 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Females were treated two weeks prior to mating and continuing through conception and implantation and males were treated for four weeks prior to mating continuing for 35 days after mating. No effects on male or female fertility parameters were observed. Decreases in the mean number of corpora lutea, implantation sites, and live embryos occurred at 4 times the MRHD on a mg/m^2 basis.

13.2 Animal Toxicology and/or Pharmacology

Cataracts were observed in dogs given repeated daily oral doses of diazoxide of approximately 40 mg/kg/day for one month. The lenticular changes resembled those which occur experimentally in animals with increased blood glucose levels.

14 CLINICAL STUDIES

The efficacy of VYKAT XR for the treatment of hyperphagia in adults and pediatric patients ages 4 years and older with PWS was established in a 16-week, double-blind, placebo-controlled, randomized withdrawal study period (Study 2-RWP; NCT03714373) that followed an open-label study period of VYKAT XR. During Study 2-RWP, 77 patients with hyperphagia and PWS were randomized in a 1:1 ratio to continue their current oral dosage using a weight-based dosage regimen of VYKAT XR or placebo *[see Dosage and Administration (2.2)]*. Prior to participating in Study 2-RWP, patients received double-blind and/or open-label VYKAT XR for a mean duration of 3.3 years (range 2.5 to 4.5 years; Study 1 and Study 2-OLE). Results from Study 2-RWP are presented below.

Demographic and baseline disease characteristics were similar for the VYKAT XR and placebo groups. The mean age was 14.9 years of age (range 7 to 29 years of age). Most of the participants were White (86%), 7% were Black or African American, and 8% were of multiple races. The majority of participants were non-Hispanic (91%) and female (56%).

The primary efficacy endpoint was the Change from Baseline in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score at Week 16. The HQ-CT is a 9-item, observer-reported outcome measure that assesses a range of hyperphagic and food-related behaviors during the prior 2 weeks. An item score of 0 indicates an absence of behaviors, with a score of 4 indicating the most frequent or severe behaviors. The HQ-CT Total Score may range from 0 to 36, with higher scores indicating greater overall severity of hyperphagic and food-related behaviors.

At the end of the 16-week randomized withdrawal study period, there was statistically significant worsening of hyperphagia in the placebo group relative to the VYKAT XR group, as assessed by the HQ-CT Total Score (see Table 5).

Table 5: Study 2-RWP HQ-CT Total Score, Least Square Mean Change from Baseline to the End of the Randomized Withdrawal Period (Week 16) in Patients with Hyperphagia and PWS

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference* (95% CI)
VYKAT XR	38	9.0 (6.3)	2.6 (1.1)	-5.0 (-8.1, -1.8)
Placebo	39	8.1 (5.1)	7.6 (1.1)	

CI, confidence interval; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; LS Mean, least squares mean; RWP, randomized withdrawal period; SD, standard deviation; SE, standard error
* VYKAT XR - placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VYKAT XR is supplied as follows:

Strength	Description	Package Configuration	NDC Number
25 mg diazoxide choline	White, capsule-shaped tablets, debossed with "S-25" on one side	30-count bottles	83860-025-01
75 mg diazoxide choline	White, round, standard convex tablets, debossed with "S-75" on one side	30-count bottles	83860-075-01
150 mg diazoxide choline	White, oval-shaped tablets, debossed with "S-150" on one side.	30-count bottles	83860-150-01

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Keep in tightly closed container. Protect from humidity. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration Instructions

Advise patients to swallow tablets whole and not to split, crush, or chew VYKAT XR *[see Dosage and Administration (2.2)]*.

Hyperglycemia

Advise the patient or caregiver that VYKAT XR can cause hyperglycemia, sometimes leading to diabetic ketoacidosis, and that the patient will have monitoring of blood glucose before and during VYKAT XR treatment. Advise patients or caregivers on the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss) and ketoacidosis (e.g., nausea, vomiting, abdominal pain, generalized malaise and shortness of breath) and to contact their healthcare provider if these signs or symptoms occur *[see Warnings and Precautions (5.1)]*.

Risk of Fluid Overload

Advise the patient or caregiver that VYKAT XR may cause edema, including severe adverse reactions associated with fluid overload. Advise patients or caregivers on the signs and symptoms of edema and to contact their healthcare provider if signs or symptoms of edema occur *[see Warnings and Precautions (5.2)]*.

Manufactured for:
Soleno Therapeutics, Inc.
100 Marine Parkway, Suite 400
Redwood City, CA 94065
© 2025 Soleno Therapeutics, Inc. All rights reserved.

MEDICATION GUIDE
VYKAT™ XR (vye kat ex ar)
(diazoxide choline)
extended-release tablets, for oral use

What is the most important information I should know about VYKAT XR?

VYKAT XR may cause serious side effects, including:

- **High blood sugar levels (hyperglycemia).** Hyperglycemia is common during treatment with VYKAT XR and can also be severe. Hyperglycemia can lead to a condition called diabetic ketoacidosis (increased ketones in the blood) in some people who take VYKAT XR. Diabetic ketoacidosis is a serious condition that needs to be treated in a hospital and can be life-threatening.

  Your healthcare provider will:

  - check your blood sugar levels before you start VYKAT XR, at least 1 time every week for the first 2 weeks of treatment, then at least 1 time every 4 weeks and as needed during treatment.
  - check your blood sugar more often during the first few weeks of treatment if you have an increased chance of getting hyperglycemia.
  - check your HbA1c, which is another measurement of blood sugar control, before starting treatment, then 1 time every 3 months and as needed during treatment.

  If you get hyperglycemia during treatment with VYKAT XR, your healthcare provider may:

  - give you medicines to treat hyperglycemia or change your dose if you already take them
  - change your dose, temporarily stop, or permanently stop VYKAT XR

  Tell your healthcare provider if you get any of the following signs and symptoms:

  - **hyperglycemia**
    - feel very thirsty
    - need to urinate more often than usual
    - have higher amounts of urine than usual
    - feel more hungry than usual
    - weight loss
  - **diabetic ketoacidosis**
    - nausea
    - vomiting
    - stomach-area (abdominal) pain
    - feel weak or very tired
    - trouble breathing

- **Too much fluid in your body (fluid overload).** Swelling in the body (edema) from too much fluid is common during treatment with VYKAT XR and can also be severe. Your healthcare provider may decrease your dose or temporarily stop VYKAT XR if you get fluid overload. Tell your healthcare provider if you have trouble breathing or get any other signs or symptoms of fluid overload such as swelling of your legs, ankles, or feet, or unusual swelling anywhere in your body.

What is VYKAT XR?

VYKAT XR is a prescription medicine used to treat extreme hunger, constant thoughts about food, and constant urge to eat that cannot be satisfied with food (hyperphagia) in adults and children 4 years of age and older with Prader-Willi syndrome (PWS). It is not known if VYKAT XR is safe and effective in children under 4 years of age.

Who should not take VYKAT XR?

Do not take VYKAT XR if you are allergic to diazoxide, any ingredients in VYKAT XR, or medicines called thiazides. See the end of this Medication Guide for a complete list of ingredients in VYKAT XR.

Before taking VYKAT XR, tell your healthcare provider about all of your medical conditions, including if you:

- have diabetes or prediabetes
- are sick
- plan to have surgery
- drink alcohol very often
- are dehydrated or have lost a lot of body fluid
- have heart problems or a history of swelling in your legs or other parts of your body
- have liver or kidney problems
- are pregnant, or plan to become pregnant. VYKAT XR may harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with VYKAT XR.
- are breastfeeding or plan to breastfeed. VYKAT XR passes into your breast milk, and it is not known if it can harm your baby. Tell your healthcare provider if you plan to breastfeed during treatment with VYKAT XR.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking VYKAT XR with certain other medicines may affect the way VYKAT XR or the other medicine works and may increase your risk of side effects.

Do not change your dose or stop any medicines you take or start any new medicines without talking to your healthcare provider first during treatment with VYKAT XR. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Especially tell your healthcare provider if you take:

- medicines to lower blood sugar
- growth hormones
- corticosteroids
- diuretics (water pills)
- phenytoin
- warfarin

How should I take VYKAT XR?

- Take VYKAT XR exactly as your healthcare provider tells you to take it. Your healthcare provider will decide how much VYKAT XR you will take and may slowly increase your dose when you first start taking VYKAT XR.
- Take VYKAT XR by mouth 1 time per day with or without food.
- Swallow VYKAT XR tablets whole. **Do not** split, crush, or chew the tablets.
- You should not miss a dose of VYKAT XR. If you miss a dose of VYKAT XR, take the missed dose as soon as you remember. Do not take 2 doses of VYKAT XR at the same time to make up for a missed dose. If you missed a dose of VYKAT XR and did not remember to take another dose, call your healthcare provider to discuss what you should do next.
- **The dose of VYKAT XR is not the same as diazoxide oral suspension. Do not change** between VYKAT XR and diazoxide oral suspension products.

If you take too much VYKAT XR, call your healthcare provider or Poison Help Line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of VYKAT XR?

- **See "What is the most important information I should know about VYKAT XR?"**

The most common side effects of VYKAT XR also include:

- increased hair growth all over the body
- rash

These are not all of the possible side effects of VYKAT XR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VYKAT XR?

- Store VYKAT XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Close the bottle tightly after each dose.
- Keep VYKAT XR tablets dry (protect from humidity).
- The bottle contains a desiccant to help keep the tablets dry. Keep the desiccant in the VYKAT XR bottle.

Keep VYKAT XR and all medicines out of the reach of children.

General information about the safe and effective use of VYKAT XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VYKAT XR for a condition for which it was not prescribed. Do not give VYKAT XR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VYKAT XR that is written for health professionals.

What are the ingredients in VYKAT XR?

Active ingredient: diazoxide choline

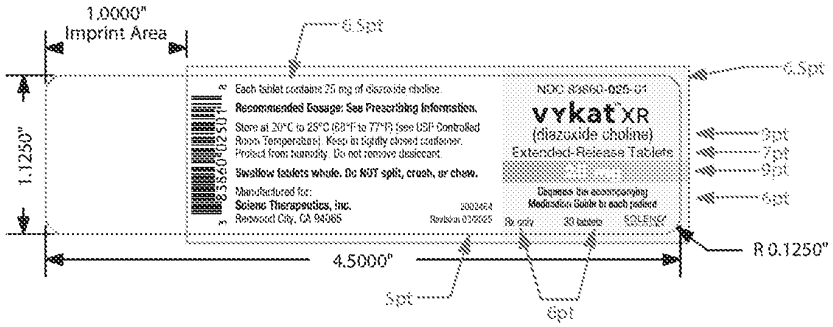
Inactive ingredients: carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose magnesium stearate, polyethylene oxide, silicified microcrystalline cellulose, talc, titanium dioxide, and triacetin.

Manufactured for: Soleno Therapeutics, Inc., 100 Marine Parkway, Suite 400, Redwood City, CA 94065

For more information, call 1-833-765-3661.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 3/2025

Flat Label



Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000806

Graphics Proof	Rev.#	Date	BC Grade	Artist
Customer: Catalent	12	01/30/25	C	LM
Product Name: 30ct 25 mg Diazoxide Choline ER Tablets (Soleno)	13	02/04/25	C	LM
Part #: 2002464	14	03/03/25	C	KH
Size (H x W): 1.1250" x 4.5000"				
Date: 03/03/25				
Rev: 14				

DRAFT

Reference ID: 5558674

Copy Position

#4

DIE LINE				
ENVR	SPOT VARNISH			

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE .....

DATE: .....

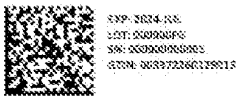
APPROVAL SIGNATURE .....

DATE: .....

THIS PROOF IS NOT TO EXCEED 100% COLOR. REPRODUCTION, DISCLOSURE, PHOTOCOPY AND TRANSMISSION OF GRAPHICS ARE ONLY

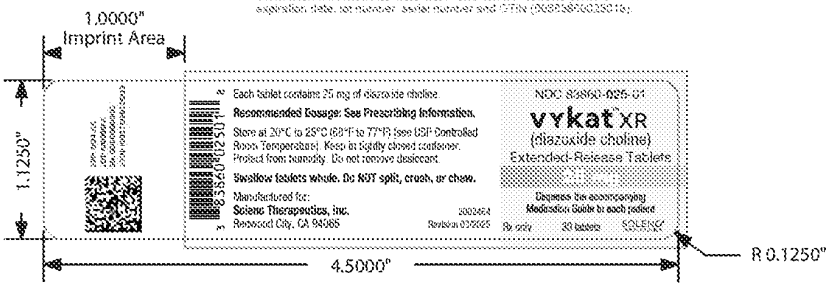
PLATINUM PRESS
4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

Flat Label



EXP: 2024-XX
LOT: XXXXXXXX
SN: XXXXXXXXXXXX
(17)YY(10)XXXXXXXX(21)XXXXXX

Note: For demonstration only. "Imprint Area" for GS1 symbology information will include 2D data matrix and human-readable product, expiration date, lot number, serial number and GTIN (01)08360250251011.



Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000806

Graphics Proof	Rev #	Date	BC Grade	Artist
Customer: Catalent	12	01/30/25	C	LM
Product Name: 30ct 25 mg Diazoxide Choline ER Tablets (Soleno)	13	02/04/25	C	LM
Part #: 2002464	14	03/03/25	C	KH
Size (H x W): 1.1250" x 4.5000"				
Date: 03/03/25				
Rev: 14				

ERASE

Copy Position

#4

DIE LINE				
ENVR	SPOT VARNISH			

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE .....

DATE: .....

APPROVAL SIGNATURE .....

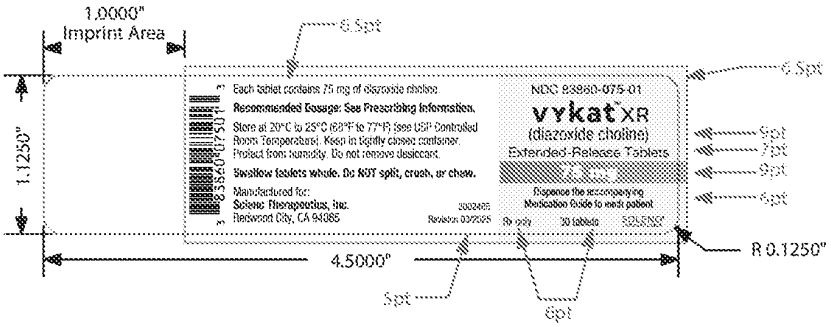
DATE: .....

THIS PROOF IS NOT TO EXCEED 100% COLOR. REPRODUCTION QUALITY MAY DIFFER FROM COPY AND IS DEPENDENT ON GRAPHICS AND COPY.

PLATINUM PRESS
4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

Reference ID: 5558674

Flat Label



Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000807

Graphics Proof	Rev #	Date	BC Grade	Artist
Customer: Catalent	1	04/23/24	A	KH
Product Name: 30ct 75 mg Diazoxide Choline ER Tablets (Soleno)	2	05/09/24	A	MG
	3	05/20/24	A	KH
Part #: 2002465	4	05/22/24	A	KH
	5	05/23/24	A	KH
Size (H x W): 1.1250" x 4.5000"	6	06/04/24	A	TA
	7	11/18/24	A	TA
Date: 02/04/25	8	12/02/24	A	MG
	9	12/03/24	A	SH
Rev: 11	10	01/30/25	C	LM
	11	02/04/25	C	LM

Copy Position

#4

DIE LINE				
ENVR	SPOT VARNISH			

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE .....

DATE: .....

APPROVAL SIGNATURE .....

DATE: .....

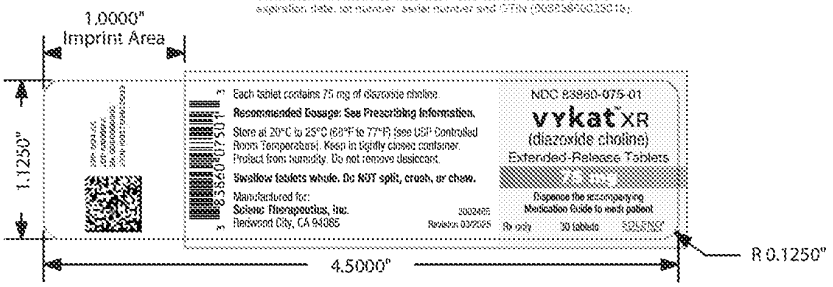
THIS PROOF IS NOT TO EXCEED 100% COLOR. REPRODUCTION, DISCLOSURE, PHYSICAL COPY AND ELECTRONIC COPY ARE STRICTLY PROHIBITED.

PLATINUM PRESS

4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

Reference ID: 5558674

Flat Label



Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000807

Graphics Proof	Rev.#	Date	BC Grade	Artist
Customer: Catalent	1	04/23/24	A	RH
Product Name: 30ct 75 mg Diazoxide Choline ER Tablets (Soleno)	2	05/09/24	A	BG
	3	05/20/24	A	RH
Part #: 2002465	4	05/22/24	A	RH
	5	05/23/24	A	RH
Size (H x W): 1.1250" x 4.5000"	6	06/04/24	A	TA
	7	11/18/24	A	TA
Date: 02/04/25	8	12/02/24	A	BG
	9	12/03/24	A	RH
Rev: 11	10	01/30/25	C	LM
	11	02/04/25	C	LM

Copy Position: #4

DIE LINE				
ENVR	SPOT VARNISH			

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE: .....

DATE: .....

APPROVAL SIGNATURE: .....

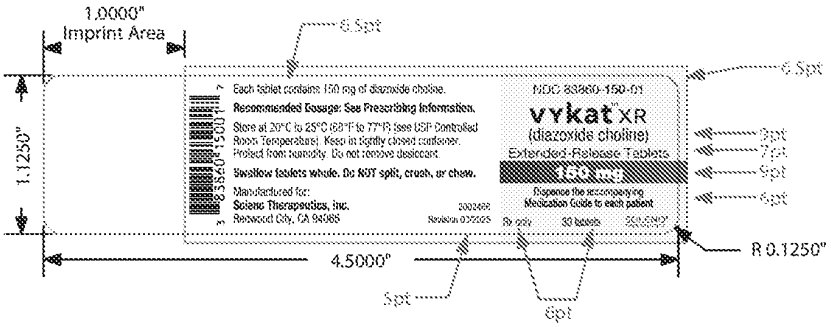
DATE: .....

THIS PROOF IS NOT TO EXCEED 100% COLOR. REPRODUCTION QUALITY MAY DIFFER FROM COPY AND IS DEPENDENT ON GRAPHICS AND COPY.

PLATINUM PRESS
4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

Reference ID: 5558674

Flat Label



Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000808

Graphics Proof	Rev.#	Date	BC Grade	Artist
Customer: Catalent	12	03/03/25	C	KH
Product Name: 30ct. 150 mg Diazoxide Choline ER Tablets (Soleno)				
Part #: 3002466				
Size (H x W): 1.1250" x 4.5000"				
Date: 03/03/25				
Rev: 12				

Copy Position: #4

DIE LINE

ENVR

SPOT VARNISH

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE

DATE:

APPROVAL SIGNATURE

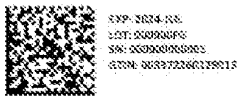
DATE:

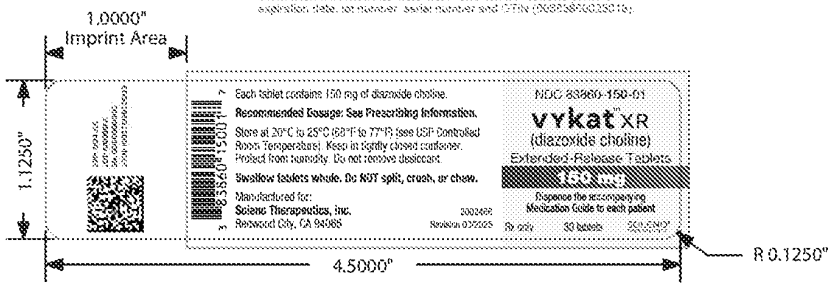
THIS PROOF IS NOT TO BE USED FOR COLOR REPRODUCTION. PLEASE REFER TO DIE COPY AND CONSULT WITH GRAPHICS AND ART.

PLATINUM PRESS
4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

Reference ID: 5558674

Flat Label





Note: Barcode scaled at 68% to fit,
this is under the recommended 80% size

L-000808

Graphics Proof	Rev #	Date	BC Grade	Artist
Customer: Catalent	12	03/03/25	C	KH
Product Name: 30ct. 150 mg Diazoxide Choline ER Tablets (Soleno)				
Part #: 2002466		DRAFT		
Size (H x W): 1.1250" x 4.5000"				
Date: 03/03/25				
Rev: 12				

Reference ID: 5558674

Copy Position

#4

DIE LINE				
ENVR	SPOT VARNISH			

Please indicate status below.
Please sign, date, and return if approved.

☐ REVISE and RE-PROOF ☐ APPROVED

APPROVAL SIGNATURE .....

DATE: .....

APPROVAL SIGNATURE .....

DATE: .....

THIS PROOF IS NOT TO EXCEED 100% COLOR. REPRODUCTION QUALITY IS DEPENDENT ON COPY AND PAPER CHOICE OF GRAPHICS AND TEXT.

PLATINUM PRESS
4251 Empire Road
Ft. Worth, TX 76155
Tel. 469.733.1586
Fax. 469.733.1510
www.platinumpress.com

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
03/26/2025 03:41:29 PM

EXHIBIT 8

Essentialis, Inc.
Changing the Course of Chronic Disease

12 July 2017

Jean-Marc Guettier, M.D
Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 73,179, Serial No. 0032
Diazoxide Choline
Notification of Change of Sponsor
Notification of Change of Sponsor's Authorized Representative

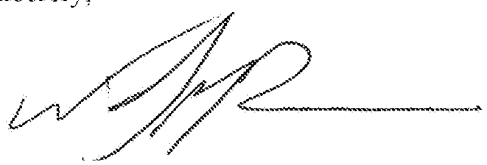
Dear Dr. Guettier,

We reference IND 73,179 for diazoxide choline formulated as diazoxide choline controlled release (DCCR) tablets, under development for the treatment of obesity.

Essentialis, Inc. (Essentialis), the original Sponsor of IND 73,179, has merged with Soleno Therapeutics and is now a wholly-owned subsidiary of Soleno Therapeutics. The purpose of this submission is to notify the Division of the new Sponsor's name, contact information, and authorized representative, as specified in Attachment 1. These changes are effective as of 12 July 2017.

If you have any questions or comments regarding this submission, please do not hesitate to contact me by telephone (760-444-0446) or by email (nmcowen@essentialistherapeutics.com).

Sincerely,



Neil M. Cowen, PhD, MBA
President and Chief Scientific Officer
Essentialis, Inc.

Enclosures

Phone 1-760-444-0446
7915 Corte Cardo
Carlsbad, CA 92009

Attachment 1:

Change in Sponsor's Name, Contact Information, and Authorized Representative

	Current through 12 March 2017	**Effective beginning 12 July 2017**
Sponsor Name	Essentialis, Inc.	Soleno Therapeutics, Inc.
Sponsor Address	7915 Corte Cardo Carlsbad, CA 92009 USA	1235 Radio Road, Suite 110 Redwood City, CA 94065 USA
Sponsor Telephone Number	760-444-0446	650-213-8444
Sponsor's Authorized Representative	Neil M. Cowen, PhD, MBA Essentialis, Inc. 7915 Corte Cardo Carlsbad, CA 92009 USA Tel: 760-444-0446 Fax: 760-634-5450 Email: nmcowen@essentialistherapeutics.com	Patricia C. Hirano, MPH Soleno Therapeutics, Inc. 1235 Radio Road, Suite 110 Redwood City, CA 94065 USA Tel: 650-353-5432 Email: phirano@soleno.life

EXHIBIT 9

Essentialis, Inc.
Changing the Course of Chronic Disease

10 March 2017

Jean-Marc Guettier, M.D
Director
Division of Metabolism and Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 132, 498, Serial No. 0002
Diazoxide Choline
Notification of Change of Sponsor
Notification of Change of Sponsor's Authorized Representative

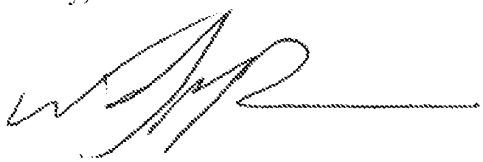
Dear Dr. Guettier,

We reference IND 132,498 for diazoxide choline formulated as diazoxide choline controlled release (DCCR) tablets, under development for the treatment of Prader-Willi Syndrome (PWS).

Essentialis, Inc. (Essentialis), the original Sponsor of IND 132,498, has merged with Capnia, Inc. (Capnia) and is now a wholly-owned subsidiary of Capnia. The purpose of this submission is to notify the Division of the new Sponsor's name, contact information, and authorized representative, as specified in Attachment 1. These changes are effective as of 13 March 2017.

If you have any questions or comments regarding this submission, please do not hesitate to contact me by telephone (760-444-0446) or by email (nmcowen@essentialistherapeutics.com).

Sincerely,



Neil M. Cowen, PhD, MBA
President and Chief Scientific Officer
Essentialis, Inc.

Enclosures

Phone 1-760-444-0446
7915 Corte Cardo
Carlsbad, CA 92009

Attachment 1:

Change in Sponsor's Name, Contact Information, and Authorized Representative

	Current through 12 March 2017	**Effective beginning 13 March 2017**
Sponsor Name	Essentialis, Inc.	Capnia, Inc.
Sponsor Address	7915 Corte Cardo Carlsbad, CA 92009 USA	1235 Radio Road, Suite 110 Redwood City, CA 94065 USA
Sponsor Telephone Number	760-444-0446	650-213-8444
Sponsor's Authorized Representative	Neil M. Cowen, PhD, MBA Essentialis, Inc. 7915 Corte Cardo Carlsbad, CA 92009 USA Tel: 760-444-0446 Fax: 760-634-5450 Email: nmcowen@essentialistherapeutics.com	Patricia C. Hirano, MPH Capnia, Inc. 1235 Radio Road, Suite 110 Redwood City, CA 94065 USA Tel: 650-353-5432 Email: phirano@capnia.com

EXHIBIT 10

Soleno Inc.
1235 Radio Road, Suite 110
Redwood City, CA 94065
650-213-8444 Main
650-213-8383 Fax

22 May 2017

Mitchell Mathis, M.D.
Director
Division of Psychiatry Products (DPP)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 132,498, Serial No. 0008
Diazoxide Choline
Administrative Change / Company Name

Dear Dr. Mathis,

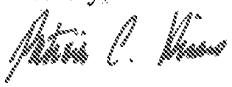
We reference IND 132,498 for diazoxide choline formulated as diazoxide choline controlled release (DCCR) tablets, under development for the treatment of Prader-Willi syndrome (PWS).

We wish to inform the Division of a corporate name change. Effective immediately, Capnia, Inc. has changed its name to Soleno Therapeutics, Inc. This change is also reflected in a change in email address. The remainder of the company information (i.e., address, telephone, and fax numbers), remain the same, and I will remain the Sponsor's authorized representative. For completeness, my full contact information is:

Patricia C. Hirano, MPH
Regulatory Affairs
Soleno Therapeutics, Inc.
1235 Radio Road, Suite 110
Redwood City, CA 94065
Main: 650-213-8444
Direct: 650-353-5432
Fax: 866-659-8949
Email: phirano@soleno.life

If you have any questions or comments regarding this submission, please do not hesitate to contact me by telephone at 650 353 5432 or by email at phirano@soleno.life.

Sincerely,



Patricia C. Hirano, MPH
Regulatory Affairs

Enclosures

EXHIBIT 11

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYKAT XR safely and effectively. See full prescribing information for VYKAT XR.

VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use
Initial U.S. Approval: 1973

INDICATIONS AND USAGE

VYKAT XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS). (1)

DOSAGE AND ADMINISTRATION

- Prior to initiation, test fasting plasma glucose and HbA1c; optimize blood glucose in patients who have hyperglycemia. (2.1)
- Do not substitute with diazoxide oral suspension. (2.1)
- Administer orally once daily. (2.2)
- Recommended starting dosage and titration schedule is based on patient's body weight. (2.2)

Weight	Starting Dosage Weeks 1 and 2	Titration Dosage Weeks 3 and 4	Titration Dosage Weeks 5 and 6	Target Maintenance Dosage
20 to <30 kg	25 mg	50 mg	75 mg	100 mg
30 to <40 kg	75 mg	150 mg	150 mg	150 mg
40 to <65 kg	75 mg	150 mg	225 mg	225 mg
65 to <100 kg	150 mg	225 mg	300 mg	375 mg
100 to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

- The maximum recommended dosage is 5.8 mg/kg/day or 525 mg per day. (2.2)
- Interrupt VYKAT XR or reduce dosage for clinically significant elevations in fasting glucose or HbA1c; consider dosage reduction or interruption for clinically significant fluid overload. (2.3)
- See full prescribing information for VYKAT XR dosage modifications due to drug interactions (2.4)
- Following dosage interruption or a missed dose of 7 days or more, re-titrate according to Table 1 or Table 2. (2.5)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 25 mg, 75 mg, and 150 mg of diazoxide choline. (3)

CONTRAINDICATIONS

Known hypersensitivity to diazoxide, other components of VYKAT XR, or to thiazides. (4)

WARNINGS AND PRECAUTIONS

- *Hyperglycemia*: Hyperglycemia, including diabetic ketoacidosis, has been reported. During treatment, monitor fasting glucose and HbA1c. Monitor fasting glucose more frequently during first few weeks of treatment in patients with risk factors for hyperglycemia. (2.3, 5.1)
- *Risk of Fluid Overload*: Edema, including severe reactions associated with fluid overload, has been reported. Monitor for signs or symptoms of edema or fluid overload. (2.3, 5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10% and at least 2% greater than in placebo) are hypertrichosis, edema, hyperglycemia, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Soleno Therapeutics, Inc. at 1-833-765-3661 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Strong CYP1A2 Inhibitors*: Reduce VYKAT XR dosage. (2.4, 7)
- *CYP1A2 Substrates*: Concomitant use with VYKAT XR is not recommended. (7)
- See full prescribing information for additional clinically significant drug interactions. (7)

USE IN SPECIFIC POPULATIONS

- *Renal Impairment or Hepatic Impairment*: Use is not recommended. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Recommendations Prior to VYKAT XR Initiation
2.2 Dosage and Administration Recommendations
2.3 Monitoring and Dosage Modifications Due to Adverse Reactions
2.4 Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors
2.5 Recommendations Regarding Dosage Interruption, Missed Dose, or Discontinuation of Treatment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hyperglycemia
5.2 Risk of Fluid Overload
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYKAT XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to VYKAT XR Initiation

Laboratory Testing Prior to VYKAT XR Initiation

Prior to initiating treatment with VYKAT XR, test fasting plasma glucose (FPG) and HbA1c and optimize blood glucose in patients who have hyperglycemia *[see Warnings and Precautions (5.1)]*.

For fasting glucose and HbA1c monitoring recommendations during VYKAT XR treatment and for dosage modifications based on results, *see Dosage and Administration (2.3)*.

Important Information Regarding Substitution

Do not substitute VYKAT XR with diazoxide oral suspension because the pharmacokinetic profiles are different *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage and Administration Recommendations

Administer VYKAT XR orally with or without food once daily *[see Clinical Pharmacology (12.3)]*.

Swallow tablets whole. Do not split, crush, or chew the extended-release tablets because doing so may compromise the extended-release characteristics, efficacy, or safety of VYKAT XR.

The recommended oral dosage of VYKAT XR is based on body weight. The recommended starting dosage and titration schedule of VYKAT XR are shown in Table 1.

Table 1: Recommended Starting Dosage and Titration Regimen in Adults and Pediatric Patients 4 Years of Age and Older

Weight	Recommended Once Daily Dosage			
	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 kg to <30 kg	25 mg	50 mg	75 mg	100 mg
30 kg to <40 kg	75 mg	150 mg	150 mg	150 mg
40 kg to <65 kg	75 mg	150 mg	225 mg	225 mg
65 kg to <100 kg	150 mg	225 mg	300 mg	375 mg
100 kg to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

The maximum recommended dosage of VYKAT XR is 5.8 mg/kg/day or 525 mg per day. Dosages above 5.8 mg/kg/day or 525 mg per day have not been evaluated in patients with PWS.

2.3 Monitoring and Dosage Modifications Due to Adverse Reactions

Elevations in Fasting Glucose or HbA1c

After initiating treatment with VYKAT XR, monitor:

- Fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated.
- HbA1c every 3 months and as clinically indicated.

Monitor fasting glucose more frequently during the first few weeks of VYKAT XR treatment in patients with risk factors for hyperglycemia.

If clinically significant elevations in fasting glucose or HbA1c occur during treatment, temporarily interrupt VYKAT XR or reduce the dosage until glycemic parameters are appropriately managed. Consider initiation or adjustment of standard antidiabetic therapy(ies). If clinically significant glucose elevations are noted during titration, titrate over a longer duration and/or to a lower dosage *[see Warnings and Precautions (5.1)]*.

Fluid Overload

Monitor for signs or symptoms of edema or fluid overload. Consider dosage reduction or temporary dosage interruption in the event of clinically significant fluid overload. If clinically significant fluid overload is noted during titration, titrate over a longer duration and/or to a lower dosage *[see Warnings and Precautions (5.2)]*.

Titration After Resolution of Fluid Overload or Elevation in Fasting Glucose or HbA1c

If fluid overload or elevations in fasting glucose or HbA1c resolve after a dosage reduction:

- For patients weighing less than 30 kg, titrate the dosage in increments of no more than 25 mg every 2 weeks or titrate over longer duration to a maximum dosage of 5.8 mg/kg/day.
- For patients weighing greater than or equal to 30 kg, titrate the dosage in increments of no more than 75 mg every 2 weeks or titrate over longer duration to a maximum dosage of 5.8 mg/kg/day.

For recommendations on resuming VYKAT XR after dosage interruption, *see Dosage and Administration (2.5)*.

2.4 Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors

VYKAT XR dosage modifications for concomitant use with strong CYP1A2 inhibitors are shown in Table 2 *[see Drug Interactions (7)]*.

Table 2: VYKAT XR Dosage Modifications for Concomitant Use with Strong CYP1A2 Inhibitors

Weight	VYKAT XR Recommended Once Daily Dosage			
	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 kg to <30 kg	25 mg	25 mg	50 mg	75 mg
30 kg to <40 kg	50 mg	100 mg	100 mg	100 mg
40 kg to <65 kg	50 mg	100 mg	150 mg	150 mg
65 kg to <100 kg	100 mg	150 mg	200 mg	250 mg
100 kg to <135 kg	100 mg	200 mg	250 mg	300 mg
≥135 kg	100 mg	200 mg	300 mg	325 mg

Based on clinical response, VYKAT XR may be titrated to a maximum recommended dosage of 3.6 mg/kg/day. The VYKAT XR daily dosage should not exceed 325 mg per day.

No dosage modification is recommended when VYKAT XR is concomitantly used with moderate CYP1A2 inhibitors.

2.5 Recommendations Regarding Dosage Interruption, Missed Dose, or Discontinuation of Treatment

Following a dosage interruption or missed dose of:

- Less than 7 days, resume VYKAT XR at the previous dosage
- 7 days or more, re-titrate VYKAT XR according to Table 1 or 2, as appropriate *[see Dosage and Administration (2.2, 2.4)]*

Treatment with VYKAT XR can be discontinued without tapering.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

- VYKAT XR 25 mg of diazoxide choline: white, capsule-shaped, film-coated, waxed tablets, debossed with S-25 on one side.
- VYKAT XR 75 mg of diazoxide choline: white, round, standard convex-shaped, film-coated, waxed tablets, debossed with S-75 on one side.
- VYKAT XR 150 mg of diazoxide choline: white, oval-shaped, film-coated, waxed tablets, debossed with S-150 on one side.

4 CONTRAINDICATIONS

VYKAT XR is contraindicated in patients with known hypersensitivity to diazoxide, other components of VYKAT XR, or to thiazides. Erythema multiforme has been reported with VYKAT XR *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperglycemia

VYKAT XR increases blood glucose, due primarily to an inhibition of insulin release from the pancreas. Hyperglycemia, including severe adverse reactions associated with diabetic ketoacidosis, occurred in VYKAT XR-treated patients during clinical trials *[see Adverse Reactions (6)]*.

Precipitating conditions for diabetic ketoacidosis may include reduction in the dosages of concomitant antihyperglycemic medications, increase in the dosages of concomitant growth hormone, intercurrent illness, surgery, volume depletion or alcohol abuse. Signs and symptoms of ketoacidosis include nausea, vomiting, abdominal pain, generalized malaise and shortness of breath.

Before initiating VYKAT XR, test fasting plasma glucose (FPG) and HbA1c; optimize blood glucose in patients who have hyperglycemia. After initiating treatment with VYKAT XR, regularly monitor fasting glucose (FPG or fasting blood glucose) and HbA1c *[see Dosage and Administration (2.3)]*. Monitor fasting glucose more frequently for the first few weeks of treatment with VYKAT XR in patients with risk factors for hyperglycemia, such as obesity, elevated FPG, HbA1c at the upper limit of normal or above, concomitant use of growth hormone, or concomitant use of systemic corticosteroids.

Advise patients of the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss). If a patient experiences hyperglycemia after initiating treatment with VYKAT XR, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. Consider monitoring ketones in patients with worsening hyperglycemia.

If hyperglycemia is treated with anti-hyperglycemic medication during VYKAT XR treatment, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare provider with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes. Based on the severity of the hyperglycemia, VYKAT XR may require dosage interruption, reduction, or discontinuation in order to avoid progression to ketoacidosis *[see Dosage and Administration (2.3)]*.

5.2 Risk of Fluid Overload

Edema, including general, localized, and peripheral edema, occurred in 27% of VYKAT XR-treated patients versus 12% of placebo-treated patients in the placebo-controlled trial with treatment-naïve subjects (Study 1). Severe adverse reactions associated with fluid overload, including pulmonary edema, were reported in VYKAT XR-treated patients during clinical trials *[see Adverse Reactions (6)]*.

The antidiuretic property of diazoxide may lead to significant fluid retention, which may precipitate congestive heart failure in patients with compromised cardiac reserve. VYKAT XR has not been studied in patients with compromised cardiac reserve and should be used with caution in these patients.

Monitor for signs or symptoms of edema or fluid overload and consider appropriate clinical management, which may include VYKAT XR dosage reduction or treatment interruption, if clinically significant *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hyperglycemia *[see Warnings and Precautions (5.1)]*
- Risk of Fluid Overload *[see Warnings and Precautions (5.2)]*

Adverse Reactions from Clinical Studies of VYKAT XR in Patients with PWS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the clinical study development program for treatment of hyperphagia in patients aged 4 years and older with PWS, a total of 125 patients received at least 1 dose of VYKAT XR. Patients received dosages of VYKAT XR up to 5.8 mg/kg/day (up to a maximum dosage of 525 mg/day) for up to 4.86 years (median: 3.0 years) in the following studies:

- Study 1: 13-week, randomized, double-blind, placebo-controlled, parallel-arm study in which 126 patients were randomized in a 2:1 ratio to VYKAT XR or placebo and received at least one dose of VYKAT XR.
- Study 2-OLE: A long-term, open-label, maintenance treatment period in 115 patients (mean duration 2.6 years; maximum duration 4.3 years) who had previously been enrolled in Study 1.
- Study 2-RWP: A 16-week, double-blind, placebo-controlled, randomized withdrawal treatment period, in which 77 patients who had completed Study 1 and Study 2-OLE were randomized in a 1:1 ratio to VYKAT XR or placebo *[see Clinical Trials (14)]*.
- Study 3: A long-term, open-label, maintenance study in 77 patients who had completed Study 1 and Study 2-OLE.

Adverse reactions leading to discontinuation in VYKAT XR-treated patients included aggression, diabetes mellitus, fluid retention, hirsutism, hyperglycemia, lower respiratory tract infection, peripheral edema, pulmonary edema, and papular rash.

The primary safety analyses are based on Study 1. The most common adverse reactions (10% or more and at least 2% greater than in placebo) in Study 1 were hypertrichosis, edema, hyperglycemia, and rash.

Table 3 presents adverse reactions that occurred in at least 5% of patients in Study 1 receiving VYKAT XR and 2% more frequently in VYKAT XR-treated patients than placebo.

Table 3: Adverse Reactions Occurring in ≥5% of Patients with PWS Receiving VYKAT XR and at Least 2% Greater than Placebo in Study 1

Adverse Reaction	VYKAT XR (N=84)	Placebo (N=42)
Hypertrichosis	36%	14%
Edema*	27%	12%
Hyperglycemia**	17%	5%
Rash***	12%	2%
Pyrexia	6%	0%
Arthralgia	5%	2%
Influenza	5%	2%
Nasopharyngitis	5%	2%

*Edema includes peripheral edema, periorbital edema, swelling face, pulmonary edema, and peripheral swelling.
**Hyperglycemia includes type 2 diabetes mellitus.
***Rash includes contact dermatitis, erythema multiforme, maculo-papular rash, papular rash, and urticaria.

In Study 2-RWP, the adverse reactions that occurred most frequently (at least 5%) and to a greater extent than placebo included:

Immune System Disorders: Seasonal allergy

Investigations: Increased weight

Nervous System Disorders: Hyperphagia, anxiety, affect lability, anger, compulsive hoarding, suicidal ideation

Respiratory Disorders: Streptococcal pharyngitis, upper respiratory infection

Skin and Subcutaneous Tissue Disorders: Hirsutism

Erythema multiforme was reported in one subject in Study 1. One subject in Study 3 experienced a serious adverse reaction of diabetic ketoacidosis.

Adverse Reactions from Clinical Trials or Postmarketing Experience of Diazoxide in An Unapproved Population

The following adverse reactions associated with use of diazoxide for an unapproved population have been identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity

Investigations: Increased serum uric acid, transient neutropenia, thrombocytopenia, decreased hemoglobin/hematocrit, eosinophilia

Respiratory Disorders: Pulmonary hypertension

Special Senses: Cataracts

Musculoskeletal and Connective Tissue Disorders: Abnormal facial features

7 DRUG INTERACTIONS

Table 4 displays clinically significant drug interactions with VYKAT XR.

Table 4: Clinically Significant Drug Interactions with VYKAT XR

Strong CYP1A2 Inhibitors[1]	
Prevention or Management	Reduce the dosage of VYKAT XR when concomitantly used with strong inhibitors of CYP1A2 *[see Dosage and Administration (2.4)]*.
Mechanism and Clinical Effect(s)	VYKAT XR is a CYP1A2 substrate. Concomitant use of VYKAT XR with strong CYP1A2 inhibitors increases exposure of diazoxide, which may increase the frequency and/or severity of adverse reactions from VYKAT XR *[see Clinical Pharmacology (12.3)]*.

CYP1A2 Substrates[1]	
Prevention or Management	Concomitant use of VYKAT XR with CYP1A2 substrates is not recommended.
Mechanism and Clinical Effect(s)	VYKAT XR is an inhibitor of CYP1A2. Concomitant use of VYKAT XR with CYP1A2 substrates increases exposure of these substrates. This may increase the frequency and/or severity of adverse reactions from such substrates.
Strong CYP3A4 Inhibitors[1]	
Prevention or Management	Monitor the frequency and severity of adverse reactions from VYKAT XR. A dosage reduction of VYKAT XR may be needed when used concomitantly with strong CYP3A4 inhibitors.
Mechanism and Clinical Effect(s)	Concomitant use of VYKAT XR with strong CYP3A4 inhibitors increases exposure of diazoxide, which may increase the frequency and/or severity of adverse reactions from VYKAT XR *[see Clinical Pharmacology (12.3)]*.
Dual Strong CYP3A4 / Moderate 1A2 Inducers[1]	
Prevention or Management	Concomitant use of VYKAT XR with dual strong CYP3A4/moderate CYP1A2 inducers is not recommended.
Mechanism and Clinical Effect(s)	VYKAT XR is a substrate of CYP3A4 and CYP1A2. Concomitant use of VYKAT XR with strong CYP3A4/moderate 1A2 inducers may decrease exposure of VYKAT XR. This may decrease the efficacy of VYKAT XR *[see Clinical Pharmacology (12.3)]*.
Drugs Highly Bound to Protein	
Prevention or Management	Monitor international normalized ratio (INR) in patients who use coumarin or its derivatives concomitantly with VYKAT XR. Dosage modification of coumarin or its derivatives may be needed when used concomitantly with VYKAT XR. Monitor diphenylhydantoin serum levels when VYKAT XR is used concomitantly with diphenylhydantoin. Dosage modification of diphenylhydantoin may be needed when used concomitantly with VYKAT XR.
Mechanism and Clinical Effect(s)	Diazoxide is highly bound to serum proteins. Diazoxide may displace other drugs which are also highly bound to protein resulting in higher or lower blood levels of the concomitantly used drugs. The impact of protein binding displacement is expected to be clinically important for drugs with narrow therapeutic range such as coumarin or its derivatives and diphenylhydantoin. Protein binding displacement may result in an increased risk of adverse reactions due to higher blood levels of coumarin or its derivative or loss of efficacy due to lower exposures of diphenylhydantoin.

Thiazide or Other Diuretics	
Prevention or Management	Monitor for signs and symptoms of hyperglycemia *[see Warnings and Precautions (5.1)]* and hyperuricemia when VYKAT XR is used concomitantly with thiazides or other diuretics. Dosage adjustment of VYKAT XR or diuretics may be needed when VYKAT XR is concomitantly used with diuretics.
Mechanism and Clinical Effect(s)	Both diazoxide and thiazides or other diuretics may produce hyperglycemia and hyperuricemia. The concomitant use of VYKAT XR with thiazides or other diuretics may potentiate the hyperglycemic and hyperuricemic effects of diazoxide *[see Adverse Reactions (6) and Clinical Pharmacology (12.2)]*.

[1]See www.fda.gov/CYPandTransporterInteractingDrugs for examples of strong CYP1A2 and CYP3A4 inhibitors, sensitive CYP1A2 substrates, and dual strong CYP3A4 / moderate 1A2 inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with diazoxide use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal outcomes.

Adverse reactions, including hyperglycemia, alopecia, and hypertrichosis lanuginosa, have been reported in neonates exposed to diazoxide in utero prior to delivery *(see Clinical Considerations).*

In animal reproduction studies, oral gavage administration of diazoxide choline to pregnant rats during organogenesis at dose exposures equal to the human exposure of 525 mg resulted in no malformations. Maternal and fetal toxicities were observed at a dose approximately equal to the maximum recommended human dose (MRHD) of 525 mg based on AUC *(see Data).*

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Diazoxide crosses the placenta and has been detected in cord blood. Based on adverse reactions reported in adults, in utero exposure of the infant prior to delivery may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions. Monitor infants who were exposed to diazoxide in utero for adverse reactions and treat accordingly.

Alopecia and hypertrichosis lanuginosa have occurred in a small number of infants whose mothers received oral diazoxide during the last 19 to 60 days of pregnancy. Abnormal hair growth was first noted at the age of one week and persisted when the infants were last seen at the ages of 5 months to one year. An infant born to a mother who was treated with oral diazoxide, 150 mg daily for 47 days prior to delivery, developed hyperglycemia which resolved after a 6-hour insulin infusion. Because there was an inappropriately low plasma insulin concentration for the degree of hyperglycemia, it was considered compatible with transplacental transfer of diazoxide causing inhibition of release of insulin from the neonatal pancreas.

Labor or Delivery

Intravenous administration of diazoxide during labor may cause cessation of uterine contractions, which may require administration of oxytocic agents to reinstate labor. However, this has not been reported with diazoxide when administered orally. Use caution in administering VYKAT XR during labor.

Data

Animal Data

Diazoxide choline was administered orally to pregnant rats during the period of organogenesis at doses of 40, 100, and 160 mg/kg/day (0.3, 0.6, and 1.2 times the MRHD of 525 mg based on AUC). No malformations were observed; however, decreased fetal body weights, delayed skeletal ossification, and increased fetal resorptions were observed at 160 mg/kg/day (a dose approximately equal to the MRHD based on AUC) which was a maternally toxic dose.

In a study in which rabbits were administered diazoxide intravenously, evidence of skeletal and cardiac teratogenic effects was noted at unknown multiples of the MRHD for diazoxide choline.

8.2 Lactation

Risk Summary

Diazoxide is present in human milk. There are no data on the effects of diazoxide on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYKAT XR and any potential adverse effects on the breastfed child from VYKAT XR or from the underlying maternal condition.

Clinical Considerations

Because of potential adverse reactions, including hyperglycemia, monitoring the infant's blood glucose may be advisable, especially during the neonatal period.

8.4 Pediatric Use

The safety and effectiveness of VYKAT XR have been established for the treatment of hyperphagia in pediatric patients 4 years of age and older with PWS. Use of VYKAT XR for this indication is supported by efficacy data from an adequate and well-controlled study that included pediatric patients with PWS *[see Clinical Studies (14)]* and safety data from additional studies that included pediatric patients with PWS *[see Adverse Reactions (6)]*, and the information on this use is described throughout the labeling.

The safety and effectiveness of VYKAT XR have not been established for the treatment of hyperphagia in pediatric patients with PWS less than 4 years of age.

Adverse Reactions in Pediatric Patients in an Unapproved Population

The following postmarketing adverse reactions have been reported with the use of other diazoxide products for the treatment of hyperinsulinemic hypoglycemia, an unapproved population *[see Adverse Reactions (6)]*:

- Pulmonary hypertension in pediatric patients less than 6 months of age, including neonates.
- Transient cataracts in association with hyperosmolar coma in a pediatric patient that subsided with correction of the hyperosmolarity.
- Development of abnormal facial features with chronic use in pediatric patients.

VYKAT XR is not approved and is not recommended for the treatment of hyperinsulinemic hypoglycemia.

Juvenile Animal Toxicity Data

Diazoxide choline was orally administered at doses of 29, 58, and 145 mg/kg/day to juvenile rats from weaning (postnatal day 21) through adulthood (postnatal day 91). Reduced body weight and body weight gains, correlated with decreased food consumption, occurred at doses ≥ 58 mg/kg/day. Delayed sexual maturation occurred in males at ≥ 58 mg/kg/day and in females at all doses. Decreased motor activity was observed in males at ≥ 58 mg/kg/day, but no effect was observed on learning and memory at any dose in both males and females. The no adverse effect level (NOAEL) was 29 mg/kg/day, which results in exposures less than the clinical exposure at the maximum recommended human dose (MRHD) of 525 mg based on AUC.

8.5 Geriatric Use

Clinical studies of VYKAT XR did not include any subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

8.6 Renal Impairment

VYKAT XR has not been studied in patients with renal impairment. VYKAT XR is not recommended in patients with renal impairment.

8.7 Hepatic Impairment

VYKAT XR has not been studied in patients with hepatic impairment. VYKAT XR is not recommended in patients with hepatic impairment.

10 OVERDOSAGE

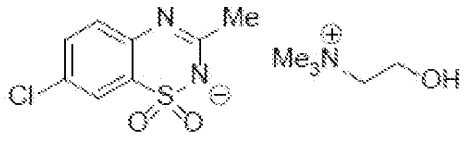
An overdosage of VYKAT XR may cause marked hyperglycemia, which may be associated with ketoacidosis *[see Warnings and Precautions (5.1)]*.

No specific antidotes for VYKAT XR are known. Monitor ketones in patients with severe hyperglycemia following overdose and consider insulin treatment if necessary. Treat severe hyperglycemia associated with ketoacidosis with prompt insulin administration and restoration of fluid and electrolyte balance. Because of VYKAT XR's long half-life (approximately 106 hours) in patients with PWS, the symptoms of overdosage (hyperglycemia, with or without ketoacidosis) require prolonged surveillance for periods up to three weeks or until blood sugar levels stabilize within the patient's normal range. Consider contacting a Poison Help line (1-800-222-1222) or a medical toxicologist for overdosage management recommendations for VYKAT XR.

11 DESCRIPTION

VYKAT XR contains diazoxide choline. Diazoxide choline is very slightly soluble to soluble in solvents dichloromethane, tetrahydrofuran, acetonitrile, and methanol and practically insoluble in solvents methyl *tert*-butyl ether. The pKa is 8.44 ± 0.01

Diazoxide choline is 7-Chloro-3-methyl-1λ6, 2,4-benzothiadiazin-2-ide 1,1-dioxide 2-hydroxyethyl(trimethyl)azanium. The empirical formula is $C_8H_6ClN_2O_2S \bullet C_5H_{14}NO$ and the molecular weight is 333.83 g/mole. The structural formula is:



VYKAT XR is for oral administration and is available as extended-release tablets in the following strengths: 25 mg tablet contains diazoxide choline 25 mg, equivalent to 17.2 mg diazoxide; 75 mg tablet contains diazoxide choline 75 mg, equivalent to 51.6 mg diazoxide; and 150 mg tablet contains diazoxide choline 150 mg, equivalent to 103.2 mg diazoxide.

Each tablet contains the following inactive ingredients: carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene oxide, silicified microcrystalline cellulose, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of diazoxide choline in the treatment of hyperphagia in patients 4 years of age and older with Prader-Willi syndrome (PWS) is unknown.

12.2 Pharmacodynamics

VYKAT XR resulted in a reduction in fasting plasma insulin from baseline through 1 year of treatment.

Diazoxide increases blood glucose, due primarily to an inhibition of insulin release from the pancreas.

Other pharmacodynamic effects of VYKAT XR include increased uric acid, renin secretion and IgG concentrations, and decreased cortisol secretion.

12.3 Pharmacokinetics

Absorption

Following oral administration, diazoxide choline is hydrolyzed to diazoxide prior to absorption. Peak diazoxide concentrations occur after 16 hours. VYKAT XR is expected to reach steady state after 7 days.

Effect of Food
Following administration of 150 mg diazoxide choline to healthy subjects, the C_{max} increased by 39% and AUC_{inf} was unchanged with a high-fat meal, compared to fasted conditions. The median T_{max} was 12 hours in the fasted state, and 8 hours in the fed state.

Distribution

The volume of distribution of diazoxide following oral administration is about 44.9 L. Diazoxide is extensively bound (91% to 93%) to plasma proteins (primarily human albumin), and crosses the blood-brain barrier.

Elimination

Metabolism

Diazoxide is mainly metabolized by CYP1A2 and to a minor extent by CYP3A4. Diazoxide is metabolized by oxidation or sulfate conjugation at the methyl group resulting in two inactive metabolites. Following long term administration in patients with PWS, only metabolite M1(3-hydroxymethyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide) is detectable in circulation.

Excretion

Diazoxide is excreted almost exclusively in urine as free or conjugated compound. In humans, following administration of radiolabeled diazoxide, 85 to 92% of the total dose was recovered in urine, with about 31% eliminated as unchanged drug. About 2% of the dose is eliminated in the feces. The terminal half-life following single-dose administration in healthy subjects was 28.7 to 32.4 hours. In patients with PWS, the estimated terminal half-life is 106 hours.

Specific Populations

Pediatric Patients

Approximately 72% of the patients with PWS were under 17 years of age at enrollment. There were no clinically relevant differences in pharmacokinetics in these participants compared to those observed in adult participants.

Male and Female Patients

No sex-related differences in pharmacokinetics have been observed in clinical trials of VYKAT XR in patients with PWS who have hyperphagia.

Patients with Renal or Hepatic Impairment

VYKAT XR has not been studied in patients with renal or hepatic impairment *[see Use in Specific Populations (8.6, 8.7)]*.

Drug Interaction Studies

Drugs That Inhibit CYP1A2

VYKAT XR is metabolized by CYP1A2 and coadministration with a strong CYP1A2 inhibitor may increase exposure of diazoxide and decrease concentrations of diazoxide metabolites. In a clinical study with fluvoxamine (a strong CYP1A2 inhibitor), coadministration with fluvoxamine at an inhibitory dose increased single dose diazoxide C_{max} by 17.5% and $AUC_{0\text{-}inf}$ by 60% compared to the same parameter measured on single dose in the absence of fluvoxamine co-administration *[see Drug Interactions (7)]*.

Strong CYP3A4 Inhibitor

Physiology-based pharmacokinetic model-based analysis suggests that concomitant use of VYKAT XR with itraconazole (a strong CYP3A4 inhibitor) may increase the AUC_{inf} of VYKAT XR by 1.1 to 2-fold, compared to VYKAT XR alone. Itraconazole did not appreciably affect the C_{max} of VYKAT XR *[see Drug Interactions (7)]*.

Strong CYP3A4 Inducers

Physiology-based pharmacokinetic model-based analysis suggests that concomitant use of VYKAT XR with rifampin (a strong CYP3A4 inducer and moderate CYP1A2 inducer) may decrease the C_{max} and AUC_{inf} of VYKAT XR by 14% to 30% and 40% to 70%, respectively, compared to VYKAT XR alone *[see Drug Interactions (7)]*.

Drugs that Alter Gastric pH

Use of VYKAT XR with gastric pH adjusting-drugs is not expected to affect the pharmacokinetics of diazoxide. Based on population pharmacokinetic modeling, use of VYKAT XR with gastric pH adjusting drugs did not significantly affect relative bioavailability or apparent clearance of diazoxide.

Protein Binding Displacement

VYKAT XR may also displace bilirubin bound to serum protein, thus resulting in higher blood levels of bilirubin.

In Vitro Studies

Enzyme systems: Diazoxide choline is an inhibitor of CYP1A2. It is not an inhibitor of CYP2B6, 2C19, 2C8, 2C9, 2D6 or 3A4. It does not an induce CYP1A2, CYP2B6 or CYP3A4 at the therapeutic dose range.

Transporter systems: Diazoxide choline is a substrate for OAT1, OAT3, and BCRP. It is an inhibitor of OAT1/3. It is not an inhibitor of P-gp, BCRP, MATE1/2-K, OATP1B1/3, OCT1/2 at the therapeutic dose range.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been performed with diazoxide choline.

Mutagenesis

Diazoxide choline was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and in the mouse lymphoma assay. Diazoxide choline was not clastogenic in the *in vivo* rat micronucleus assay.

Impairment of Fertility

Diazoxide choline was orally administered to male and female rats at doses of 58, 116, and 232 mg/kg/day (1, 2, and 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Females were treated two weeks prior to mating and continuing through conception and implantation and males were treated for four weeks prior to mating continuing for 35 days after mating. No effects on male or female fertility parameters were observed. Decreases in the mean number of corpora lutea, implantation sites, and live embryos occurred at 4 times the MRHD on a mg/m^2 basis.

13.2 Animal Toxicology and/or Pharmacology

Cataracts were observed in dogs given repeated daily oral doses of diazoxide of approximately 40 mg/kg/day for one month. The lenticular changes resembled those which occur experimentally in animals with increased blood glucose levels.

14 CLINICAL STUDIES

The efficacy of VYKAT XR for the treatment of hyperphagia in adults and pediatric patients ages 4 years and older with PWS was established in a 16-week, double-blind, placebo-controlled, randomized withdrawal study period (Study 2-RWP; NCT03714373) that followed an open-label study period of VYKAT XR. During Study 2-RWP, 77 patients with hyperphagia and PWS were randomized in a 1:1 ratio to continue their current oral dosage using a weight-based dosage regimen of VYKAT XR or placebo *[see Dosage and Administration (2.2)]*. Prior to participating in Study 2-RWP, patients received double-blind and/or open-label VYKAT XR for a mean duration of 3.3 years (range 2.5 to 4.5 years; Study 1 and Study 2-OLE). Results from Study 2-RWP are presented below.

Demographic and baseline disease characteristics were similar for the VYKAT XR and placebo groups. The mean age was 14.9 years of age (range 7 to 29 years of age). Most of the participants were White (86%), 7% were Black or African American, and 8% were of multiple races. The majority of participants were non-Hispanic (91%) and female (56%).

The primary efficacy endpoint was the Change from Baseline in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score at Week 16. The HQ-CT is a 9-item, observer-reported outcome measure that assesses a range of hyperphagic and food-related behaviors during the prior 2 weeks. An item score of 0 indicates an absence of behaviors, with a score of 4 indicating the most frequent or severe behaviors. The HQ-CT Total Score may range from 0 to 36, with higher scores indicating greater overall severity of hyperphagic and food-related behaviors.

At the end of the 16-week randomized withdrawal study period, there was statistically significant worsening of hyperphagia in the placebo group relative to the VYKAT XR group, as assessed by the HQ-CT Total Score (see Table 5).

Table 5: Study 2-RWP HQ-CT Total Score, Least Square Mean Change from Baseline to the End of the Randomized Withdrawal Period (Week 16) in Patients with Hyperphagia and PWS

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference* (95% CI)
VYKAT XR	38	9.0 (6.3)	2.6 (1.1)	-5.0 (-8.1, -1.8)
Placebo	39	8.1 (5.1)	7.6 (1.1)	

CI, confidence interval; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; LS Mean, least squares mean; RWP, randomized withdrawal period; SD, standard deviation; SE, standard error
* VYKAT XR - placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VYKAT XR is supplied as follows:

Strength	Description	Package Configuration	NDC Number
25 mg diazoxide choline	White, capsule-shaped tablets, debossed with "S-25" on one side	30-count bottles	83860-025-01
75 mg diazoxide choline	White, round, standard convex tablets, debossed with "S-75" on one side	30-count bottles	83860-075-01
150 mg diazoxide choline	White, oval-shaped tablets, debossed with "S-150" on one side.	30-count bottles	83860-150-01

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Keep in tightly closed container. Protect from humidity. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration Instructions

Advise patients to swallow tablets whole and not to split, crush, or chew VYKAT XR *[see Dosage and Administration (2.2)]*.

Hyperglycemia

Advise the patient or caregiver that VYKAT XR can cause hyperglycemia, sometimes leading to diabetic ketoacidosis, and that the patient will have monitoring of blood glucose before and during VYKAT XR treatment. Advise patients or caregivers on the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss) and ketoacidosis (e.g., nausea, vomiting, abdominal pain, generalized malaise and shortness of breath) and to contact their healthcare provider if these signs or symptoms occur *[see Warnings and Precautions (5.1)]*.

Risk of Fluid Overload

Advise the patient or caregiver that VYKAT XR may cause edema, including severe adverse reactions associated with fluid overload. Advise patients or caregivers on the signs and symptoms of edema and to contact their healthcare provider if signs or symptoms of edema occur *[see Warnings and Precautions (5.2)]*.

Manufactured for:
Soleno Therapeutics, Inc.
100 Marine Parkway, Suite 400
Redwood City, CA 94065
© 2025 Soleno Therapeutics, Inc. All rights reserved.

MEDICATION GUIDE
VYKAT™ XR (vye kat ex ar)
(diazoxide choline)
extended-release tablets, for oral use

What is the most important information I should know about VYKAT XR?

VYKAT XR may cause serious side effects, including:

- **High blood sugar levels (hyperglycemia).** Hyperglycemia is common during treatment with VYKAT XR and can also be severe. Hyperglycemia can lead to a condition called diabetic ketoacidosis (increased ketones in the blood) in some people who take VYKAT XR. Diabetic ketoacidosis is a serious condition that needs to be treated in a hospital and can be life-threatening.

  Your healthcare provider will:

  - check your blood sugar levels before you start VYKAT XR, at least 1 time every week for the first 2 weeks of treatment, then at least 1 time every 4 weeks and as needed during treatment.
  - check your blood sugar more often during the first few weeks of treatment if you have an increased chance of getting hyperglycemia.
  - check your HbA1c, which is another measurement of blood sugar control, before starting treatment, then 1 time every 3 months and as needed during treatment.

  If you get hyperglycemia during treatment with VYKAT XR, your healthcare provider may:

  - give you medicines to treat hyperglycemia or change your dose if you already take them
  - change your dose, temporarily stop, or permanently stop VYKAT XR

  Tell your healthcare provider if you get any of the following signs and symptoms:

  - **hyperglycemia**
    - feel very thirsty
    - need to urinate more often than usual
    - have higher amounts of urine than usual
    - feel more hungry than usual
    - weight loss
  - **diabetic ketoacidosis**
    - nausea
    - vomiting
    - stomach-area (abdominal) pain
    - feel weak or very tired
    - trouble breathing

- **Too much fluid in your body (fluid overload).** Swelling in the body (edema) from too much fluid is common during treatment with VYKAT XR and can also be severe. Your healthcare provider may decrease your dose or temporarily stop VYKAT XR if you get fluid overload. Tell your healthcare provider if you have trouble breathing or get any other signs or symptoms of fluid overload such as swelling of your legs, ankles, or feet, or unusual swelling anywhere in your body.

What is VYKAT XR?

VYKAT XR is a prescription medicine used to treat extreme hunger, constant thoughts about food, and constant urge to eat that cannot be satisfied with food (hyperphagia) in adults and children 4 years of age and older with Prader-Willi syndrome (PWS). It is not known if VYKAT XR is safe and effective in children under 4 years of age.

Who should not take VYKAT XR?

Do not take VYKAT XR if you are allergic to diazoxide, any ingredients in VYKAT XR, or medicines called thiazides. See the end of this Medication Guide for a complete list of ingredients in VYKAT XR.

Before taking VYKAT XR, tell your healthcare provider about all of your medical conditions, including if you:

- have diabetes or prediabetes
- are sick
- plan to have surgery
- drink alcohol very often
- are dehydrated or have lost a lot of body fluid
- have heart problems or a history of swelling in your legs or other parts of your body
- have liver or kidney problems
- are pregnant, or plan to become pregnant. VYKAT XR may harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with VYKAT XR.
- are breastfeeding or plan to breastfeed. VYKAT XR passes into your breast milk, and it is not known if it can harm your baby. Tell your healthcare provider if you plan to breastfeed during treatment with VYKAT XR.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking VYKAT XR with certain other medicines may affect the way VYKAT XR or the other medicine works and may increase your risk of side effects.

Do not change your dose or stop any medicines you take or start any new medicines without talking to your healthcare provider first during treatment with VYKAT XR. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Especially tell your healthcare provider if you take:

- medicines to lower blood sugar
- growth hormones
- corticosteroids
- diuretics (water pills)
- phenytoin
- warfarin

How should I take VYKAT XR?

- Take VYKAT XR exactly as your healthcare provider tells you to take it. Your healthcare provider will decide how much VYKAT XR you will take and may slowly increase your dose when you first start taking VYKAT XR.
- Take VYKAT XR by mouth 1 time per day with or without food.
- Swallow VYKAT XR tablets whole. **Do not** split, crush, or chew the tablets.
- You should not miss a dose of VYKAT XR. If you miss a dose of VYKAT XR, take the missed dose as soon as you remember. Do not take 2 doses of VYKAT XR at the same time to make up for a missed dose. If you missed a dose of VYKAT XR and did not remember to take another dose, call your healthcare provider to discuss what you should do next.
- **The dose of VYKAT XR is not the same as diazoxide oral suspension. Do not change** between VYKAT XR and diazoxide oral suspension products.

If you take too much VYKAT XR, call your healthcare provider or Poison Help Line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of VYKAT XR?

- **See "What is the most important information I should know about VYKAT XR?"**

The most common side effects of VYKAT XR also include:

- increased hair growth all over the body
- rash

These are not all of the possible side effects of VYKAT XR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VYKAT XR?

- Store VYKAT XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Close the bottle tightly after each dose.
- Keep VYKAT XR tablets dry (protect from humidity).
- The bottle contains a desiccant to help keep the tablets dry. Keep the desiccant in the VYKAT XR bottle.

Keep VYKAT XR and all medicines out of the reach of children.

General information about the safe and effective use of VYKAT XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VYKAT XR for a condition for which it was not prescribed. Do not give VYKAT XR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VYKAT XR that is written for health professionals.

What are the ingredients in VYKAT XR?

Active ingredient: diazoxide choline

Inactive ingredients: carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose magnesium stearate, polyethylene oxide, silicified microcrystalline cellulose, talc, titanium dioxide, and triacetin.

Manufactured for: Soleno Therapeutics, Inc., 100 Marine Parkway, Suite 400, Redwood City, CA 94065

For more information, call 1-833-765-3661.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 3/2025

EXHIBIT 12

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT CORRESPONDENCE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
COOLEY LLP ATTN: IP DOCKETING DEPARTMENT 1299 PENNSYLVANIA AVENUE, NW SUITE 700 WASHINGTON, DC 20004	58249	UNDISCOUNTED	11/08/2024 16:19:35

Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
9757384	14940018	11/12/2015	09/12/2017

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
02/24/2021	02/24/2021	E20212N846132225		$2,000.00

Fee Code	Description	Item ID	Fee Amount
1551	MAINTENANCE FEE DUE AT 3.5 YEARS	E20212N846132225	$2,000.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution the payment will be void and the maintenance fee and any necessary surcharge unpaid.

EXHIBIT 13

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT CORRESPONDENCE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
COOLEY LLP ATTN: IP DOCKETING DEPARTMENT 1299 PENNSYLVANIA AVENUE, NW SUITE 700 WASHINGTON, DC 20004	58249	UNDISCOUNTED	01/22/2025 20:06:01

Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
9757384	14940018	11/12/2015	09/12/2017

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
01/13/2025	01/13/2025	E20251C750505651		$3,760.00

Fee Code	Description	Sale ID	Fee Amount
1552	MAINTENANCE FEE DUE AT 7.5 YEARS	E20251C750505651	$3,760.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution the payment will be void and the maintenance fee and any necessary surcharge unpaid.

EXHIBIT 14

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 73,179

Essentialis, Inc.
Attention: Neil M. Cowan, Ph.D., MBA
CEO and President
7915 Corte Cardo
Carlsbad, CA 92009

Dear Dr. Cowan:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	73,179
Sponsor:	Essentialis, Inc.
Name of Drug:	diazoxide choline controlled release tablets
Date of Submission:	August 22, 2006
Date of Receipt:	August 22, 2006

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before September 21, 2006, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Madara
8/31/2006 11:35:27 AM

EXHIBIT 15

Exhibit 15
IND 73,179
Diazoxide Choline Controlled Release Tablets
Anniversary Date: 22nd August

Date	Serial No.	Description
2006 Aug 22	0000	Original IND Submission
2006 Sep 01	0001	Response to information request: References (Dayton et al 1975; Pruitt et al 1974; Hyperstat label; Hyperstat SBA); Report AB27VS.704.BTL (mouse lymphoma assay); Report AB27VS.503.BTL (bacterial reverse mutation assay)
2006 Oct 02	0002	Study PK001 Protocol Amendment 1.0
2006 Nov 13	0003	Notification of Change in Address
2006 Nov 17	0004	Complete Response to a Partial Clinical Hold • Protocol TR002 • FDA Form 1572 • Investigator Curricula Vitae • Appendix A: Final Report Mammalian Erythrocyte Micronucleus Test • Appendix B: Final Report MTD Study 1270-002 – Diazoxide: A Dose Range-Finding Oral Toxicity Study in Rats • Appendix C: Copies of cited references • Appendix D: Final Data from PK001 • Appendix E: Final Report Determination of Diazoxide in Human Plasma by LC/MS/MS (PRACS Protocol No. R06-0537)
2006 Dec 21	0005	Response to Request for Additional Information • Comparison of Quality of Diazoxide Choline Controlled-Release Tablets and Proglycem Capsules and Hyperstat IV • Protocol 90-day toxicity study in rats
2007 Jan 24	0006	Complete Response to a Partial Clinical Hold • TR002 Protocol Post-amendment 1

Exhibit 15
IND 73,179
Diazoxide Choline Controlled Release Tablets
Anniversary Date: 22nd August

Date	Serial No.	Description
2007 Mar 02	0007	Complete Response to a Partial Clinical Hold • TR002 Protocol Amendment 4 • Final Report: Diazoxide: A Dose Range-Finding Oral Toxicity Study in Rats (amended to include histopathology evaluations) • Summary: Comparative Quality of Diazoxide Choline, Diazoxide Choline Controlled-Release Tablets and Proglycem Oral Suspension – Metrics QA reviewed report provided in submission • Summary: Safety information and clinical studies of Proglycem. • Summary: Predicted peak and trough circulating drug levels at steady state for the proposed dose range for Diazoxide Choline Controlled-Release Tablets (100 mg/day to 600 mg/day) compared to published clinical studies in obese patients. • Summary: Comparison of peak drug levels for the proposed dose range to the peak drug levels in various controlled clinical studies and at the NOAEL • Summary: Pharmacokinetic Comparison of Diazoxide Choline Controlled Release Tablets with Proglycem Oral Suspension
2007 Aug 15	0008	TR002 Protocol Amendments 5, 6, 7, 8, 9, 10, and 11 FDA Form 1572 • Principal Investigator and Sub-Investigator's Curricula Vitae and licensure • Laboratory certification • Financial disclosure forms Final Report: In Vitro Metabolism Studies of Diazoxide Choline (Report No.: BD00107)
2007 Oct 31	0009	TR002 Protocol Amendment 13
2007 Nov 07	0010	Annual Report
2008 Jan 02	0011	New Protocol Clinical Study EC004 FDA Form 1572 • Investigator Curricula Vitae and licensure • Laboratory certification • Financial disclosure forms

Exhibit 15
IND 73,179
Diazoxide Choline Controlled Release Tablets
Anniversary Date: 22nd August

Date	Serial No.	Description
2008 Jan 29	0012	Chemical, manufacturing and control update • Summary information from the manufacture of a clinical batch of Diazoxide Choline Controlled-Release Film Coated Tablets and corresponding placebo tablets • Updated stability data on Drug Active and Drug Product
2008 Feb 07	0013	Final Study Report: Diazoxide: A 13-Week Oral Toxicity Study in Rats (Study No. 1270-001)
2008 May 22	0014	New Protocol Clinical Study PK008 FDA Form 1572 • Investigator Curricula Vitae and licensure • Laboratory certification
2008 Jun 02	0015	New Protocol Clinical Study PC007 FDA Form 1572 • Investigator Curricula Vitae and licensure • Laboratory certification Summary of published non-clinical studies evaluating the effects of diazoxide in obese and obese diabetic dyslipidemic animal models and of published clinical studies evaluating the effects of diazoxide in obese and non-obese dyslipidemic patients Executive summaries of clinical studies TR002 and EC004
2008 Jul 02	0016	New Investigators for Clinical Study PC007 • FDA Form 1572 • Investigator Curricula Vitae
2008 Jul 24	0017	Clinical Study PC007 Protocol Amendment 2 In-Vitro hERG Study Report
2008 Aug 15	0018	Request for Additional Information • Rationale for the Increase in Dose in the 24July08 Amendment of Protocol PC007 • PK008 Pharmacokinetic Results • Timing of Availability of Clinical Study Reports for Completed Clinical Studies • New Investigators for Clinical Study PC007 o FDA Form 1572 o Investigator Curricula Vitae and licensure
2008 Sep 02	0019	Final Study Report Clinical Study PK001

Exhibit 15
IND 73,179
Diazoxide Choline Controlled Release Tablets
Anniversary Date: 22nd August

Date	Serial No.	Description
2008 Sep 19	0020	Final Report: Diazoxide Choline: Preliminary Embryo-Fetal (Study No. 06-4323) Final Report: Embryo-Fetal Toxicity Study in Rates (Study No. 06-4324)
2008 Nov 19	0021	Annual Report
2009 Feb 04	0022	Final Clinical Study Report Clinical Study PK008
2009 Feb 16	0023	Final Clinical Study Report Clinical Study EC004
2009 Oct 29	0024	Notification of submission of the clinical study report for study PC007 to new linked IND 104,978
2010 Jan 11	0025	Annual Report
2011 Jul 25	0026	Annual Report
2014 Jan 13	0027	New Protocol: Clinical Study PC025 FDA Form 1572 FDA Form 3674 Labels for approved products (Proglycem and Hyperstat) Background information covering PWS including the mortality and morbidity associated with the syndrome, the most critical unmet need in the condition, the mode-action of DCCR in PWS, results from informative animal models and all relevant clinical information Summary of clinical experience with DCCR
2014 Jun 04	0028	Clinical Study PC025 Protocol Amendment 1
2015 May 06	0029	General correspondence - post-meeting letter PIND 125634
2015 Jul 28	0030	Annual Report
2015 Aug 11	0031	Clinical Study PC025 Protocol Amendment 4
2017 Jul 12	0032	Notification of Change of Sponsor Notification of Change of Sponsor's Authorized Representative
2017 Oct 25	0033	Annual Progress Report Reporting Period: 25 July 2015 through 22 August 2017
2018 Mar 20	0034	Study PC025 Final Draft Clinical Study Report Datasets and programs used to prepare the tables, figures, and listings

EXHIBIT 16

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
13 Jan 2015	Correspondence: Telecon Summary	PMadara/ NCowen	Discussion to identify best path forward for the PWS program – new IND or convert IND 73,179 to PWS.
04 Feb 2015	Submission		PIND Meeting Request (PIND 125634)
12 Feb 2015	Correspondence	From FDA	PIND number assignment (PIND 125634)
23 Feb 2015	Correspondence	From FDA	PIND Meeting granted. (PIND 125634)
02 Mar 2015	Submission		PIND meeting briefing document (PIND 125634)
30 Apr 2015	Submission		Request for PIND meeting minutes and summary of Essentialis' understanding of agreements and commitments from PIND meeting. (PIND 125634)
07 May 2015	Correspondence	From FDA	PIND meeting minutes (PIND 125634)
10 Oct 2016	Submission	**0000**	Original IND
18 Oct 2016	Letter	From FDA	IND Acknowledgement letter
07 Nov 2016	Correspondence: Telecon Summary	NCowen/PMadara	Summary of CMC information requested during IND review.
07 Nov 2016	Submission	0001	Response to FDA request for Information Information Amendment: CMC
18 Nov 2016	Letter	From FDA	Additional information request after completing review of original IND submission (clinical, non-clinical, CMC).
09 Mar 2017	Submission	**0002**	Notification of Change in Sponsor, Sponsor's Authorized Representative
13 Mar 2017	Submission	**0003**	Meeting Request: Request for Type C Meeting, PWS
05 Apr 2017	Letter	From FDA	Meeting Request Granted
21 Apr 2017	Submission	**0004**	Meeting Briefing Information; includes C601 Protocol Synopsis
08 May 2017	**Submission**	**0005**	Response to FDA Request for Information

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
16 May 2017	Submission	**0006**	Errata Sheet for Meeting Briefing Information
16 May 2017	**Email**	MYoon / PHirano	Copy of errata sheet for meeting briefing information
18 May 2017	**Email**	MYoon / PHirano	Submission list of final list of Sponsor attendees for 25th May 2017 meeting
19 May 2017	**Email**	PHirano / MYoon	List of FDA attendees for 25th May 2017 meeting.
19 May 2017	Submission	**0007**	Response to FDA Request for Information – Clinical Pharmacology / Cardiac Safety
22 May 2017	Submission	**0008**	Administrative Change / Company Name
02 Jun 2017	Submission	**0009**	Information Amendment: Pharmacology / Toxicology
10 Jun 2017	Submission	**0010**	Information Amendment: Clinical HQ-CT and supporting documentation
13 Jun 2017	Email		Electronic Submission of Nonclinical Study Reports (SPT-001 to SPT-008)
24 Jun 2017	Correspondence	From FDA	Meeting Minutes from a 25th May 2017 Meeting
25 Aug 2017	Submission	**0011**	Information Amendment: Pharmacology / Toxicology Juvenile Toxicology Protocol
27 Sep 2017	Submission	**0012**	Information Amendment: Clinical CSR Synopses for Studies PK001, PK008, PK015, EC004, PC007, TR002
06 Oct 2017	Submission	**0013**	Information Amendment: Clinical ECG Data and Request for TQT Study Waiver
10 Oct 2017	Submission	**0014**	Meeting Request: Request for Type B (EOP2) Meeting
16 Oct 2017	Voicemail	M Yoon / PHirano	Voicemail message inquiring about submission status for serial numbers 0010, 0011, and 0013.

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
31 Oct 2017	Email	M Yoon / PHirano	Follow-up to 2017 Oct 16 voicemail request for status update of submissions for HQ-CT and juvenile tox protocol and estimated review completion date for TQT data / waiver request.
06 Nov 2017	Email	M Yoon / PHirano	Follow-up to 31 October 2017 email requesting status update of submissions for HQ-CT and juvenile tox protocol and estimated review completion date for TQT data / waiver request.
27 Nov 2017	Submission	0015	EOP2 (Clinical) Meeting Briefing Information
28 Nov 2017	Email	PHirano / MYoon MYoon / PHirano PHirano / MYoon	Request for ecopy of meeting briefing information; email copy of briefing information; receipt of ecopy of briefing information.
11 Dec 2017	Submission	0016	First Annual Progress Report
12 Dec 2017	Email	MYoon / PHirano	Tentative list of attendees at EOP2 meeting
12 Dec 2017	Email	MYoon / PHirano PHirano / MYoon MYoon / PHirano PHirano / MYoon	Follow-up to tentative list and prior submissions referenced in briefing information Acknowledgement of submissions referenced. Request for ecopies of of ECG data Emailed ecopies of ECG data Acknowledgement of receipt
22 Dec 2017	Submission	0017	PC025 Clinical Study Report
02 Jan 2018	Email	PHirano / MYoon	Followup to question regarding timing for preliminary comments
08 Jan 2018	Email	PHirano / MYoon	Request for ecopy of PC025 draft cSR
16 Jan 2018	Correspondence	From FDA	Preliminary comments for EOP2 Meeting.
16 Jan 2018	Emails	MYoon / PHirano PHirano / MYoon MYoon / PHirano	List of in-person vs remote meeting attendees. Notification of winter weather advisory, offer to switch meeting to teleconference. Confirmation that planning for in-person attended, but will change to teleconference depending on weather.

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
17 Jan 2018	Email	PHirano / MYoon MYoon / PHirano	Request for electronic copy of PC025 CSR Confirmation that the PDF of the draft report was being compiled. Datasets had been included in submission. Meeting follow-up regarding additional anchors for HQ-CT
22 Jan 2018	Email	PHirano / MYoon	Confirmation of receipt of electronic copy of PC025 CSR. Confirmation that request for additional anchors for HQ-CT will be forwarded to the review team.
10 Feb 2018	Submission	0018	Protocol Amendment: Change in Protocol. C601, Amendment 1 Protocol Amendment: new Investigator (JMiller) Clinicaltrials.gov certification form 3674 Sponsor meeting summary from EOP2 clinical meeting.
14 Feb 2018	Correspondence	From FDA	Final EOP2 meeting minutes
15-16 Feb 2018	Email	MYoon / PHirano PHirano / MYoon MYoon / PHirano PHirano / MYoon MYoon / PHirano	Follow-up to meeting minutes and submission serial no. 0018 Recommendation to withdraw protocol from IND and submit new version. Clarification that request for withdrawal would be done as an IND amendment Confirmation that withdrawal would be done via IND Amendment; request for an electronic copy. Confirmation that an ecopy of the protocol would be provided
16 Feb 2018	Submission	0019	Request to Withdraw Protocol C601 dated 10 February 2018 from IND and Review
20 Feb 2018	Submission	0020	C601 Protocol Amendment 1: Change in Protocol
21 Feb 2018	Email	MYoon / PHirano PHirano / MYoon	PDF copy of protocol Notification that the revised protocol has been sent to the review team

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
6 Mar 2018	Submission	0021	1.14.4.1 Investigational Brochure 1.14.4.2 Investigational Product Labeling 3.2.S Drug Substance Information 3.2.P. Drug Product [DCCR] 3.2.P Drug Product [Placebo for DCCR]
16 Mar 2018	Submission	0022	Initial Pediatric Study Plan
19 Mar 2018	Email	PHirano / MYoon MYoon / PHirano PHirano / MYoon	Request for electronic copies of submission serial no. 0021 Email copies of submission 0021 Confirmation of receipt
27 April 2018	Submission	0023	3.2.P.5.4 Batch analysis section update to include DCCR 75 mg tablet lots M10397 and M10492
31 May 2018	Submission	0024	Request for Fast Track Designation
14 June 2018	Email	P Hirano / M Yoon	C601 Protocol Amendment 1 Review comments
15 June 2018	Email	P Hirano / M Yoon	iPSP review comments
27 June 2018	Email	MYoon / PHirano	Follow-up to 14 June Protocol Review Comments. Request for discussion re: C-SSRS
20 July 2018	Submission	0025	C601 Protocol Amendment 2, 19 July 2018
30 Jul 2018	Submission	0026	C602 Protocol
07 Aug 2018		PHirano / HPatel	Request for IB to be submitted to the IND and courtesy copy to Dr. Patel. Courtesy copy of IB submitted in Serial No. 0021 provided via email. Request for clarification if re-submission was required.
15 Aug 2018	Correspondence	From FDA	Grant Fast Track letter.
04 Sep 2018	Email	PHirano / HPatel	Protocol comment for C602 protocol received 31 Jul 2018 for more frequent urinalysis to monitor for emergence of diabetes / glucose intolerance.
13 Sep 2018	Submission	0027	PSP

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
24 Sep 2022	Email	P Hirano / H Patel	Protocol comments on study C602 protocol
31 Oct 2018	Submission	0028	C601 New Investigator Information (Abuzzahab, Bird, Chan, Miller, Salehi, Schillaci, Shoemaker, Stevenson) C601 SAP C602 New Investigator Information (Salehi) C602 Certificate of Compliance
12 Nov 2018	Submission	0029	C601 Amendment 3
07 Dec 2018	Email	P Hirano / H Patel	C602 comments re: protocol
10 Dec 2018	Submission	0030	2nd APR
18-23 Dec 2018	Email	HPatel / PHirano PHirano / HPatel	Inquiring regarding SAP submission in serial No. 0028. Checking with statistical reviwers.
03 Jan 2019	Email	P Hirano / H Patel	Comments re: C601 SAP
14 Mar 2019	Email	P Hirano / H Patel	Comment re: C601 amendment 3 rlated to home visits
22 Mar 2019	Submission	0031	IND Safety Report: Initial Written Report
22-25 Mar 2019	Email	HPatel / PHirano PHirano / HPatel	Email notification of IND safety report submitted as 0031 Acknowledgement and notification of clinical reviwer.
26 Apr 2019	Submission	0032	IND Safety Report: Follow-up Report
29 April 2019	Submission	0033	Protocol Amendment: C601 Amend 4 Information Amendment: Pharm/Tox SPT009 (GLP hERG)
28 May 2019	Submission	0034	Protocol Amendment: C602 Amend 1
31 May 2019	Submission	0035	IND Safety Report: Follow-up Report

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
20 Jun 2019	Submission	0036	Protocol Amendment: C601 Amend 4a C601 new/updated investigator info (New: Angulo, Butler, Fleischman, Kimonis, McCandless, Obrynba, Yanovski; revised: Bird, Miller, Salehi, Schillaci, Stevenson) C602 new/updated investigator info (New: Angulo, Bird, Butler, Miller, Schillaci, Shoemaker, Stevenson; revised: Salehi)
06 Sep 2019	Submission	0037	CMC amendment – add AMRI Grafton
15 Sep 2019	Correspondence	From FDA	Acknowledgement of change of address
27 Sep 2019	Submission	0038	C602 Amendment 2
10 Dec 2019	Submission	0039	Third Annual Progress Report
26 Dec 2019	Submission	0040	Request for Type B Meeting Type B meeting request for EOP2 CMC meeting
07 Jan 2020	Email	HPatel / PHirano PHirano / HPatel	Meeting request includes multidisciplinary questions. Can remove 2 questions and meeting becomes a CMC meeting or keep in and meeting becomes a general meeting request. Preference to include 1 question if it would not incur a potential delay.
09-10 Jan 2020	Email	PHirano / TBouie	Notification that CMC EOP2 meeting will be granted. Confirm availability for proposed meeting date/time
09 – 10 Jan 2020	Email	HPatel / PHirano PHirano / HPatel	Request for confirmation that PGI question can remain a meeting topic. Confirmed
15 Jan 2020	Correspondence	From FDA	Meeting Granted Letter
15 Jan 2020	Email	PHirano / TBouie TBouie / PHirano PHirano / TBouie	Notification that CMC meeting package was due on 14th Jan. Request to submit ASAP. Notification briefing document would be submitted on 16th Jan. Confirmed acceptability
16 Jan 2020	Submission	0041	EOP2 CMC Meeting Briefing Information

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
16-17 Jan 2020	Email	TBouie / PHirano PHirano / TBouie	Courtesy copy of EOP2 CMC meeting briefing information Confirmation of receipt of hard copies.
26 Feb 2020	Email	TBouie / PHirano PHirano / TBouie	Notification of final list of meeting attendees; request for confirmation of forthcoming preliminary comments. Acknowledgment of final attendees. Notification that prelim comments expected to be sent on 27th Feb.
27 Feb 2020	Correspondence	From FDA	Preliminary meeting comments
02 Mar 2020	Email	TBouie / PHirano	Confirmation that meeting will proceed as a teleconference. ID of questions to be discussed. Meeting slides for meeting.
17 Apr 2020	Email	TBouie / PHirano	Request for date meeting minutes should be expected.
17 Apr 2020	Correspondence (via Email)	From FDA	EOP2 CMC meeting minutes. Not able to send hard copy since everyone is working rmotely.
20 Apr 2020	Submission	0042	C601 SAP, Version 3.0 Study C601 COVD-19 Contingency Plans for US and UK
5 May 2020	Submission	0043	C601 SAP Version 3, Addendum C602 Interim Analysis SAP, Version 1.0 CAS-SOL001-01 PWS Outcomes Sub-Study to C601 and C602 – Protocol and SAP C602 Contingency Plans for US and UK

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
4 June 2020	Submission	0044	New Investigator Information C601: Barrett, Bridges, Das, Felner, Gevers, Goldstone, Harwood, Holland, Kimonis, Littlejohn, Mathew, Shaikh, Shea, Viskochil, Wilding C602: Barrett, Bridges, Felner, Fleischman, Gevers, Goldstone, Harwood, Holland, Kimonis, Lah, Littlejohn, Mathew, McCandless, Obrynba, Shaikh, Shea, Viskochil, Wilding, Yanovski Updated Investigator Information: C601: Bridges, Goldstone, Littlejohn, Miller (2), Shaikh, Viskochil, Yanovski C602: Bridges, Shoemaker
19 Aug 2020	Submission	0045	Meeting Request: Request for Type C / End of Phase 3 meeting
21 Aug 2020	Email	PHirano / ELee ELee / PHirano	Request for completion of clin pharm summary table. Confirmation that it will be submitted with briefing document
26-27 Aug 2020	Email	PHirano / LWilson LWilson/PHirano PHirano / LWilson	Inquiring if meeting briefing document could be submitted by 28th Aug to support a 14th Oct meeting Reply that soonest timing for briefing doc would be 4th Sep to support meeting on 21st Oct Meeting rescheduled for 12th Nov, 10 AM Eastern
31 Aug 2020	Correspondence	From FDA	Meeting Granted letter
23 Sep 2020	Submission	0046	EOP3 meeting briefing information
15 Oct 2020	Submission	0047	C602 protocol amendment 3 Juvenile tox studyreport (SPT-010)
03 Nov 2020	Submission	0048	CMC Amendment
04 Nov 2020	Email	LWilson / PHirano	Questions regarding teleconference Responses to questions / dial-in information

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
05 Nov 2020	Correspondence	From FDA	Preliminary meeting comments.
05 Nov 2020	Email	PHirano / LWilson LWilson / PHirano	Courtesy copy of prelim comments Request to discuss preliminary response to question 1a.
11 Nov 2020	Email	PHirano / LWilson	Slides to be presented at meeting and final list of participants
12-13 Nov 2020	Email	PHirano / LWilson LWilson / PHirano	Follow-up to meeting with regards to natural history studies. Confirmation of receipt; acknowledgement that comments will be shared with reviewers.
20 Nov 2020	Email	PHirano / LWilson LWilson / PHirano	Sponsor's meeting minutes by email to Dr. Latrice Wilson and follow-up questions. Request to speak regarding follow-up proposals Due to workload, propose to follow-up via email.
2 Dec 2020	Submission	0049	Sponsor's meeting minutes.
10 Dec 2020	Correspondence	From FDA	Final meeting minutes
21 Dec 2020	Submission	0050	Meeting Request
28 Dec 2020	Correspondence	From FDA	Meeting request granted as WRO
18 Jan 2021	Submission	0051	Meeting briefing info
18 Feb 2021	Email	LWilson / PHirano	Request for biometrics information regarding meeting briefing info
26 Feb 2021	Email	LWilson / PHirano	Response to biometrics information request related to meeting request.
26 Feb 2021	Submission	0052	Meeting request for Type C CP Meeting

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
01-10 Mar 2021	Email	PHirano / LWilson LWilson / PHirano PHirano / LWilson LWilson / PHirano PHirano / LWilson	Confirmation of receipt of IR response and request to submit to IND. Clarification request regarding Type C CP meeting request. Clarification to CP meeting request Ackowledgement of clarification Request to withdraw request for Type C meeting Confirmation that meeting request is withdrawn.
04 Mar 2021	Submission	0053	Response to FDA request for information on 18 Feb 2021 Updated Investigator's Brochure New Protocol: C605 C605 New Investigator Information: Bundrant (1572 and CV) Pharm/Tox Report: Rpt SPT-011, rabbit ventricular wedge
04 Mar 2021	Submission	0054	APR in DSUR format
05 Mar 2021	Correspondence	From FDA	Type C WRO minutes
15 Mar 2021	Submission	0055	Response to WRO Minutes
25 Mar 2021	Email	PHirano / LWilson L Wilson / P Hirano	Request for clin pharm information regarding C605 Confirmation that responses will be submitted.
9 Apr 2021	Submission	0056	Response to FDA Request for information C605
4 May 2021	Submission	0057	C605 Protocol Amendment 1 New Investigator Information: Pak (1572 and CV)
25 May 2021	Submission	0058	C609 (C601/C602 and NIH NHS) Analysis Plan

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
15-16 June 2021	Email	LWilson and HPatel / PHirano P Hirano and HPatel / LWilson LWilson and HPatel / PHirano P Hirano and HPatel / LWilson	Courtesy copy of FPWR and PWSA-USA Joint Letter and Petition to FDA Acknowledgement of letter; Request that FPWR and PWSA-USA Joint Letter and Petition to FDA is submitted to the IND; Confirmation that letter was submitted to the IND. Confirmation of receipt
15 June 2021	Submission	0059	FPWR and PWSA-USA Joint Letter and Petition to FDA
17 June 2021	Submission	0060	C605 SAP, Version 1.0
21 June 2021	Submission	0061	C602 SAP – Final draft
2 July 2021	Submission	0062	C610 (C601/C602 and PATH for PWS) Analysis Plan
21 Jul 2021	Submission	0063	Information Amendment: CMC Minor clarifications to DP specification, DP IPC
6 Aug 2021	Submission	0064	Final SAPs for C602, C609, C610
20 Aug 2021	Correspondence	From FDA	Advice letter re: SAPs for C602, C609, and C610
13-22 Sep 2021	Email	LWilson and AKamath / PHirano PHirano and AKamath / LWilson LWilson and AKamath / PHirano	Followup to PIND (155838) meeting with DDLO. Confirmation that DP will be the primary review division with DDLO consult. Follow-up teleconference is recommended. Acknowledgement of email. Notification of delay in draft report submission
4 Oct 2021	Submission	0065	Amended SAP for CAS-SOL001-01 Town Hall Summaries
21 Sep 2021	Submission	0066	Request for Trade Name Review
5 Oct 2021	Submission	0067	C602 Protocol Amendment 4
12 Oct 2021	Submission	0068	Draft clinical study reports for studies C601, C602, C609, C610

Exhibit 16
IND 132,498
Regulatory Log

Date	Type	To/From or Serial No.	Description
12 Oct 2021	Submission	0069	Meeting Request: Request for a Type C Meeting
17 Oct 2021	Submission	0070	Draft Clinical Study Report for Study CAS-SOL001-01 Meeting request replacement page 8
18 Oct 2021	Email	PHirano / PBNguyen	Request to provide information regarding proposed packaging configurations for proposed proprietary name
19 Oct 2021	Email	PHirano / TTaylor TTaylor / PHirano	Introduction as new RPM. Notification that meeting request received. Request for confirmation of availability. Confirmation of availability for 21st Dec meeting
19 Oct 2021	Correspondence	From FDA	Meeting granted letter for Type c meeting
20 Oct 2021	Email	PHirano / TTaylor TTaylor / PHirano	Notification of potential rescheduling Type C meeting to 19th Jan. Preference to keep 21st Dec meeting date.
21 Oct 2021	Submission	0071	Proprietary Name Review – Requested Information
26 Oct 2021	Email	TTaylor / PHirano PHirano / TTaylor PHirano / TTaylor	Request for clarification regarding briefing document due date Confirmation of briefing document due date Acknowledgement of due date
1 Nov 2021	Submission	0072	Information Amendment – Clinical Pharmacology – clinical pharmacology summary table
3 Nov 2021	Submission	0073	Meeting Briefing Information for Type C Meeting
17 Nov 2021	Email	TTaylor / PHirano PHirano / TTaylor	Request for information regarding CAS-SOL001-01 draft report. Confirmation of receipt of IR.
13 Dec 2021	Submission	0074	Response to request for information