

Pharmaceutical Interview Form

Prepared in accordance with the IF description guidelines set forth by the Japanese Society of Hospital Pharmacists (September 1998)

Anticonvulsant

Nobelbar® 250 mg for intravenous infusion

(lyophilized phenobarbital sodium formulation)

Nobelbar® 250 mg for injection

Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)}

Note 1) Caution: habit-forming

Note 2) Caution: use only by prescription from a physician, etc.

Dosage form	Injection
Standards / Content	Nobelbar 250 mg for intravenous injection: Each vial contains 274 mg of phenobarbital sodium (250 mg phenobarbital)
Generic name	Japanese name: Phenobarbital Sodium (JAN) English name: Phenobarbital Sodium (JAN, INN)
Date of Approval for Manufacture/Import Listed in the Japan's National Health Insurance (NHI) Drug Price Standard - Sales start date	Date of manufacturing approval: October 16, 2008 Date of NHI drug price standard listing: December 12, 2008 Sales start date: December 16, 2008
Name of Development/manufa cturing/ importing/marketing/p artner/distribution company	Manufactured and distributed by: Nobelpharma Co., Ltd. Sold by: Alfresa Pharma Corporation Manufactured by: Toyobo Co., Ltd.
Contact information/phone number/fax number	

This interview form (IF) was prepared based on the attached document revised in July 2010 (3rd edition).

Outline of IF Usage Guide Japan Society of Hospital Pharmacists

1. Pharmaceutical Interview Form Preparation Details

In 1988, the Second Academic Subcommittee of the Japanese Society of Hospital Pharmacists (hereinafter referred to as "JSHP") clarified the role played by interview forms and created a format for them. A "Pharmaceutical Interview Form" (hereinafter abbreviated as "IF") is used as a source of drug information necessary to interview pharmaceutical company medical representatives (hereinafter abbreviated as "MRs") and other personnel to evaluate the drug in question.

2. What is an IF?

The IF acts as "a comprehensive drug information manual that supplements information in the package inserts of ethical drugs, and provides pharmacists and other healthcare professionals with information necessary for the proper use and evaluation of drugs, as well as information to support the provision of drug information in their daily work. The JSHP has established guidelines for what to include in this form and requests that pharmaceutical companies prepare and provide this document for pharmacists, etc.

However, information related to regulations of the Pharmaceutical Affairs Law or confidentiality of pharmaceutical companies, information contrary to the intent of pharmaceutical companies to formulate products, and items that should be evaluated, judged, and provided by pharmacists themselves are not to be included in IFs.

3. Format/preparation/publication of IFs

As a general rule, the standard format should be A4 size, horizontally written, with a font size of 9 points or larger, and printed in one color. The entries on the cover page should be standardized and, in principle, prepared by route of administration of the drug product. IFs must be written in accordance with the "Guidelines for IFs" established by JSHP, but these guidelines are only enforced for new drugs approved after January 1999. For products that went on the market before then, it is not mandatory to prepare an IF in accordance with these guidelines. In addition, IFs must be revised/reissued when the currently available information becomes significantly different from the content of the existing IF as a result of reexaminations and reevaluations (due to clinical trials) and/or expansion, etc. of indications.

4. Using IFs

Based on the starting point of the IF system, it is necessary to enrich the content of the IF by adding data from interviews with MRs and self-surveys to enhance the usability of the IF.

Items to be investigated and supplemented in interviews with MRs include the history of development, formulation characteristics, pharmacological actions, clinical results, and non-clinical studies. In addition, with the cooperation of the pharmaceutical companies, pharmacists and others should add and maintain information on precautions for use, etc., which are revised from time to time, using the ethical drug package inserts, notification documents, emergency safety information, Drug Safety Update (information on drug safety measures), and other documents. As a reference to that end, the date of preparation or revision of the attached document on which the IF was based is listed at the bottom of the cover page. In addition, items such as "clinical results" and "major foreign marketing status" that are listed from the standpoint of ensuring proper use and safety may include unapproved dosage and administration and indications, and should be handled with caution.

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I. Overview

I-1. History of development

Phenobarbital, created by Hoerlein in 1912, is a drug with anticonvulsant, as well as hypnotic/sedative effects that has since become popular worldwide.

Phenobarbital has been an important drug for more than 50 years, but in Japan, the medical community has indicated that there is no intravenous formulation available, no indication for neonatal seizures, and no pediatric dosage regimen, except for suppositories.

On the subject of the need for an intravenous phenobarbital preparation, an application to include an indication for neonatal seizures was submitted to the Minister of Health, Labor and Welfare by the Japan Pediatric Society on October 8, 2004, and a letter of request for additional indication for status epilepticus was submitted jointly by the Japan Pediatric Society and the Japanese Society of Child Neurology on November 24, 2005.

In response to this, a physician-initiated clinical trial for neonatal seizures with intravenous phenobarbital was adopted under the Clinical Trial Promotion Project by the Japan Medical Association Center for Clinical Trials, a 2004 Health and Labor Sciences Research Grant project. The clinical trial was successfully conducted. Subsequently, in October 2008, the first intravenous phenobarbital formulation in Japan was approved for the treatment of neonatal seizures and status epilepticus.

I-2. Product features and efficacy

1. The drug is an intravenous phenobarbital formulation that meets the needs of the medical community.
2. It is the first drug indicated for neonatal seizures in Japan.
3. It can be administered to children and adults with status epilepticus.
4. This preparation does not contain any additives.
5. Exhibits inhibition against maximal electroconvulsive seizures and metrazol-induced seizures. (in mice)
6. Of the 10 cases in which safety was evaluated in a Japanese clinical study conducted for neonatal seizures, 6 (60%) cases of adverse reactions (including abnormal laboratory values) occurred. Included in these were: respiratory depression in 3 patients (30%), decreased oxygen saturation in 2 patients (20%), decreased blood pressure in 1 patient (10%), bradycardia in 1 patient (10%), decreased body temperature in 1 patient (10%), Increased bronchial secretion in 1 patient (10%), and decreased urine output in 1 patient (10%; at the time of approval)

1.
Since the most serious side effects may include Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis), hypersensitivity syndrome, dependency, granulocytopenia, thrombocytopenia, hepatic dysfunction, and respiratory depression, the patient should be carefully monitored. If any of these symptoms is observed, appropriate measures such as discontinuation of administration should be taken. Clinical trials for status epilepticus have not been conducted.

II. Name

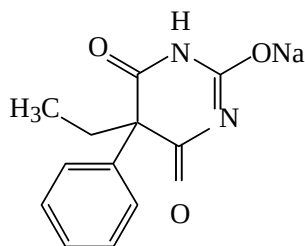
II-1. Trade name

- (1) Japanese name: Nobelbar® 250 mg for intravenous injection
- (2) English name : Nobelbar[®] 250mg for Injection
- (3) Origin of the name: Derived from NobelpharmaCo., Ltd., the company that developed the drug, and Phenobarbital.

II-2. Generic name

- (1) Japanese name (nomenclature): Phenobarbital sodium (JAN)
- (2) English name (nomenclature): Phenobarbital sodium (JAN, INN)

II-3. Structural or rational formula



II-4. Molecular formula and molecular weight

Molecular formula: $C_{12}H_{11}N_2NaO_3$ Molecular weight: 254.22

II-5. Chemical name (nomenclature)

5-Ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)- pyrimidinetrione, monosodium salt

II-6. Conventional name, other names, abbreviations, drug identification number

Abbreviation: PB-Na

Symbol No.: NPC-03 (clinical trial number)

II-7. CAS registration number

57-30-7

III. Active ingredients

III-1. Regulatory classification of active ingredients

Deleterious drugs, psychotropic drugs, addictive drugs, prescription drugs

III-2. Physicochemical Properties

- (1) Appearance/properties
White crystals or crystalline powder, odorless, bitter taste.
- (2) Solubility
Extremely soluble in water, slightly soluble in 95% ethanol, almost insoluble in diethyl ether, chloroform and dichloromethane.
- (3) Hygroscopicity
Hygroscopic and gradually decomposes when left in moist air.
- (4) Melting point (decomposition point), boiling point, freezing point
Approx. 274°C
- (5) Acid dissociation constant
pKa1: 7.41
pKa2: 11.77
- (6) Distribution coefficient
Not applicable
- (7) Other major characteristic values
pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water)

III-3. Stability of active ingredients under various conditions

In addition to the long-term storage test, confirmation tests (melting point and infrared absorption spectrum) and microbial limit tests were conducted at the beginning and at the end of the storage period in the long-term storage test. There was no change in any of the test items.

Type of test	Storage conditions	Storage method	Storage period
Long-term storage test	25±2°C/60±5%RH	Airtight container, dark area	60 months
Accelerated test	40±2°C/75±5%RH	Airtight container, dark area	6 months
Interim test	30±2°C/65±5%RH	Airtight container, dark area	12 months

III-4. Confirmation test methods for active ingredients

Infrared absorption
spectroscopy, qualitative
reaction of sodium salts

III-5. Determination of active ingredients

Liquid chromatography

IV. Formulations

IV-1. Dosage form

- (1) Dosage form classification, specifications and properties
White mass or powder, lyophilized injection
- (2) pH, osmotic ratio, viscosity, specific gravity, stable pH range, etc. in solution and dissolution
pH: 9.2 to 10.2 (when 1.0 g is dissolved in 10 mL water)
Osmotic pressure ratio: 2.5 to 2.6 (1.0 g dissolved in 10 mL of water, relative to saline)
- (3) Presence and type of special gases in the container of the injectable drug
dry nitrogen

IV-2. Composition of the preparation

- (1) Content of active ingredient (active constituent)
1 vial contains 274 mg of Phenobarbital Sodium
(250 mg as phenobarbital)
- (2) additive
not including

IV-3. Methods of preparation of injectable drugs

- 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours).
- 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate).

IV-4. Attention to dispersibility of suspensions and emulsions

Not applicable

IV-5. Stability of the formulation under various conditions

The drug was stored under various conditions and the following tests were conducted on it: property tests, confirmatory tests (infrared absorption spectroscopy and qualitative reaction of sodium salt), pH, solubility, related substances, moisture, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, sterility, and content. Other than moisture content, there was no change in any of the test items under any of the storage conditions. Moisture content tended to increase compared to the start of the study, but was thought to originate from the rubber stopper of the vial.

Type of test	Storage conditions	Storage method	Storage period
Long-term storage test	25±2°C/60±5%RH	The sealed container was placed in a paper box.	36 months
Accelerated test	40±2°C/75±5%RH	The sealed container was placed in a paper box.	6 months
Relative comparison test	40±2°C/75±5%RH	Sealed container in upright and inverted position*1 and placed in a paper box.	3 months
Rigorous testing	50±2°C	The sealed container was placed in a paper box.	3 months
	Light (1000±100 Lux at D65)	Sealed containers only. No packaging.	8 weeks

*1. Before starting storage, the rubber stopper side and the bottom of the vial were grasped with fingers and shaken up and down for about 1 minute with an amplitude of 10 to 20 cm, and then visually confirmed that the product was uniformly crushed.

IV-6. Stability after dissolution

The product was dissolved in water for injection and physiological saline solution and examined for stability.

Stability after dissolution in water for injection (10% solution, stored at 25±2°C in room under diffused light)

Test item	Storage period		
	At the start	6 hours	24 hours
Appearance	Clear and colorless	Clear and colorless	Clear and colorless
pH	9.6	9.6	9.6
Osmotic coefficient (compared to saline)	2.8	2.8	2.8
Foreign insoluble matter test	a	a	a
Content (% residual)	100.0	99.5	99.5
Concentration of related substances (%)	0.09	0.19	0.49

Stability after dissolution in saline solution (5% solution, stored at 25±2°C in room under diffused light)

Test item	Storage period		
	At the start	6 hours	24 hours
Appearance	Clear and colorless	Clear and colorless	Clear and colorless
pH	9.5	9.5	9.5
Osmotic coefficient (compared to saline)	2.5	2.5	2.5
Foreign insoluble matter test	a	a	a
Content (% residual)	100.0	100.0	99.5
Concentration of related substances (%)	0.09	0.19	0.49

a: Clear and free of clearly recognizable foreign insoluble matter

IV-7. Change in formulation with other agents (physicochemical change)

This document tests the physicochemical stability of the drug when combined with other drugs, and does not examine the physicochemical stability of other drugs.

Some of the drugs tested in the combination studies may have different dosage and administration of the phenobarbital, so please check the package insert of each drug before concomitant use.

Method

Nobelbar 250 mg for intravenous injection was dissolved in 10 mL of saline solution, and the test drug was added in the proportions shown in the table. The residuals were examined by appearance, pH, and liquid chromatography at room temperature and under room fluorescent light over time.

Preparation Method:

Precautions for application (excerpt)

- 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution (concentration after dissolution: 50 mg/mL of phenobarbital). After dissolving, it should be used immediately (within 6 hours).
- 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate).

Generic name, etc.	Conjugated drug name	Mixing ratio ¹⁾ Nobelbar: test drug	Storage conditions: room temperature, under indoor fluorescent light				
			Test item	Immediately after dissolution	1 hour	3 hours	6 hours
Glucose solution	Otsuka Sugar Solution 20%.	1:10	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.4	8.5	8.4	8.4
			Residual content (%)	100	100	100	100
Sodium bicarbonate	Meylon 84	1:10	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.0	8.1	8.2	8.2
			Residual content (%)	100	100	100	100
Replenishment solution	KN Replenishment solution MG3	1:100	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	5.3	5.2	5.2	5.1
			Residual content (%)	100	100	99	99
Calcium gluconate	Calcicol injection 8.5%	1:2.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.9	8.9	8.9	8.8
			Residual content (%)	100	100	100	100
Calcium chloride hydrate	Otsuka Calcium Chloride Injection 2%	1:10	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.3	8.6	8.5	8.6
			Residual content (%)	100	100	100	100
Multivitamin	Solita No. 3 ²⁾	1:1	Appearance	Pale yellow, clear	Pale yellow, clear	Pale yellow, clear	Pale yellow, clear
			pH	9.2	9.2	9.1	9.1
			Residual content (%)	100	101	101	100
Complete amino acid mix	Pleamin -P Injection	1:100	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	7.1	7.0	7.1	7.0
			Residual content (%)	100	100	100	100
Cefazolin sodium hydrate	Cefamedin α for injection 1g ³⁾	1:5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear yellowish-white
			pH	8.6	8.5	8.3	8.1
			Residual content (%)	100	100	100	100
Ampicillin sodium and Cloxacillin sodium hydrate	Bicillin S ⁴⁾ for injection	1:0.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	9.4	9.2	9.0	8.9
			Residual content (%)	100	100	100	100
Furosemide	Lasix Injection 20 mg	1:1	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	9.3	9.3	9.2	9.2
			Residual content (%)	100	101	100	100
Potassium canrenoate	Soldactone 100mg ³⁾	1:5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	9.6	9.6	9.5	9.4
			Residual content (%)	100	100	99	99
Gabexate mesylate	FOY for injection 100 ⁵⁾	1:250	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	7.6	7.2	7.0	6.7
			Residual content (%)	100	100	100	100
Nafamostat mesylate	Futhan for injection 10 ⁵⁾	1:250	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	7.7	7.4	7.1	6.9
			Residual content (%)	100	100	99	98
Sodium heparin	Novo Heparin Injection 1000	1:2.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	9.3	9.3	9.3	9.2
			Residual content (%)	100	99	100	100

Generic name, etc.	Conjugated drug name	Mixing ratio ¹⁾ Nobelbar: test drug	Storage conditions: room temperature, under indoor fluorescent light				
			Test item	Immediately after dissolution	1 hour	3 hours	6 hours
Calcium heparin	Calcium heparin injection	1:5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	9.0	9.0	8.9	8.9
			Residual content (%)	100	100	100	101
Adrenalin	Bosmin injection	1:0.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Slight yellowish-red, clear
			pH	8.7	8.7	8.7	8.7
			Residual content (%)	100	100	100	100
Aminophylline hydrate	Neophyllin injection 250 mg	1:5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless (slight white precipitation occurred)
			pH	9.2	9.1	9.1	9.1
			Residual content (%)	100	101	101	100
Sodium hydrocortisone succinate	Solu-Cortef injection 100 mg	1:1	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.7	8.6	8.5	8.4
			Residual content (%)	100	100	100	100
Sodium hydrocortisone phosphate	Hydrocortone injection 100 mg	1:1	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.7	8.6	8.6	8.6
			Residual content (%)	100	100	100	100
Dexamethasone sodium phosphate	Decadron phosphate injection	1:0.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	8.8	8.8	8.8	8.8
			Residual content (%)	100	100	101	100
Albumin	Human Serum Albumin Wf25%	1:10	Appearance	Yellow, clear	Yellow, clear	Yellow, clear	Yellow, clear
			pH	7.1	7.1	7.1	7.1
			Residual content (%)	100	99	99	99

Do not mix the following drugs.

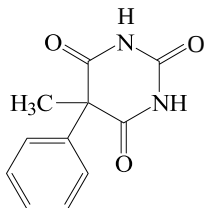
Generic name, etc.	Conjugated drug name	Mixing ratio ¹⁾ Nobelbar: test drug	Storage conditions: room temperature, under indoor fluorescent light				
			Test item	Immediately after dissolution	1 hour	3 hours	6 hours
Dopamine hydrochloride	Inovan injection 50 mg	1:2.5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless (slight white precipitation occurred)	Clear and colorless (slight white precipitation occurred)
			pH	8.1	8.1	8.2	8.2
			Residual content (%)	100	100	100	80
Potassium L-Aspartate	Aspara Potassium Injection 10mgEq	1:5	Appearance	Clear and colorless	Clear and colorless	Clear and colorless (slight white precipitation occurred)	Clear and colorless (slight white precipitation occurred)
			pH	7.9	7.9	8.0	8.0
			Residual content (%)	100	100	100	99
Menatetrenone	Kaytwo N injection 10mg	1:1	Appearance	Cloudy, pale yellowish-white suspension	Pale yellowish-white suspension	Pale yellowish-white suspension	Pale yellowish-white suspension
			pH	8.6	8.6	8.6	8.6
			Residual content (%)	100	100	100	100
Vecuronium bromide	Masculax for Intravenous Injection 4mg ⁶⁾	1:0.5	Appearance	White suspension	Clear and colorless (slight white precipitation occurred)	Clear and colorless (slight white precipitation occurred)	Clear and colorless (slight white precipitation occurred)
			pH	7.4	7.4	7.4	7.5
			Residual content (%)	100	Not measurable	Not measurable	Not measurable
Amikacin Sulfate	"Banyu" Amikacin sulfate for injection 100mg ⁷⁾	1:0.5	Appearance	White suspension	White suspension	White suspension	White suspension
			pH	7.5	7.5	7.8	7.9
			Residual content (%)	Not measurable	Not measurable	Not measurable	Not measurable
Gentamicin Sulfate	Gentacin Injection 40	1:0.5	Appearance	Clear and colorless	Clear and colorless (white precipitation occurred)	Clear and colorless (white precipitation occurred)	Clear and colorless (white precipitation occurred)
			pH	7.4	8.0	8.0	8.0
			Residual content (%)	100	33	38	Not measurable
Erythromycin lactobionate	Erythrocin for intravenous infusion	1:10	Appearance	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
			pH	7.9	7.8	7.9	7.9
			Residual content (%)	100	93	92	90

- 1) Volume: volume
- 2) Solita No. 1, No. 2, and No. 3 are all included in the packaging, but only No. 3 was used.
- 3) Dissolve in 10mL of saline solution
- 4) Dissolved in 1mL of water for injection
- 5) Dissolved in 500mL of 5% glucose injection solution
- 6) Dissolve in 1mL of the attached dissolving solution
- 7) Dissolve in 1mL of saline solution

IV-8. Electrolyte concentration
Not applicable

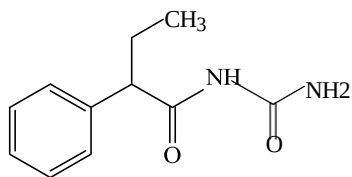
IV-9. Adulterants that may be contaminants

Analogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug are as follows



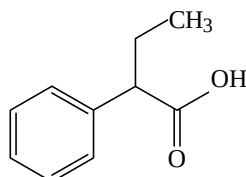
5-methyl-5-phenyl-barbituric acid

Analogues that may be generated in the formulation manufacturing process are as follows



2-phenylbutyrylurea

or



2-phenylbutyric acid

IV-10. Biological test methods
Not applicable

IV-11. Confirmation test methods for active ingredients in preparations
Infrared absorption
spectroscopy, qualitative
reaction of sodium salts

IV-12. Methods for determination of active ingredients in preparations
Liquid chromatography

IV-13. Titer
Not applicable

IV-14. Material of the container
Colorless glass,
butyl rubber
stopper

IV-15. Other
Not applicable

V. Treatment with the drug

V-1. Indications/effects

Neonatal seizures,
status epilepticus

Precautions for use in relation to indications/effects

Because of its slow onset of action and long duration of action, faster-acting agents should be used as a first-line treatment for patients with status epilepticus, with the drug used as a second-line treatment or later. (See the "Pharmacodynamics" section)

<Explanation>

Since the onset of action of this drug is slower than that of benzodiazepines and its action is sustained over a longer period of time, it is appropriate that a fast-acting drug (diazepam for intravenous administration) be the first choice when administered to patients with status epilepticus, and this drug be used as the second or subsequent choice, as recommended in various medical literature and treatment guidelines.

The treatment guidelines for status epilepticus in Japan include the treatment guidelines of the Japanese Society of Neurology, which, as in other countries, state that the first-line drug diazepam should be administered intravenously, the second-line drug phenytoin should be administered intravenously, and the third-line drug phenobarbital should be administered intravenously (*). The guidelines are currently being revised by the relevant academic societies.

(*: Note that the intravenous formulation is not marketed)

V-2. Dosage and administration

Neonatal seizure

Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously.

Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily.

Status epilepticus

Phenobarbital administered intravenously at a dose of 15 to 20 mg/kg once daily.

Precautions related to dosage and administration

<Neonatal seizures and status epilepticus>

Since impaired consciousness, hypotension, and respiratory depression may occur, it is advisable to measure the blood concentration of the drug in order to make appropriate dose adjustments. If respiratory depression is observed, appropriate measures such as artificial respiration should be taken immediately. (See the "Administration to children" and "Overdose" sections.)

<Neonatal seizures>

In newborns, the drug should be administered slowly over 5 to 10 minutes. However, a more gradual administration should be considered depending on the patient's condition. When administering additional doses, the patient's condition should be monitored and a sufficient interval should be allowed after the initial dose (See the "Clinical Results" section).

<Status epilepticus>

In children and adults, the drug should be administered slowly over a period of at least 10 minutes. However, the dosage rate should not exceed 100 mg/min.

<Explanation>

Because increased blood concentrations may cause impaired consciousness, decreased blood pressure, and respiratory depression,

The measurement of blood levels of phenobarbital is recommended at the time of administration. If the administration rate is too fast, the side effects are at risk of occurring, again due to a rapid increase in blood concentration. The dosage for neonatal seizures should be administered slowly over 5 to 10 minutes, in light of the results of clinical studies.

The dosage for status epilepticus is to be administered slowly over at least 10 minutes, and the dosage rate is not to exceed 100 mg/minute. The descriptions in international standard textbooks, foreign formularies, and national and international review articles for both children and adults vary.

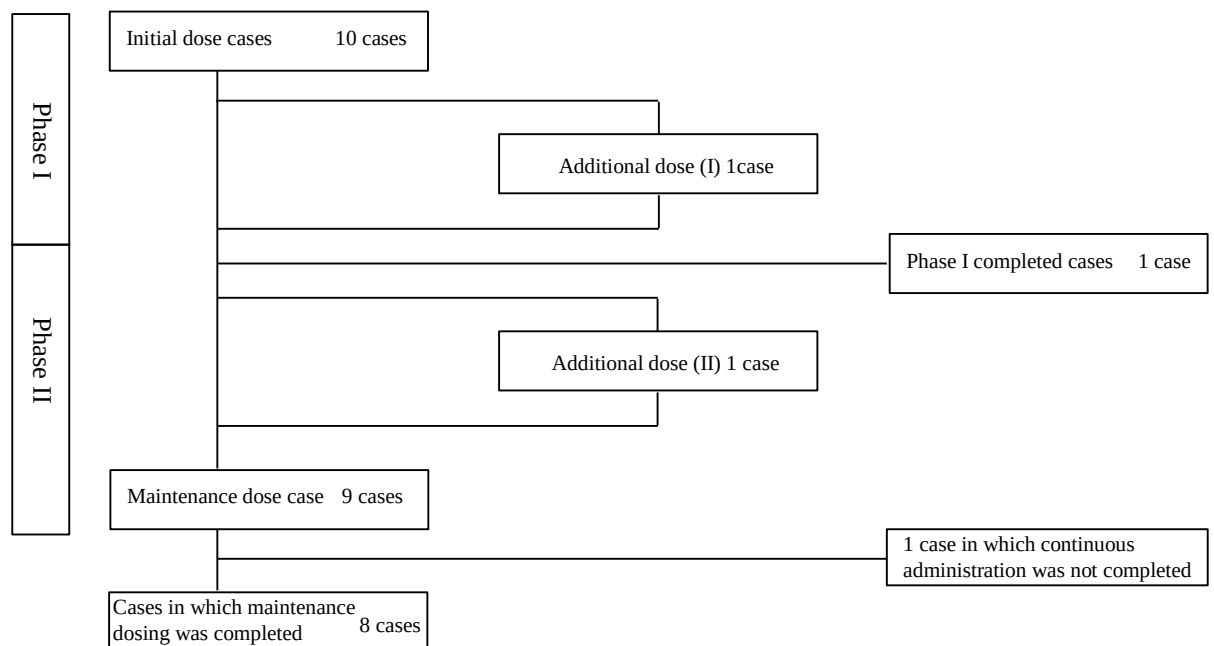
V-3. Clinical outcomes

(1) Clinical efficacy

Neonatal seizures¹⁾

Ten subjects were included in the investigator-initiated clinical trial, and no subjects were excluded from the analysis. Age averaged 2.5 days old (range: 1-5 days old), birth weight averaged 2,867.7 g (range: 1,144-3,796 g), and weeks of gestation averaged 38.23 weeks (range: 33.1-41.1 weeks). Of the subjects who received the study drug, there were no very low birth weight infants weighing less than 1,000 g, but there were two preterm infants born at less than 37 weeks of gestation.

A breakdown of the subjects in this study is shown below.



Doses in Phase I averaged 19.84 mg/kg (range: 17.5-20.8 mg/kg) for the initial dose. An additional dose (I) was administered in one patient, 20.1 mg/kg. In this patient, the frequency of seizure-like movements decreased after the first dose (efficacy evaluation at 30 minutes after the first dose: effective), but because the seizures continued intermittently after the first dose, an additional dose (I) was administered, and the seizures disappeared after the additional dose. One case was discontinued after the end of Phase I. This was a case in which an additional dose (I) was administered, but the dose was discontinued without conducting Phase II because a prohibited drug (pentobarbital sodium) was used to sedate the patient for CT and MRI examinations to investigate the cause of neonatal seizures.

Phase II was conducted with 9 patients. An additional dose (II) was administered in one patient, 17.5 mg/kg.

In the patient in question, convulsions developed approximately 12 hours after the first dose, and an additional dose (II) was administered to treat the convulsions, which were suppressed until similar convulsions developed approximately 9 hours after the additional dose (II). Maintenance dosing was performed in 9 patients and ranged from 2.2 to 5.0 mg/kg/day, with no changes except for one patient who received 5 mg/kg/day for 3 days and then changed to 2.5 mg/kg/day. Of the 9 patients who received maintenance dosing, one was discontinued on the third day of maintenance dosing due to the use of a prohibited concomitant drug (pentobarbital sodium) for sedation for an MRI scan. The prescribed six maintenance doses were administered in eight cases.

Drug blood concentrations ranged from 18.8 to 25.8 µg/mL at 2 hours after the first dose in 9 patients

for whom no additional dose (I) was administered, and 42.8 µg/mL in 1 patient for whom additional dose (I) was administered. Regarding the blood concentration during maintenance dosing, the blood concentration was slightly high at 45.3 µg/mL in one subject who received the maintenance dose of 5.0 mg/kg/day for 3 days and then switched to 2.5 mg/kg/day, but the other subjects generally maintained stable blood concentrations between 20 and 40 µg/mL.

Efficacy was excellent in all 10 patients for the primary endpoint of efficacy at 30 minutes after the first dose (or additional dose (I)). Nine patients had a significant response at 30 minutes after the first dose, and one patient had a significant response at 30 minutes after the additional dose (I). The secondary endpoint of efficacy at 1 hour after the first dose (or additional dose (I)) was also significant in all patients. The evaluation by the video review committee, which examined the validity of the diagnosis and efficacy evaluation of neonatal seizures based on videos taken of each subject as a third-party organization, showed 7 cases of significant efficacy, 1 case of efficacy, and 2 cases of unknown (due to imaging reasons), in good agreement with the evaluation by the primary investigator or sub-investigator.

¹⁾ Susumu Ito, *et al.* Clinical trial for neonatal seizures: Physician-initiated clinical trial (in-house document)

Status epilepticus ²⁻⁷⁾

Not applicable (Clinical trials have not been conducted in Japan)

Note) The application was submitted and approved after analyzing and evaluating the domestic and foreign literature, as the drug has already been used in clinical settings in sufficient formulation and pharmacological studies.

<Major reports on status epilepticus>

● Subject: Children

Reported by	Number of subjects	Age	Main etiology	Intravenous dosage	Efficacy	Safety
Kokwaro ²⁾	12 cases	25 months (median: 7-62 months)	• Tropical malaria	Initial dose: 15 mg/kg Duration: 20 min Maintenance dose: 5 mg/kg (after 24 and 48 hours)	66%	Hypoxia 1 case 1 death likely due to various factors (respiratory failure)
Sugita ³⁾	56 cases	N/A	• Epilepsy: 23 cases • Central nervous system infections: 15 cases • Febrile seizures: 11 cases • Other: 7 cases	15-20 mg/kg Dosing rate: 100 mg/min	Unknown (Effective in 6 cases)	Unknown (Respiratory depression is listed as a common side effect, although not specifically mentioned)

● Target: Adults

Reported by	Number of subjects	Age	Main etiology	Intravenous dosage	Efficacy	Safety
Mayer ⁴⁾	21 of 26 cases	63 years old (21 to 97 years old)	- Nonorganic - Epilepsy-related - Organic	10.3mg/kg (average dose)	48-57%	Refractory status epilepticus (26 patients): respiratory failure 88%, fever 81%, pneumonia 65%, hypotension 65%, anemia treated with blood transfusion 50%, urinary tract infection 46%, bacteremia 46%, Tachycardia 42%, Hyperglycemia 31%
Treiman ⁵⁾	Obvious status epilepticus: 91 cases	58.6±15.6 years old	- Neurological causes - Life-threatening medical conditions - Cardiopulmonary arrest, etc.	15 mg/kg Dosing rate: 100mg/min or less	58.2%	Hypotension 34.1%, decreased ventilation 13.2%, arrhythmia 3.1%
	Slight status epilepticus 33 cases	62.0±15.1 years old			24.2%	Hypotension 48.5%, decreased ventilation 15.2%, arrhythmia 9.1%
Shaner ⁶⁾	18 cases	55.9±19.4 years old	- Alcohol withdrawal: 5 cases - Sub-therapeutic doses of antiepileptic drugs: 7 cases - Organic lesions: 7 cases - Toxicity/metabolic 2 cases	5-23 mg/kg Dosing rate: 100 mg/min	Efficacy rate as single agent: 61%	2 cases of hypotension, 1 case of arrhythmia

● Target: Unknown age

Reported by	Number of subjects	Age	Main etiology	Intravenous dosage	Efficacy	Safety
Czapinski ⁷⁾	60 cases	-		10-20 mg/kg Dosing time: 1 hour	83.3%	Adverse reactions occurred in 23.3% (details unknown)

²⁾ Kokwaro GO, *et al.* Br J Clin Pharmacol. 2003;56:453

³⁾ Sugita T, *et al.* Pediatrics. 1987;19:1329

⁴⁾ Mayer SA, *et al.* Arch Neurol. 2002;59:205

⁵⁾ Treiman DM, *et al.* N Engl J Med. 1998;339:792

⁶⁾ Shaner DM, *et al.* Neurology. 1988;38:202

⁷⁾ Czapinski P. J Neurol. 1995;424:S83

(2) Clinical pharmacology studies: Tolerability studies
Not applicable

(3) Exploratory study: Dose-response exploratory study
Not applicable

(4) Validation test
Not applicable

(5) Therapeutic Use

1) Use-results surveys, special surveys, and post-marketing clinical trials
No applicable data at this time

2) Description of what is planned to be conducted as a condition of approval or a summary of the tests conducted
Not applicable

VI. Pharmacodynamics

VI-1. Pharmacologically relevant compounds or groups of compounds

Phenytoin
Carbamazepine
Diazepam

VI-2. Pharmacological action

- (1) Site of Action/Mode of Action ^{8,9)}Site of Action:
CNS Mode of Action:

Phenobarbital, like the other antiepileptic drugs phenytoin, carbamazepine, and diazepam, activates GABA_A receptors and may also act directly on chloride channels, opening them. Phenobarbital has been reported to work by increasing the duration of GABAergic opening of chloride channels, and diazepam by increasing the frequency of GABAergic opening of chloride channels, thereby increasing intracellular influx of chloride ions.

⁸⁾ Nami Obara. Japanese Journal of Neuropsychopharmacology. 1995;15:31

⁹⁾ Twyman RE, *et al.* Ann Neurol. 1989;25:213

- (2) Test results supporting the drug's efficacy

- 1) Maximal Electroshock Seizure (MES Method)¹⁰⁾

The effect of subcutaneous administration of phenobarbital to pure strain mice weighing 20 g or more on the suppression of seizures in the MES method is shown below. Small doses of phenobarbital prolonged the tonic flexion phase and shortened the tonic extension phase, whereas large doses abolished the tonic extension phase and produced a tonic flexion phase followed by a clonic phase, and all seizures disappeared with larger doses.

Seizure suppression effect in MES method (mice)

Dose (mg/kg, sc)	Ankylosing flexion phase	Tonic-extensile phase	Clonic phase
	Average seizure time (seconds)		
0	1	12	6
20	3	8	6
30	5	5	10
50	4	0	5
75	0	0	4
100	0	0	0

Current: 50 mA, energization time: 0.2 sec, (mean value, n=10, standard deviation, etc. not shown)

¹⁰⁾ Tanaka, J., System of Clinical Pharmacology, Vol. 4, Tokyo, Nakayama Shoten, 1963,88

2) Electroconvulsive Threshold Method (ET Method)¹¹⁾

In SD rats, the anticonvulsant protective index using the ET method is shown below. Phenytoin was ineffective with this approach, but phenobarbital and other anticonvulsants showed efficacy.

Anticonvulsant protective index, ET method (rat)

Compound	Dosing regimen	Protective index
Phenobarbital	sc	1.75±0.19
Phenytoin	sc	Ineffective
Trimethadione	sc	1.51±0.17
Phenylacetylurea	po	18.7±3.70

Phenylacetylurea is suspended in 10% gum arabic and administered orally, others are dissolved in water and administered subcutaneously (Mean ± SE, n=5-6).

Protective index: $\text{TD}_{50}(\text{mg/kg})/\text{ED}_{50}(\text{mg/kg})$

TD₅₀ : Dose which produces ataxia in 50% of rats.

ED₅₀ : Dose which reduces duration of tonic-extension phase of supramaximal seizures by 50% in rats.

¹¹⁾ Swinyard EA. J Am Pharm Assoc. 1949;38:201

3) Metrazol-induced seizures¹²⁾

An anticonvulsant drug was orally administered to mice (20-25 g) and the central stimulant metrazol (100 mg/kg) inhibition against induced seizures is shown below. For comparison, the amount of inhibition against minimal seizures with 80 mg/kg metrazol and the amount of inhibition in the MES method are also shown. Phenytoin inhibited only tonic seizures, whereas phenobarbital sodium inhibited all convulsive manifestations.

Suppressive effect of anticonvulsants on high-dose metrazol seizures (mice)

	PD50 (mg/kg, po)				
	Metrazol				MES method
	80 mg/kg, sc	100 mg/kg, sc			
	Minimal seizures	Clonic	Tonic	Death	
Phenobarbital sodium	25.3	38.2	20.7	26.8	18.7
Phenytoin	Ineffective	Ineffective	12.0	Ineffective	12.1
Trimethadione	465.4	571.4	498.0	459.4	864.0

PD50 : Protective dose in 50% of mice. MES method: 48 mA, 0.2 sec , (mean values, n=10 to 15)

¹²⁾ Ahmad A, *et al.* Jpn J Pharmacol. 1969;19:472

4) Brain protective action¹³⁾

Phenobarbital sodium was administered 150 mg/kg intraperitoneally 1 hour before decapitation of mice, and the amount of change in the parameter was measured 10 seconds after decapitation. Phenobarbital sodium suppressed the variability of all parameters. These results suggest that phenobarbital may prevent brain cell damage in hypoxic (ischemic) conditions by suppressing brain metabolism, minimizing the consumption of available energy, and inhibiting acidosis caused by lactate.

Effects on brain parameter changes (10 sec after decapitation) (mice)

	Parameter change (μmoles/g/min)	
	Control	Phenobarbital sodium (150 mg/kg, ip)
P-creatine	11.28	4.74
Adenosine triphosphate	2.64	0.90
Glucose	6.18	3.90
Glycogen	2.40	0.18
Lactate	13.14	6.28

Mean, phenobarbital sodium (150 mg/kg) administered intraperitoneally 1 h before decapitation, (n=12)

¹³⁾ Yasuda H. Arch int Pharmacodyn. 1979;242:77

VII. Items related to pharmacokinetics

VII-1. Changes in Blood Concentration and Measurement Methods

- (1) Therapeutically effective blood concentration
The therapeutically effective blood phenobarbital concentration is encompassed by 15-40 $\mu\text{g/mL}$ (as anticonvulsant effect) in domestic and foreign textbooks, European and American drug collections, and medicinal dosage handbooks.
- (2) Time to reach maximum blood concentration 1)
Single dose
Not applicable

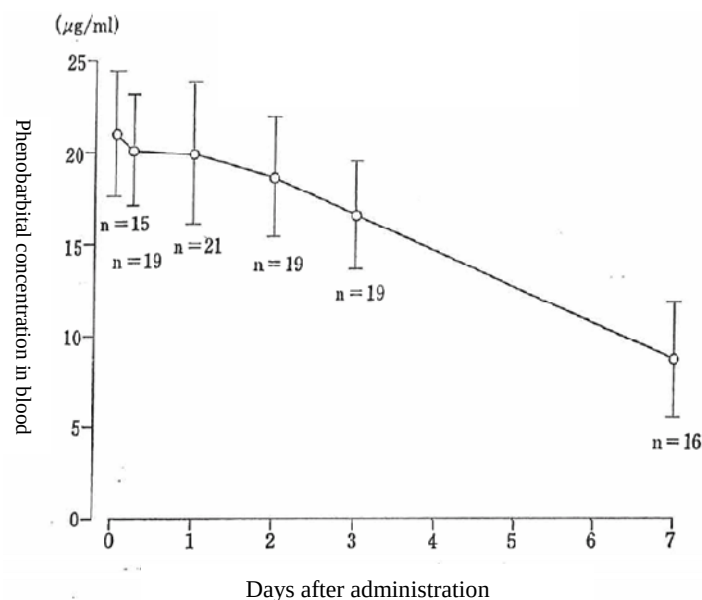
2) Repeated dosing
Not applicable
- (3) Blood concentrations at normal doses^{1,14)}

Phenobarbital sodium was administered intravenously for neonatal seizures at an initial dose of 20 mg/kg, an additional dose at the same dose if seizures were not controlled, and a maintenance dose of 2.5-5 mg/kg once daily. The blood concentration at 2 hours after the first dose (9 patients) was $22.38 \pm 2.34 \mu\text{g/mL}$ (mean $\pm$ standard deviation) [18.8-25.8 $\mu\text{g/mL}$ (min-max)] and 42.8 $\mu\text{g/mL}$ in one patient who received an additional dose (30 minutes after the first dose). The blood concentration before the last maintenance dose (at the time of discontinuation) was $27.65 \pm 9.46 \mu\text{g/mL}$ (18.7-45.3 $\mu\text{g/mL}$) in 10 subjects.

¹⁾ Susumu Ito, *et al.* Clinical trial for neonatal seizures: Physician-initiated clinical trial (in-house document)

Pharmacokinetic parameters of a single intravenous dose of phenobarbital sodium were studied in 29 Japanese children with neonatal seizures.

Change in blood concentration of phenobarbital sodium at 20 mg/kg intravenously



¹⁴⁾ Takashi Shibata, *et al.* Hospital Pharmacy. 1991;17:421

- (4) Blood concentration at which intoxication symptoms develop¹⁵⁾
Above 40-45 µg/mL, drowsiness, nystagmus, and ataxia occur, and in severe cases of poisoning, coma may result. Respiration is suppressed starting in the early stage, pulse is weak, skin has cold sweats, and body temperature falls. There is also a risk of pulmonary complications and kidney damage.

¹⁵⁾ Mamoru Yamashita. *Clinical Pediatrics*. 1987;40, Unabridged: 2923

VII-2. Drug kinetic parameters

- (1) Absorption rate constant
Not applicable (this is an intravenous formulation).
- (2) Bioavailability
Not applicable (this is an intravenous formulation).
- (3) Elimination rate constant¹⁴⁾
The rate constant (Ke) of disappearance of a single intravenous dose of 20 mg/kg of phenobarbital sodium in Japanese infants with neonatal seizures was $0.00512 \pm 0.00297 \text{ hr}^{-1}$.
¹⁴⁾ Takashi Shibata, *et al.* *Hospital Pharmacy*. 1991;17:421
- (4) Clearance^{16,17)}
<Reference>
Newborns (0-4 weeks, 5-10 mg/kg, IV): $5.71 \times 10^{-4} \text{ mL/h/kg}$ Infants (2-3 months, 10 mg/kg, IV): $9.59 \times 10^{-4} \text{ mL/h/kg}$
Infants (4-12 months, 10 mg/kg, IV): $7.01 \times 10^{-4} \text{ mL/h/kg}$ Child (>12 months, 10 mg/kg, IV): $8.12 \times 10^{-4} \text{ mL/h/kg}$
¹⁶⁾ Heimann G, *et al.* *Eur J Clin Pharmacol*. 1977; 12:305
Adult epilepsy patients (90 mg/day, IV): $0.0709 \pm 0.0268 \text{ mL/min/kg}$ (Day 1)
¹⁷⁾ Browne TR, *et al.* *J Clin Pharmacol*. 1985;25:51
- (5) Distribution volume^{14,17)}
The volume of distribution (Vd) of a single intravenous dose of 20 mg/kg of phenobarbital sodium in a Japanese neonatal seizure patient was $0.924 \pm 0.247 \text{ L/kg}$.
¹⁴⁾ Takashi Shibata, *et al.* *Hospital Pharmacy*. 1991;17:421
<Reference>
Phenobarbital sodium was administered intravenously at 90 mg/day to an adult epileptic patient with a volume of distribution (Vd) of $0.624 \pm 0.045 \text{ L/kg}$ (day 1).
¹⁷⁾ Browne TR, *et al.* *J Clin Pharmacol*. 1985;25:51
- (6) Plasma protein binding rate^{18,19)}
Newborns and children: protein binding rate (%) 0-3 months
 $37.0 \pm 4.2\%$ (%)
4 months to 2 years old: 45.2 ± 3.5
2-15 years old $45.2 \pm 3.0\%$ (%)
¹⁸⁾ Tanaka, J., *et al.* *Clinical Pediatrics*. 1984;37:2329
<Reference>
Adult: protein binding rate (%) 50.5-52.5
¹⁹⁾ Ehrnebo M, *et al.* *Eur J Clin Pharmacol*. 1971;3 :189

VII-3. Absorption

Not applicable (this is an intravenous formulation)

VII-4. Distribution

(1) Blood-brain barrier crossing ^{20,21)}

<Reference>

The drug crosses the blood-brain barrier. The O/P ratio between cerebral phenobarbital concentration (O) and plasma phenobarbital concentration (P) was 0.82 ± 0.22 in the cerebrum, showing a good correlation with the blood concentration.

<Reference>

Brain O/P ratios were compared with the duration of phenobarbital treatment, and no accumulation of phenobarbital in the brain due to the extended duration of treatment was observed.

²⁰⁾ Miho Ohki. Journal of Nagoya City Univ. 1981;32:56

²¹⁾ Painter MJ, *et al.* Neurology. 1981;31:1107

(2) Transfer to fetus ²²⁾

<Reference>

Phenobarbital equivalent to 95% of the concentration in maternal serum was detected in human cord blood, suggesting placental passage.

²²⁾ Melchior JC, *et al.* Lancet. 1967;2(7521):860

(3) Migration into milk ²³⁾

<Reference>

Phenobarbital equivalent to 50% of maternal serum was detected in breast milk, and transfer to milk was observed. In addition, *p*-hydroxyphenobarbital (PHPB) was detected in breast milk at the same level as in maternal serum, indicating that PHPB, the major metabolite, is transferred into milk as phenobarbital.

²³⁾ Nau H. *et al.* Eur J Clin Pharmacol. 1980 ;18 :31

(4) Migration to spinal fluid

Not applicable

(5) Migratability to other tissues ²⁰⁾

Tissue translocation of phenobarbital was high in the liver, followed by the lungs, spleen, kidneys, and pancreas. The tissue and plasma concentrations of phenobarbital show a good correlation, and the translocation of phenobarbital into the tissues is considered to be proportional to the plasma concentration. The O/P ratios of tissue phenobarbital concentration (O) to plasma phenobarbital concentration (P) were 1.38 ± 0.38 for liver, 1.27 ± 0.44 for lung, 1.10 ± 0.60 for spleen, 1.03 ± 0.38 for kidney and pancreas.

The organ was 0.99 ± 0.41 .

²⁰⁾ Miho Ohki. Journal of Nagoya City Univ. 1981;32:56

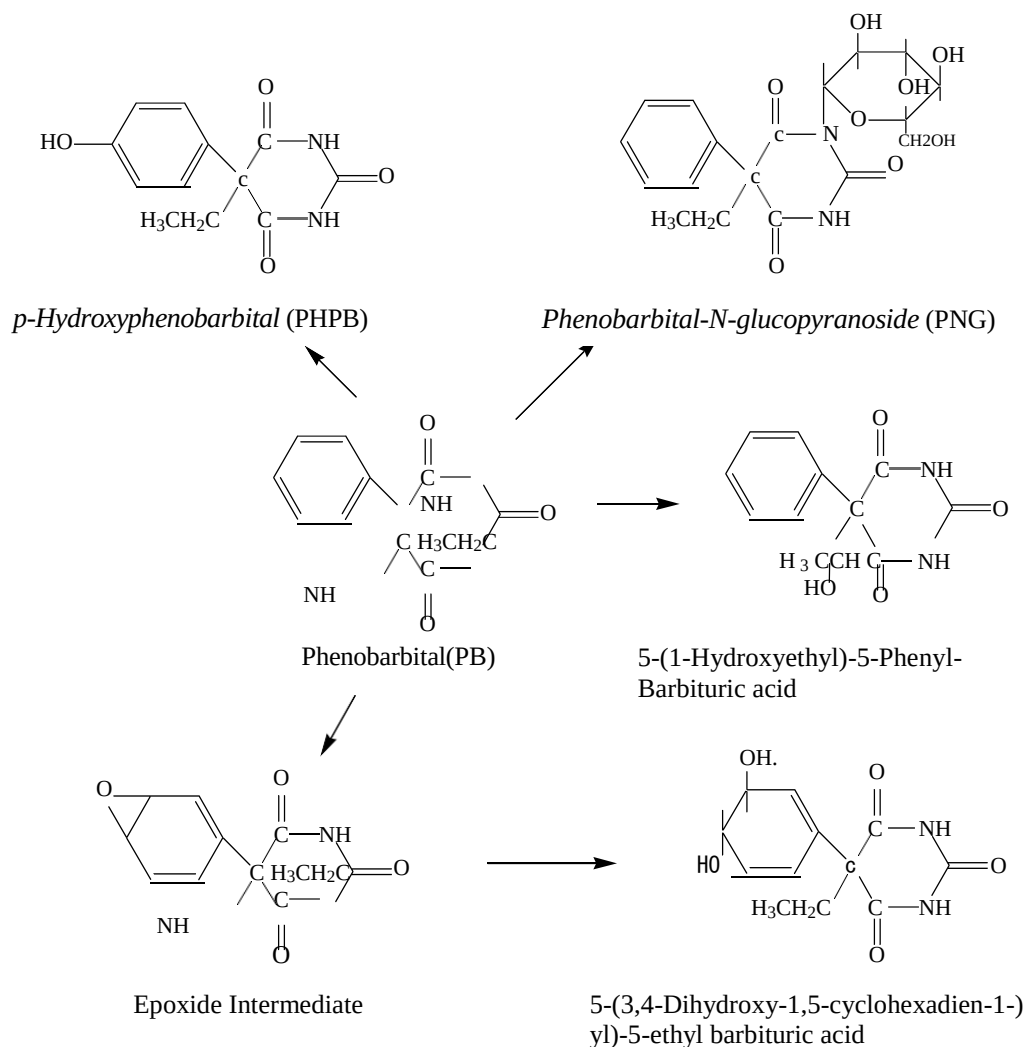
VII-5. Metabolism

(1) Metabolic sites and routes of metabolism

It is metabolized mainly in the liver.

<Reference>

Phenobarbital is metabolized in the liver mainly via *p*-hydroxyphenobarbital (PHPB) to glucuronide conjugates and phenobarbital-N-glucopyranoside (PNG). As other trace metabolites, 5-(3,4-Dihydroxy-1,5-cyclohexadien-1-yl)-5-ethyl barbituric acid, an intermediate metabolite of epoxide, and 5-(1-hydroxyethyl)-5- phenylbarbituric acid, in which the ethyl side chain is hydroxylated.



- (2) Molecular species of enzymes involved in metabolism (CYP450, etc.)^{24,25)}
 It is metabolized mainly by CYP2C9, CYP2C19 and CYP2E1, UGTs and enzymes involved in N-glucosidation. There are no identified reports of enzymes related to N-glucosidation metabolism. In newborns, metabolism to PNG is not developed at birth and is established by around 20 days of age, after which it is suggested to become the primary pathway of phenobarbital metabolism.
- ²⁴⁾ Ryuichi Kato, Clinical Pharmacokinetics, Tokyo, Nankendo, 2001, 133
²⁵⁾ Chiba, H. Jpn. J. Pharm. Health Care Sci. . 1994;76:2214
- (3) Presence or absence of first-pass effect and percentage of first-pass effect
 Not applicable
- (4) Presence or absence and ratio of metabolite activity²⁶⁾
 <Reference>
 The major metabolite PHPB has been reported to have very weak sedative effects in animal studies (dogs and mice).
- ²⁶⁾ Butler TC. J Pharmacol Exper Ther. 1956;116:326

- (5) Kinetic parameters of active metabolites
Not applicable

VII-6. Excretion

- (1) Excretion site ²⁷⁾
The major route of excretion is in the urine.
²⁷⁾ Tang BK. Drug Metab Dispos. 1979;7:315
- (2) Excretion rate ²⁷⁾
<Reference>
In urine, 68-81% of the administered dose was excreted, and PHPB, glucuronide conjugate of PHPB, PNG, and unchanged forms were observed as metabolites.
²⁷⁾ Tang BK. Drug Metab Dispos. 1979;7:315
- (3) excretion rate
Not applicable

VII-7. Removal rate by dialysis, etc.

- (1) Peritoneal dialysis
Not applicable
- (2) Hemodialysis ²⁸⁾
The decrease in blood concentrations is approximately 30-70%.
²⁸⁾ Hirai, M., *et al.* Brain and Development. Brain and Development. 1983;15:153
- (3) Direct blood perfusion
Not applicable

VIII. Safety (precautions for use, etc.)

VIII-1. Warnings and reasoning for them

Not stipulated at this stage.

VIII-2. Contraindications and reasoning for them (including general rules used as contraindications)

Contraindications (should not be administered to the following patients)

- (1) Patients with a history of hypersensitivity to any component of this drug or to barbiturates
- (2) Patients with acute intermittent porphyria [porphyrin synthesis may increase and symptoms may worsen].
- (3) Patients receiving voriconazole or tadalafil (Adsilca) (see the "Interactions" section)

<Explanation>

- (1) The information is provided as a general precaution.
- (2) The porphyrin synthesis may increase and symptoms may worsen due to the porphyrin synthase-inducing effect of this drug.
- (3) The drug's induction of hepatic drug-metabolizing enzyme (CYP3A4) may accelerate the metabolism of these drugs and decrease their blood concentrations (see "Contraindications to Concomitant Use" in "Interactions").

VIII-3. Indication/effect-related precautions and reasons for use

Indication/effect-related precautions and reasons for use

Because of its slow onset of action and long-acting nature, it is recommended that fast-acting agents be used as first-line therapy in patients with status epilepticus, and this drug be used as a second-line therapy or later.

(See the "Pharmacodynamics" section)

<Explanation>

Since the onset of action of this drug is slower than that of benzodiazepines and its action is sustained and long-acting, it is appropriate that a fast-acting drug (diazepam for intravenous administration) be the first choice when administered to patients with status epilepticus, and this drug be used as the second or more-subsequent choice, as recommended in various medical literature and treatment guidelines.

The treatment guidelines for status epilepticus in Japan include the treatment guidelines of the Japanese Society of Neurology, which, as in other countries, state that the first-line drug diazepam should be administered intravenously, the second-line drug phenytoin should be administered intravenously, and the third-line drug phenobarbital should be administered intravenously(*). The guidelines are currently being revised by the relevant academic societies.

(*: Note that the intravenous formulation is not marketed)

VIII-4. Precautions related to dosage and administration and reasoning for them

Precautions related to dosage and administration and reasoning for them

<Neonatal seizures and status epilepticus>

Since impaired consciousness, hypotension, and respiratory depression may occur, it is advisable to measure the blood concentration of the drug in order to make appropriate dose adjustments. If respiratory depression is observed, appropriate measures such as artificial respiration should be taken immediately. (See the "Administration to Children" and "Overdose" sections.)

<Neonatal seizures>

In newborns, the drug should be administered slowly over 5 to 10 minutes. However, a more gradual administration should be considered depending on the patient's condition. When administering additional doses, the patient's condition should be monitored and a sufficient interval should be allowed after the initial dose (See the "Clinical Results" section).

<Status epilepticus>

In children and adults, the drug should be administered slowly over a period of at least 10 minutes. However, the dosage rate should not exceed 100 mg/min.

<Explanation>

Since high blood levels may cause impaired consciousness, hypotension, and respiratory depression, measurement of blood levels of the drug is recommended at the time of administration. If the administration rate is too fast, the side effects are at risk of occurring, again due to a rapid increase in blood concentration.

The dosage for neonatal seizures should be administered slowly over 5 to 10 minutes, in light of the results of clinical studies.

The dosage for status epilepticus is to be administered slowly over at least 10 minutes, and the dosage rate is not to exceed 100 mg/minute. The descriptions in international standard textbooks, foreign formularies, and national and international review articles for both children and adults vary.

VIII-5. Details of and reasons for prudent administration

Careful dosage (should be administered with caution to the following patients)

- (1) Low birth weight infants [There is little experience in administering this product to these patients. (See the "Administration to children" section)]
- (2) Elderly people (see "Administration to the elderly" section)
- (3) Patients who are frail or have impaired respiratory function [may cause respiratory depression].
- (4) Patients with sequelae of head trauma or advanced arteriosclerosis. [The effects of this drug may be intensified.]
- (5) Patients with cardiac disorders [may cause hypotension and decreased heart rate].
- (6) Patients with hepatic or renal impairment [These symptoms may be aggravated and blood levels may increase.]
- (7) Patients with drug sensitivity
- (8) Patients with alcohol intoxication [central depressant effects are enhanced].
- (9) Patients with a tendency or history of drug dependence [may exhibit psychiatric and physical dependence].
- (10) Patients with severe neurological disorders [may exhibit dependence].
- (11) Patients with hypothyroidism [may cause abnormal thyroid function.]

<Explanation>

- (1) The number of cases of administration to low-birth-weight infants in investigator-initiated clinical trials was 3 (1144 g, 2121 g, and 2274 g), which is a small number based on clinical practice, and therefore it is listed.
- (2) The information in the above items (2) to (11) is provided for patients with complications related to the central depressant effect, respiratory depressant effect, cardiovascular depressant effect, dependence, etc. of this drug, so that this drug should be administered with caution. The entries are the same for all phenobarbital products, regardless of dosage form, indication/effect, and dosage and administration.

VIII-6. Important basic precautions, reasoning for them and procedures

Important basic precautions

- (1) A sudden decrease in dosage or discontinuation of the drug during continuous use may cause status epilepticus, so the dosage should be decreased gradually and with caution. Special care should be taken with the elderly and frail.
- (2) Periodic liver and kidney function and blood tests should be performed during continuous use.
- (3) Since continuous use may cause drug dependence, the drug should be carefully monitored and administered with caution(see "Adverse Reactions").
- (4) Since drowsiness and decreased alertness, concentration, and motor reflexes may occur, patients receiving this drug should be cautioned not to engage in the operation of dangerous machinery such as driving a car.

<Explanation>

Considering the indication/effect and dosage of this product, it is assumed that long-term continuous administration is unlikely, but this information is included to avoid the occurrence of serious side effects.

Furthermore, this section is the same for all phenobarbital products, regardless of dosage form, indication/effect, and dosage and administration.

Interactions ²⁹⁾

This drug induces the drug-metabolizing enzyme CYP3A and other enzymes.

²⁹⁾ Iwahashi, K., *et al.* Clinical Psychopharmacology. 1998;1:721

(1) Contraindications (not to be used concomitantly) and reasons

Contraindications (not to be used concomitantly) and reasons

Drug name, etc.	Clinical symptoms/necessary measure	Mechanism/risk factors
Voriconazole (Vfend) Tadalafil (Adcirca)	Metabolism of these drugs may be accelerated and blood levels may decrease.	Due to the induction of hepatic drug-metabolizing enzyme (CYP3A4) of the drug.

(2) Concomitant Use (Cautionary Note for Concomitant Use) ³⁰⁻³⁶⁾

Concomitant use precautions (use with caution)

Drug name, etc.	Clinical symptoms/necessary measure	Mechanism/risk factors
Central nervous system (CNS) depressant Phenothiazine derivatives Barbiturates derivatives Tranquilizers Topiramate and other antihistamines Diphenhydramine and other alcohols	Since their effects may be mutually reinforcing, care should be taken to reduce the dosage.	Due to additive CNS depression.
MAO inhibitor		Mechanism unknown
Tricyclic antidepressants imipramine, etc. Tetracyclic antidepressants maprotiline, etc.	(1) Since the effects of the two drugs may be mutually potentiated, caution should be exercised by reducing the dosage or by other means. (2) Blood levels of these antidepressants may ^{Note 3)} .	(1) Due to additive CNS depression. (2) Due to the induction of hepatic drug-metabolizing enzymes acting on phenobarbital.
Methylphenidate	Since the blood concentration of phenobarbital may increase, care should be taken to reduce the dosage of phenobarbital.	Methylphenidate is thought to inhibit hepatic metabolism.
Valproic acid	(1) Blood levels of the drug may increase and its effects may be potentiated. (2) Blood levels of valproic acid may decrease ^{Note 3)} .	(1) Valproic acid inhibits hepatic metabolism. (2) Due to the drug's induction of hepatic drug-metabolizing enzymes.
Clobazam	(1) Blood levels of this drug may increase. (2) Blood levels of clobazam may decrease ^{Note 3)} .	(1) Mechanism unknown (2) Due to the drug's induction of hepatic drug-metabolizing enzymes.
Irinotecan	The active metabolite of irinotecan may decrease blood levels and weaken the action of irinotecan, so concomitant use should be avoided.	Due to the drug's induction of hepatic drug-metabolizing enzymes.

Drug name, etc.	Clinical symptoms/necessary measure	Mechanism/risk factors
Drugs metabolized mainly by CYP3A4 azelnidipine Imatinib Injunavir Carbamazepine saquinavir Cyclosporine tacrolimus felodipine verapamil Montelukast, etc. adrenal corticosteroids Dexamethasone, etc. Follicle and progestin hormones Norgestrel ethinyl estradiol, etc. PDE5 inhibitor Tadalafil (Cialis), sildenafil, vardenafil	The blood concentration of these drugs may decrease and their effects may be attenuated, so the dosage should be carefully monitored ^{Note 3)} .	Due to the drug's induction of hepatic drug-metabolizing enzymes.
Aminophylline hydrate chloramphenicol theophylline Tropisetron paroxetine Flecainide		
Griseofulvin		Inhibition of griseofulvin absorption by the drug's gastrointestinal tract hypermotility is thought to be the cause.
Lamotrigine Deferasirox	Blood levels of these drugs may decrease ^{Note 3)}	This drug promotes glucuronidation of these drugs.
Doxycycline	The blood concentration half-life of doxycycline may be shortened.	
Coumarin anticoagulant Warfarin	Since the action of coumarin anticoagulants may be weakened, the clotting time should be measured more frequently than usual and the dose of coumarin anticoagulants should be adjusted.	Due to the drug's induction of hepatic drug-metabolizing enzymes.
Diuretic Thiazide antihypertensive diuretics, etc.	Since orthostatic hypotension may be enhanced, care should be taken to reduce the dose.	Although the mechanism is unknown, high doses of phenobarbital may decrease blood pressure.

Drug name, etc.	Clinical symptoms/necessary measure	Mechanism/risk factors
Acetazolamide	Kuru and osteomalacia are more likely to appear.	Acceleration of vitamin D inactivation by the drug or renal tubular damage and metabolic acidosis caused by acetazolamide are considered.
Acetaminophen	Long-term users of this drug are more likely to develop liver damage due to metabolites of acetaminophen.	The drug's hepatic drug-metabolizing enzyme-inducing effect is believed to accelerate the metabolism of acetaminophen to the hepatotoxic <i>N-acetyl-p-benzoquinoneimine</i> .
<i>Hypericum perforatum</i> Foods containing St. John's wort	Since the metabolism of St. John's wort may be accelerated and blood levels of the drug may decrease, care should be taken not to consume foods containing St. John's wort when the drug is administered.	This is thought to be due to St. John's wort's ability to induce hepatic drug-metabolizing enzymes.

Note 3) When reducing or discontinuing the dosage of phenobarbital, care should be taken to avoid increases in the blood concentrations of these drugs.

<Explanation>

This section is common to all phenobarbital products, and the same description was used for this product. However, when materials describing interactions with phenobarbital were found in the package inserts of other drugs, etc., the drug in question was newly added to the list of interactions. The following is a categorization of possible cases of interaction with phenobarbital and a description of the interactions.

(1) Interactions due to induction of drug-metabolizing enzymes, etc. acting on phenobarbital

Phenobarbital has a pronounced enzyme-inducing effect and induces CYP450s, including CYP1A, CYP2A6, CYP2B, CYP2C, and CYP3A. Therefore, it enhances the metabolism of drugs and other substances metabolized by these enzymes, thereby altering their pharmacological actions and physiological activities. Of these, CYP3A has the lowest substrate specificity and is reported to be involved in the metabolism of more than 50% of drugs.

The following drugs fall into this type:

Voriconazole, tadalafil, sildenafil, vardenafil, imipramine, maprotiline, valproic acid, clobazam, irinotecan, corticosteroids, carbamazepine, cyclosporine, theophylline, aminophylline, follicle hormone and progestin agents (norgestrel, ethinylestradiol, etc.), verapamil, felodipine, chloramphenicol, flecainide, paroxetine, doxycycline, tacrolimus, saquinavir, indinavir, tropisetron, imatinib, azelnidipine, coumarin anticoagulants (warfarin) montelukast, acetaminophen, etc.

(2) Interactions due to inhibition of hepatic drug-metabolizing enzymes by concomitant medications

Drugs that inhibit drug-metabolizing enzymes in the liver may increase blood levels of the drug. Agents of this type include methylphenidate and valproic acid.

(3) Interactions due to accelerated metabolism of phenobarbital

Concomitant use with drugs that accelerate phenobarbital metabolism may decrease blood phenobarbital levels.

This type of drug (food) includes foods containing St. John's wort.

(4) Other

In addition to the above, pharmacodynamic interactions due to pharmacological actions similar to those of phenobarbital (phenothiazine derivatives, barbiturate derivatives, tranquilizers, CNS depressants such as topiramate, etc.), absorption inhibition due to gastrointestinal tract hypermobility caused by phenobarbital (griseofulvin), glucuronide conjugation enhancement of phenobarbital (lamotrigine, deferasirox), etc.

²⁴⁾ Ryuichi Kato, Clinical Pharmacokinetics, Tokyo, Nankendo, 2001, 133

- 25) Chiba, H. Jpn. J. Pharm. Health Care Sci. 1994;76:2214
- 30) Anderson GD. Neurology. 2004;63(10 Suppl 4):S3
- 31) Crews KR, *et al.* Clin Cancer Res. 2002;8:2202
- 32) Greb WH, *et al.* Acta Psychiatr Scand. 1989;80(Suppl 350):95
- 33) Holland S, *et al.* Clin Pharmacol Ther. 1998;63:231
- 34) Garrettson LK, *et al.* J Am Med Assoc. 1969;207:2053
- 35) Scheyer RD, *et al.* Antiepileptic Drugs, 4th ed. 1995;621
- 36) Bray GP, *et al.* Human Experimental Toxicol. 1992;11:265

VIII-8. Side effects

(1) Overview of Side Effects

4. Side effects

In a Japanese clinical study conducted for neonatal seizures, 6 cases (60%) experienced adverse reactions (including abnormal laboratory values) out of 10 patients evaluated for safety, including 3 cases (30%) of respiratory depression, 2 cases (20%) of decreased oxygen saturation, 1 case (10%) of decreased blood pressure, 1 case (10%) of bradycardia, 1 case (10%) of decreased body temperature, 1 case (10%) of increased bronchial secretion, and 1 case (10%) of decreased urine output (at the time of approval).

<Explanation>

This is a summary of adverse drug reactions includes adverse drug reactions (including laboratory abnormalities) observed in clinical studies for neonatal seizures. Clinical studies for status epilepticus have not been conducted.

1) Serious side effects ³⁷⁻⁴³⁾

Serious side effects

- (1) Cutaneous mucous membrane eye syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), erythroderma (exfoliative dermatitis) (frequency unknown): The patient should be carefully observed and administration should be discontinued if abnormal symptoms such as fever, erythema, blister/erosion, itching, sore throat, red eyes, and stomatitis are observed. Appropriate measures such as administration of corticosteroids should then be taken.
- (2) Hypersensitivity syndrome (frequency unknown): Initial symptoms include rash and fever, followed by delayed onset of severe hypersensitivity symptoms such as lymphadenopathy, organ damage including liver dysfunction, increased white blood cell count, eosinophilia, and atypical lymphocytes; if such symptoms occur, administration should be discontinued and appropriate measures should be taken. Note that reactivation of viruses such as human herpesvirus 6 (HHV-6) is often accompanied by reactivation of the virus, and symptoms such as rash, fever, and liver dysfunction may flare up or become prolonged.
- (3) Dependence (frequency unknown): Since continuous use may cause drug dependence, the drug should be carefully administered under close observation and not exceeding the dosage. A sudden decrease or discontinuation of dosage during continuous use may cause withdrawal symptoms such as anxiety, insomnia, seizures, nausea, hallucinations, delusions, excitement, confusion, or depression.
- (4) Granulocytopenia, thrombocytopenia (frequency unknown): Careful observation should be made, and if any abnormality is observed, administration should be discontinued and appropriate measures taken.
- (5) Hepatic dysfunction (frequency unknown): Hepatic dysfunction accompanied by increases in AST (GOT), ALT (GPT), γ -GTP, etc. may occur. Therefore, careful observation should be made, and appropriate measures such as discontinuation of administration should be taken if any abnormality is observed.
- (6) Respiratory depression (5% or more): Careful observation is suggested, and if any abnormality is observed, appropriate measures such as discontinuation of administration should be taken.

<Explanation>

Although there have been no reports of adverse reactions listed under "Serious Adverse Reactions" other than "respiratory depression" with this product, it is listed here because it is common in other phenobarbital products regardless of dosage form, indication, and dosage and administration, and may occur with this product as well.

However, the precautions regarding "local necrosis" described for the intramuscular or subcutaneous formulations are not listed because they are not considered applicable to the intravenous formulation of the drug.

³⁷⁾ Matsumoto, R., *et al.* Clinical Dermatology. 1970;12:973

³⁸⁾ Tomita, H., *et al.* Journal of the Japanese Pediatric Society. Japanese Journal of Pediatrics. 1987;91:1465

³⁹⁾ Inoue, M., *et al.* Yamada Red Cross Hospital Journal. 1988;10:100

⁴⁰⁾ Ozaki M., *et al.* Acta Dermatologica Kyoto . 1979;74:51

⁴¹⁾ Sexton DL, *et al.* J Am Med Assoc. 1941;116:700

⁴²⁾ Kano, Y. Clinical Allergy. 2001;21:355

⁴³⁾ Tashiro, T., *et al.* Psychiat. Neurol. Jap. 1986;88:441

2) Other side effects

1. Side effects

Other side effects

Type \ Frequency	5% or more	Frequency unknown
Hypersensitivity ^{Note 4)}		Scarlet fever-like rash, measles-like rash, toxicoderma-like rash
Blood ^{Note 5)}		Thrombocytopenia, megaloblastic anemia
Liver ^{Note 6)}		Hepatic dysfunction such as increased AST (GOT), ALT (GPT), γ -GTP, jaundice
Kidney ^{Note 7)}		Proteinuria and other renal disorders
Psychoneurotic system		Drowsiness, asterixis, vertigo, headache, delirium, stupor, dullness, dysarthria, dysesthesia, ataxia, mental function Decline
Circulatory organ	Blood pressure decreased, bradycardia	
Digestive organs		Anorexia
Bones/teeth		Kuru disease ^{Note 8)} , osteomalacia ^{Note 8)} , dysplasia of the teeth ^{Note 8)} , hypocalcemia
Endocrine		Abnormal thyroid function test values (serum T ₄ level, etc.)
Other	Decreased oxygen saturation, increased bronchial secretion, decreased urine output, decreased body temperature	Decreased serum folate level, hematoporphyria ^{Note 7)} , fever

Note 4) Discontinue administration.

Note 5) Appropriate measures such as discontinuation of administration should be taken.

Note 6) If any abnormality is observed, appropriate measures such as discontinuation of administration should be taken.

Note 7) May occur with repeated use.

If abnormalities (such as increased serum alkaline phosphatase level, decreased serum calcium and inorganic phosphorus) are observed, appropriate measures such as dose reduction or administration of vitamin D should be taken.

<Explanation>

Adverse reactions (including laboratory abnormalities) observed in clinical studies of this drug for neonatal seizure

are listed. Adverse reactions common to all phenobarbital products regardless of formulation, indication, or dosage and administration may also occur with this product, so they are listed as infrequent or unknown.

- (2) Overview of the frequency of occurrence of adverse reactions and laboratory test abnormalities by category
No applicable data at this stage
- (3) Frequency of adverse drug reactions by underlying disease, complications, severity of illness, and presence or absence of surgery
No applicable data at this stage
- (4) Precautions and drug allergy testing methods

Contraindications (not to be administered to the following patients) (excerpt)
(1) Patients with a history of hypersensitivity to any component of this drug or to barbiturates

Other side effects (excerpts)

	5% or more	Frequency unknown
Hypersensitivity Note 4)		Scarlet fever-like rash, measles-like rash, toxicoderma-like rash

Note 4) Discontinue administration

VIII-9. Administration to the elderly

Administration to the elderly

The dosage should be administered on the side of caution, starting with a small dose. If administration is discontinued, the dosage should be reduced gradually and with caution. [In the elderly, respiratory depression, agitation, depression, confusion, etc. are likely to occur(see the "Important basic precautions" section) .

<Explanation>

The elderly generally have impaired physiological functions of metabolism and excretion, and therefore, this information is included because they require caution, such as starting with a low dosage to avoid the development of adverse effects of this drug, such as respiratory depression and central nervous system suppression.

Furthermore, this section is the same for all phenobarbital products, regardless of dosage form, indication/effect, and dosage and administration.

VIII-10. Administration to pregnant women, woman nearing childbirth, lactating women, etc.

Administration to pregnant women/woman nearing childbirth/lactating women

- (1) Pregnant women or women who may be pregnant should receive this product only if the therapeutic benefit (prevention of frequent epileptic seizures in the mother and protection of the fetus from hypoxia) is judged to outweigh the risks. [Epidemiologic studies have reported a high incidence of births with malformations (cleft lip, cleft palate, cardiac malformations, aortic stenosis, etc.) among patients treated with this drug alone or in combination during pregnancy].
- (2) Administration during pregnancy may cause bleeding tendency and respiratory depression in newborns.
- (3) If used before delivery, withdrawal symptoms (hyperactivity, tremor, hyperreflexia, hypertonia, etc.) may occur in newborns after delivery.
- (4) It has been reported that administration during pregnancy causes a decrease in folic acid.
- (5) Administration to nursing women should be avoided, but if administration is unavoidable, nursing should be avoided. [It may be transferred into human breast milk, causing somnolence and decreased feeding in newborns and infants].

<Explanation>

Phenobarbital has been reported to cause teratogenicity, placental passage, and milk transfer; therefore, it is listed to avoid its effects on pregnant and nursing women as well as newborns.

Furthermore, this section is the same for all phenobarbital products, regardless of dosage form, indication/effect, and dosage and administration.

- ⁴⁴⁾ Holmes LB, *et al.* Arch Neurol. 2004;61:673
- ⁴⁵⁾ Arpino C, *et al.* Epilepsia. 2000;41:1436
- ⁴⁶⁾ Thakker JC, *et al.* Indian Pediatr. 1991;28:73
- ⁴⁷⁾ Anderson RC. J Pediatr. 1976;89:318
- ⁴⁸⁾ Annegers JF, *et al.* Birth Defects Orig Artic Ser. 1975;11:157
- ⁴⁹⁾ Delgado-Escueta AV, *et al.* Neurology 1992;42(Suppl 5):149
- ⁵⁰⁾ Suzuki, K., *et al.* Perinatal Medicine. 1979;9:1259
- ⁵¹⁾ Isobe, K., *et al.* Journal of Developmental Pharmacology. 1992;5:68

VIII-11. Administration to children, etc.⁵²⁾

Administration to children, etc.

Since it has been reported that the major metabolic system of this drug is completed in the first 10 to 20 days of life, blood concentration monitoring should be conducted especially in low birth weight infants and newborns.

<Explanation>

The major metabolic system of phenobarbital, hydroxylation and its glucuronidation and N-glucosidation, is reported to be completed at 10 to 20 days of age. Therefore, this information is included to be aware of the occurrence of adverse effects associated with elevated blood levels, especially in low birth weight infants and newborns.

(See section 8. Overdose).

- ⁵²⁾ Bhargava VO, *et al.* Dev Pharmacol Ther. 1988;11:8

VIII-12. Effects on laboratory test results

No applicable data at this stage

VIII-13. Overdose¹⁵⁾

Overdose

- (1) Symptoms: central nervous system and cardiovascular depression. Blood levels of 40-45 µg/mL or higher cause drowsiness, nystagmus, ataxia, and in severe cases of poisoning, coma. Respiration is suppressed starting in the early stage, pulse is weak, skin has cold sweats, and body temperature falls. There is also a risk of pulmonary complications and kidney damage.
- (2) Treatment: Respiratory management. Urine alkalinization by administration of sodium bicarbonate and diuretics to promote drug excretion. In severe cases, hemodialysis or hemoperfusion should be considered.

<Explanation>

In case of overdose, respiratory depression and cardiovascular depression, which are side effects of the drug, may occur, leading to coma. The blood concentrations listed here are approximate values because they vary from person to person.

Furthermore, this section is the same for all phenobarbital products, regardless of dosage form, indication/effect, and dosage and administration.

- ¹⁵⁾ Mamoru Yamashita. Clinical Pediatrics. 1987;40, Unabridged: 2923

VIII-14. Precautions regarding the decision to use the drug

Precautions regarding the decision to use the drug

- (1) This drug should only be administered intravenously.
- (2) Preparation Method
 - 1) For administration, one vial is usually dissolved in 5 mL of water for injection or saline solution. (Concentration after dissolution: 50 mg/mL phenobarbital). After dissolution, it should be used immediately (within 6 hours).
 - 2) Do not mix with the following injectable drugs, as they have been shown to cause a change in formulation. Dopamine hydrochloride, potassium L-aspartate, menatetrenone (vitamin K), vecuronium bromide, amikacin sulfate, gentamicin sulfate, erythromycin for injection (erythromycin lactobionate).

<Explanation>

- (1) This drug is intended for intravenous administration and is described for intravenous administration only.
- (2) 1) Since this product is a lyophilized preparation, the preparation method for administration should be

described in detail.

The expiration date was 6 hours after which no change was observed in the stability test after the expiration date.

- 2) The names of ingredients that are likely to be concomitantly administered with phenobarbital and for which a change in combination was observed are specifically listed. In addition to the drugs studied above, there is a possibility that other drugs may cause changes in the combination of this drug and the drug. If any changes are observed, administration should be discontinued and the drug should not be combined with such drugs.

VIII-15. Other precautions⁵³⁻⁵⁷⁾

Other precautions

- (1) A large repeated dose (60 mg/kg subcutaneously) in neonatal rats has been reported to suppress brain growth compared to controls.
- (2) There are reports that long-term high-dose administration (rats: 25 mg/kg, mice: 75 mg/kg) to rats and mice significantly increased the incidence of liver tumors compared to the control group.
- (3) Possibility of abnormalities in serum immunoglobulins (IgA, IgG, etc.).

<Explanation>

- (1) The dose is listed because it has been reported that repeated high-dose administration (60 mg/kg subcutaneously for 14 or 19 days) to neonatal rats decreased brain weight compared to the control group.
- (2) This information is included because the incidence of liver tumors was reported to be significantly increased in rats and mice following long-term high-dose administration (rats: 25 mg/kg for 152 weeks by mixed feeding; mice: 75 mg/kg for 110 weeks by mixed feeding), compared to the control group.
- (3) This information is included because there are reports of effects on IgA, IgG, and IgM. The citation is a report on hypoglycemia.

Furthermore, (2) and (3) are common to all phenobarbital products regardless of dosage form, indication, or dosage and administration.

⁵³⁾ Schain RJ, *et al.* *Exper Neurol.* 1975;47:509

⁵⁴⁾ Diaz J, *et al.* *Biol Newborn.* 1977;32:77

⁵⁵⁾ Thorpe E, *et al.* *Food Cosmet Toxicol.* 1973;11:433

⁵⁶⁾ Rossi L, *et al.* *Int J Cancer.* 1977;19:179

⁵⁷⁾ Kuno Y., *et al.* *Clinical Pediatrics.* 1978;31:1681

VIII-16. Other

Not applicable

IX. Non-clinical studies

IX-1. General pharmacology

(1) Effects on the central nervous system ^{58,59)}

When phenobarbital was administered subcutaneously at 50 mg/kg to male S mice, motor depression was observed, gait ataxia was observed at 75 mg/kg, and an anesthetic state was observed at 100 mg/kg. These symptoms were observed around 1 hour after administration, peaking at 1.5 to 2 hours and continuing for several hours.

⁵⁸⁾ Kawasaki, Y. J Yonago Med Ass. 1957;8:234

When phenobarbital sodium was administered to white male rabbits at 150 mg/kg intramuscularly, all of the muscles in their body relaxed, their movements became sluggish, and they entered a state of lying down and sleeping. From 30 to 150 minutes, the patient was in a state of deep anesthesia with disappearance of corneal and contralateral light reflexes, dilatation (later constriction) of the ear veins, and decrease in respiratory rate. Body temperature dropped markedly after 1 hour (about 5 degrees), but gradually recovered after 8 to 12 hours.

⁵⁹⁾ Tomoeda, Seiichiro. Journal of Tokyo Med. 1958;14:621

(2) Effects on the cardiovascular system ⁶⁰⁻⁶²⁾

Subcutaneous administration of 1% phenobarbital sodium to male Wistar rats (130-180 g) resulted in a drop in blood pressure of 12-18 mmHg in the 10 mg/kg dose group 10-15 minutes after administration, followed by rapid recovery and return to pre-dose values 30 minutes later. In the 30 mg/kg dose cases, the peak blood pressure drop was reached 10 to 15 minutes after administration, with a maximum drop of 20 mmHg. Thereafter, it gradually recovered and returned to the pre-dose value at 60 min.

⁶⁰⁾ Kohei Isamu. Journal of The Jikei University Hospital. 1959;65:989

Intraperitoneal administration of phenobarbital sodium to male Wistar rats (180-235 g) resulted in a mild decrease in rectal temperature over 40-80 minutes of administration in the 40 mg/kg dose group. ⁶¹⁾ Carpenter, DC, et al. Res Commun Chem Pathol Pharmacol.

1977;18:613

Phenobarbital administered to pig newborns (1-3.5 days old) resulted in decreased cerebral blood flow at 15 minutes and increased partial pressure of carbon dioxide at 60 minutes in the 15 mg/kg dose group and decreased cerebral blood flow at 30 minutes and increased partial pressure of carbon dioxide at 60 minutes in the 45 mg/kg dose group.

⁶²⁾ Scalais E. Dev Pharmacol Ther. 1992;19:10

(3) Action on the respiratory system ⁶³⁾

In humans, normal doses of anesthesia only suppress cortical and mesencephalic functions, and have no inhibitory effect on the respiratory center of the medulla oblongata. However, large oral doses or rapid intravenous administration can cause respiratory depression due to the medullary suppressive function.

⁶³⁾ Hara, Saburo, *et al.* System of Clinical Pharmacology, Vol. 4, Tokyo, Nakayama Shoten, 1965, 84

(4) Action on the digestive system ⁶⁴⁾

In humans, anesthetic doses do not appear to have a significant effect on gastric evacuation.

⁶⁴⁾ Brunton LL, *et al.* Goodman & Gilman's The Pharmacological basis of therapeutics 11th ed., New York, McGraw-Hill, 2006,414

(5) Other pharmacological actions

Not applicable

IX-2. Toxicity

(1) Single-dose toxicity study⁶⁵⁻⁶⁷⁾

The LD₅₀ values for intraperitoneal administration of phenobarbital sodium were 340 mg/kg for mice and 190 mg/kg for rats.

Animal species	Route of administration	LD ₅₀ (mg/kg)
Mouse	Intraperitoneal administration	340
Rat	Intraperitoneal administration	190
Rabbit	Intravenous administration	185
Cat	Oral administration	175
Newborn rats (male and female)	Oral administration	121
	Subcutaneous administration	83
100-day-old rats (male and female)	Oral administration	487
	Subcutaneous administration	210

⁶⁵⁾ Gruber CM, *et al.* J Pharmacol Exper Ther. 1944;81:254

⁶⁶⁾ Krop S, *et al.* J Pharmacol Exper Ther. 1946;88:260

⁶⁷⁾ Weinberg MS, *et al.* Toxicol Appl Pharmacol. 1966;9:234

(2) Repeated dose toxicity studies^{53,54)}

Phenobarbital was administered subcutaneously to neonatal rats at 30 and 60 mg/kg for 19 days from 3 to 21 days of age. Phenobarbital-induced hypnotic effects were seen in both groups, with the first dose in the 60 mg/kg group lasting up to 9 hours. Hypnotic effects decreased gradually and did not occur in the third week. The 60 mg/kg dose group showed suppressed body weight gain, decreased brain weight (cerebrum and cerebellum), decreased DNA, RNA, PT and Chol in the cerebrum, and decreased Chol in the cerebellum.

⁵³⁾ Schain RJ, *et al.* Exper Neurol. 1975;47:509

To avoid hyponutrition due to the hypnotic effect of phenobarbital, 60 mg/kg of phenobarbital was administered subcutaneously to male rats aged 5 to 18 days for 14 days while the rats were artificially fed by a gastric cannula. Phenobarbital-induced hypnotic effects were observed early in the course of administration, but resolved with repeated dosing. Body weight was not different compared to the control group. Brain weight showed significant gain inhibition, with decreases in DNA, RNA, PT and Chol in the cerebrum and decreases in RNA and Chol in the cerebellum.

⁵⁴⁾ Diaz J, *et al.* Biol Newborn. 1977;32:77

(3) Reproductive and developmental toxicity tests

Not applicable (some one-off reports, but no systematic studies have been conducted)

(4) Local irritation test⁶⁸⁾

In a vascular stimulation study in rabbits, an aqueous solution of sodium phenobarbital had a mild vascular stimulation effect, but to a lesser degree than phenytoin injection and sodium sulfobromophthalein solution.

⁶⁸⁾ Vascular irritation study of PB-Na (NPC-03) in rabbits (in-house data)

(5) Other unique toxicities^{55,56)}

After long-term high-dose administration to rats and mice (rats: 25 mg/kg, drinking water, 152 weeks; mice: 75 mg/kg, mixed diet, 110 weeks), the incidence of liver tumors was significantly increased compared to the control group.

⁵⁵⁾ Thorpe E. Food Cosmet Toxicol. 1973;11:433

⁵⁶⁾ Rossi L. Int J Cancer. 1977;19:179

X. Handling precautions, etc.

X-1. Use-by period or expiration date

Use-by date: 3 years (indicated on outer box, etc.)

X-2. Storage methods/storage conditions

Store at room temperature

X-3. Drug handling precautions

Deleterious substances, psychotropic drugs, addictive drugs^{Note 1)}, prescription drugs^{Note 2)}

Note 1) Caution: habit-forming

(Note 2) Caution: use only by prescription from a physician or other health care provider.

X-4. Approval conditions

None

X-5. Packaging

Nobelbar for Intravenous Injection 250 mg, 6 vials

X-6. Drugs with the same ingredients/same effect

Drugs with the same ingredients

Phenobarbital sodium or phenobarbital as oral, intramuscular or subcutaneous injection, suppository

<Drugs with the same effect>

Diazepam injection, oral diazepam

Phenytoin injection, oral phenytoin (phenobarbital mixture)

X-7. International birth date

October 16, 2008

X-8. Date of manufacture/import approval and approval number

Date of approval: October 16, 2008 Approval

number: 22000AMX02374000

X-9. Date of NHI drug price listing

December 12, 2008

X-10. Date and details of additional indications, additional dosage and administration changes, etc.

Not applicable

X-11. Date and details of reexamination and reevaluation results publications

Not applicable

X-12. Reexamination period

Neonatal seizure 10 years: October 16, 2008 - October 15, 2018

6 years, status epilepticus; October 16, 2008 - October 15, 2014

X-13. Feasibility of long-term administration

Not applicable

- X-14. MHLW drug codes listed in the NHI Drug Price Standard
1139400F1023
- X-15. Precautions related to insurance benefits
Not applicable

1. XI. Literatures

XI-1. Sources

- 1) Susumu Ito, *et al.* Clinical trial for neonatal seizures: Physician-initiated clinical trial (in-house document)
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XI-2. Other references

XI-3. Literature requests

Literature requests

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2. XII. Reference Materials

XII-1. The state of global sales

This section contains information other than the approved indications and dosage and administration.

Approved indications for this drug
Neonatal seizures
Status epilepticus
Approved dosage and administration of this drug
Neonatal seizures
Initial dose: 20 mg/kg of phenobarbital administered intravenously. If the seizures are uncontrolled, adjust the dose according to the patient's condition, not exceeding the initial dose, and administer additional doses intravenously.
Maintenance dose: 2.5 to 5 mg/kg of phenobarbital administered intravenously once daily.
Status epilepticus
Phenobarbital is administered intravenously at a dose of 15 to 20 mg/kg once daily.

Outside of Japan, phenobarbital sodium is marketed in the United States, the United Kingdom, and Germany for neonatal seizures and in the United States, the United Kingdom, Australia, Canada, Germany, and France for status epilepticus.

Country name	United States of America
Company name	Wyeth
Brand name	Phenobarbital sodium injection, USP
Dosage form/specifications	Injection: 1 mL contains 30 mg, 50 mg, 60 mg, or 130 mg of phenobarbital sodium.
Indications/effects	- Tranquilizer - Sleeping pills for short-term treatment of insomnia, because barbiturate derivatives appear to lose their effectiveness in sleep onset and sleep maintenance after 2 weeks. - Preanesthetic administration - Treatment of generalized tonic-clonic and cortical focal seizures. Phenobarbital sodium is used as an emergency anticonvulsant intramuscularly or intravenously in the emergency treatment of certain acute convulsive seizures associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, strychnine, or toxic reactions to local anesthetics. For intravenous administration, it may take more than 15 minutes to reach the highest brain concentration. Thus, continued injection of phenobarbital sodium until the seizure disappears may result in severe barbiturate-induced depression as brain concentrations exceed those required to suppress the seizure.

Dosage/administration	Pediatric dosage: Recommended by the American Academy of Pediatrics (for reference) Preoperative sedation: 1-3 mg/kg intramuscularly or intravenously Anticonvulsant: 4-6 mg/kg/day for 7-10 days or 10-15 mg/kg/day intramuscularly or intravenously with a target blood concentration of 10-15 µg/mL; Status epilepticus: 15-20 mg/kg IV for 10-15 minutes Adult dosage: (for reference only) Daytime sedation: 30-120 mg/day in 2 to 3 divided doses intramuscularly or intravenously Sleep hypnosis: 100-320 mg intramuscularly or intravenously Preoperative sedation: intramuscular administration only: 100-200 mg 60-90 minutes before surgery Acute seizures: 200-300 mg intramuscularly or intravenously, repeated every 6 hours if necessary
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3. XIII. Remarks

XIII-1. Other Related Materials