Report on Investigation Results

March 1, 2018
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Propofol
[Brand name]	1% Diprivan Injection, others (as shown in Attachment 1)
[Approval holder]	Aspen Japan K.K., others (as shown in Attachment 1)
[Indications]	Induction and maintenance of general anesthesia Sedation during artificial ventilation in intensive care
[Dosage and Administration]	As shown in Attachment 1
[Investigating office]	Office of Safety II

II. Background of this investigation

In Japan, manufacturing and distribution of propofol were approved with the indication for "induction and maintenance of general anesthesia" in September 1995 and "sedation during artificial ventilation in intensive care" in March 1999.

Pregnant women are listed in the section of Contraindications in the current package insert of propofol. A "written request for revision of the package inserts of propofol" requesting the revision of the package inserts to allow use of propofol in pregnant women was submitted to the Pharmaceutical Safety Division, the Pharmaceutical Safety and Environmental Health Bureau, MHLW (hereinafter, "Safety Division") by the Japanese Society of Anesthesiologists on February 15, 2016, (1) because pregnant women are not listed in Contraindications in foreign package inserts of propofol, and (2) use of propofol is positioned as the standard therapy for pregnant women in Europe and the United States. The Safety Division requested the Pharmaceuticals and Medical Devices Agency (hereinafter, "PMDA") to conduct an investigation regarding the adequacy of the cancellation of listing of propofol in Contraindications for pregnant women on December 20, 2017. In response to the request, PMDA conducted an investigation and considered the revision of the package inserts of propofol.

PMDA has held an Expert Discussion as part of the investigation. The expert advisors for the Expert Discussion were nominated based on their declarations, concerning the products, in accordance with the provisions of "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8 dated December 25, 2008).

III. Investigation by PMDA

1. Prior to approval in Japan

There was no effect on parental animals, fetuses or neonates in the reproductive and developmental toxicity studies submitted at the application for the marketing authorization of propofol[1]. However, it had been reported that when propofol was administered to pregnant

[1] Interview Form of "1% Diprivan Injection" (16th version)

women, (1) propofol was found in umbilical venous and arterial blood, and transferred to fetuses, and (2) hypotonia was observed in neonates (Anesthesiology 1989; 71: 827-34, Br. J. Anaesthesia 1989; 62: 649-54); therefore, administration to pregnant women was listed in Contraindications in the package insert at the time of marketing authorization. The authorization holder explained that no additional reproductive and developmental toxicity study was conducted after the approval was obtained in Japan.

2. Descriptions in package inserts in Europe and the United States

The descriptions regarding administration to pregnant women in the package inserts of propofol in the United States and Britain were as follows (Attachment 2).

2.1 United States Package Insert

Pregnant women are not listed in the section of Contraindications in the United States package inserts. It is described that no carcinogenicity study has been conducted, and there has been no effect on mutagenicity or fertility in the sections of Carcinogenesis, Mutagenesis, and Impairment of Fertility in Precautions. The following are described in the sections of Pregnancy and Labor and delivery.

- There has been no clinical study in pregnant women.
- There was no effect on the fetuses when propofol was administered intravenously at a dose of 0, 5, 10 or 15 mg/kg/day [2] to pregnant rats during the period of organogenesis (gestational days 6-15); however, there was a decrease in the percentage of weight increase in the maternal animals in all treatment groups.
- Although there was decreased corpus luteum when propofol was administered intravenously at a dose of 0, 5, 10 or 15 mg/kg/day[3] to pregnant rabbits during the period of organogenesis (gestational days 6-18), there was no fetal malformation in all groups. There was a case of death in maternal animals due to respiratory depression by narcotic effects in the high-dose group.
- When propofol was administered intravenously at a dose of 0, 10 or 15 mg/kg/day[1] to pregnant rats between the third trimester of pregnancy and the lactation period (gestational day 16 to lactation day 22), there was a decrease in offspring survival and deaths of maternal animals due to respiratory depression by narcotic effects in each group. The effects on neurological functions including learning and memory of the newborns were not investigated in this study.
- When propofol was administered intravenously at a dose of 0, 10 and 15 mg/kg/day[1] to female rats from 2 weeks before mating to gestational day 7, there were maternal toxicity in 10 and 15 mg/kg/day groups and a decrease in offspring survival on lactation days 15 and 22. When the newborns from the maternal animals in the 15 mg/kg/day group were mated, there was an increase in postimplantation loss after mating.
- According to the publication of an investigation in primates, there was an increase of apoptosis of the brain neurons and oligodendrocytes of the fetuses when isoflurane or propofol was administered for 5 hours on gestational day 120. From the perspective of brain development, the exposure period of isoflurane or propofol in this publication corresponds to the third trimester of pregnancy in humans. Although the significance of these findings in clinical use is unknown, it is suggested that apoptosis of the

[2] The doses of 5, 10 and 15 mg/kg/day correspond to 0.3 times, 0.65 times and the same dose of the human clinical dose of 2.5 mg/kg based on body surface area.
[3] The doses of 5, 10 and 15 mg/kg/day correspond to 0.65, 1.3, and 2 times the human clinical dose of 2.5 mg/kg based on body surface area.

neurons may be related to long-term cognitive disorder in juvenile animal studies.

- Propofol is not recommended for use in the field of obstetrics including cesarean section. Similar to other general anesthetics, propofol may pass through the placenta and cause neonatal suppression.

2.2 British Summary of Product Characteristics

Pregnant women are not listed in the section of Contraindications in the British summary of product characteristics. The following are described in the sections of Fertility, and Pregnancy and lactation.

- The safety of propofol during pregnancy has not been established. Propofol should not be used in pregnant women except in unavoidable circumstances.
- Propofol may pass through the placenta and cause neonatal suppression. Propofol should not be used as an obstetric anesthetic in pregnant women except in unavoidable circumstances.

3. Guidelines, textbooks, and publications in Japan and overseas

3.1 Guidelines

3.1.1 Usage Guidelines for Anesthetics and Drugs Related to Anesthetics Third Version (Japanese Society of Anesthesiologists, 2012, hereinafter, "Japanese guidelines")

The following contents are described as the indications of propofol in the section of the obstetric anesthetics.

[1] Induction and maintenance of general anesthesia for cesarean section
[2] Induction and maintenance of general anesthesia for gynecological surgical procedures including dilation and evacuation, except for cesarean section
[3] Anesthesia for nonobstetric surgical procedures during pregnancy and the puerperium
[4] Sedation during artificial ventilation in intensive care

In Dosage and Administration, it is described that propofol "should be administered at a dose of 2.0 to 2.5 mg/kg as intravenous injection" for induction, and propofol "should be administered within the range not exceeding the rate of administration of 6 mg/kg/hour for maintenance. It is recommended that administration of propofol should be performed through observation of the patient's general condition to achieve the appropriate anesthetic depth in combination with analgesics and other anesthetics." for (1) in the above. For (2) through (4), it is described that propofol is used in accordance with the Dosage and Administration in the package inserts.

3.1.2 The American College of Obstetricians and Gynecologists Practice Bulletin No. 177: Obstetric Analgesia and Anesthesia, 2017 (hereinafter, "US guideline")

It is described that general anesthesia during cesarean section should be limited to emergency cesarean section and the cases where regional anesthesia is not applicable, and that propofol is an induction agent for general anesthesia that is used in the standard approach of general anesthesia. There is no description related to dosage and administration.

3.2 Textbooks

The following contents are described in representative foreign textbooks related to anesthesia.

3.2.1 Miller's Anesthesia, 8th edition (Elsevier/Saunders, 2014, USA)

In the United States, propofol has been commonly used as an induction agent for general anesthesia during cesarean section in recent years. There is no effect on the Apgar score of neonates with the usual dose of propofol (2.5 mg/kg); however, it is associated with significant neonatal suppression when it is repeatedly administered and when the total dose is high (9 mg/kg). Although the reasons why the effects of propofol on neonates are limited have not been revealed, rapid distribution in maternal animals and rapid metabolism in the liver of neonates can be considered as the reasons.

3.2.2 Shnider and Levinson's Anesthesia for Obstetrics, 5th edition (Lippincott Williams & Wilkins, 2012, USA)

Propofol has been most commonly used as an induction agent for general anesthesia during cesarean section. When the inhibitory effect of the cardiac function of the maternal body is concerned, propofol should be used at a low dose with opioids. At the usual induction dose of propofol 2 to 3 mg/kg, placental transfer is considered comparable to thiopental. The effects of propofol on neonates are considered to be limited since propofol is rapidly distributed in the maternal body and metabolized in the liver of the neonates.

3.2.3 Chestnut's Obstetric Anesthesia, 5th edition (Elsevier/Saunders, 2014, USA)

In the United States, propofol (2 to 2.8 mg/kg) has been commonly used as an induction agent for general anesthesia during cesarean section in recent years. Propofol has a stronger suppressive effect on neonates at the dose (2.5 mg/kg) that shows adequate effects on loss of consciousness of the maternal body compared to thiopental.

3.3 Publications

The major publications related to use of propofol in pregnant women are as follows[4].

3.3.1 Adv Biomed Res. 2014; 3: 234

In an overseas double-blind, randomized, controlled study conducted at an institution in 90 pregnant women who were scheduled to undergo cesarean section, the Apgar scores of neonates were investigated when propofol 1.5 mg/kg was administered as the induction agent for general anesthesia, and propofol 100 μg/kg/min or isoflurane 1 MAC (minimum alveolar concentration) (45 patients per group) was administered as the maintenance agent during cesarean section. The Apgar score (mean ± SD) of neonates in the propofol group and the isoflurane group was 8.24 ± 1.15 and 8.18 ± 1.09 at 1 minute after birth, and 9.20 ± 0.76 and 9.22 ± 0.79 at 5 minutes after birth, respectively. There was no significant difference between the groups at any time point (p=0.78 at 1 minute after birth and p=0.89 at 5 minutes after birth; t test).

[4] Among the publications searched by the query ("Obstetric anesthesia or caesarean section or pregnant women" and propofol) in PubMed, the publications related to controlled clinical studies of propofol in pregnant women published between 2007 and 2017 were extracted.

3.3.2 Turk J Anaesthesiol Reanim 2015; 43: 106-12

In an overseas randomized, controlled study conducted at an institution in 70 pregnant women who were scheduled to undergo cesarean section, the Apgar scores of neonates were investigated when propofol 2 mg/kg or thiopental 5 mg/kg (35 patients per group) was administered as the induction agent for general anesthesia during cesarean section. Sevoflurane was administered as the maintenance agent for anesthesia in both groups. The Apgar score (mean ± SD) of neonates in the propofol group and the thiopental group was 8.63 ± 0.97 and 8.80 ± 0.83 at 1 minute after birth, and 9.80 ± 0.53 and 9.94 ± 0.23 at 5 minutes after birth, respectively. There was no significant difference between the groups at any time point (p=0.145 at 1 minute after birth, p=0.219 at 5 minutes after birth; Mann-Whitney U test). The results of umbilical venous blood gas measurement are as shown in Table 1, and there was no significant difference between the groups in any measurement.

Table 1 Results of umbilical venous blood gas measurement

	Propofol group (35 patients) (Mean ± SD)	Thiopental group (35 patients) (Mean ± SD)	p value (t test)
pH	7.34 ± 0.03	7.33 ± 0.05	0.264
Partial pressure of carbon dioxide (mmHg)	44.13 ± 6.20	45.13 ± 9.53	0.606
Partial pressure O2 (mmHg)	43.44 ± 21.73	38.98 ± 11.78	0.290
Base excess(mmoL/L)	-1.26 ± 1.40	-2.01 ± 1.89	0.067

3.3.3 Taiwan J Obstet Gynecol 2017; 56: 521-26

In an overseas double-blind, randomized, controlled study conducted at an institution in 40 pregnant women who were scheduled to undergo cesarean section, the Apgar score of neonates and transfer to the fetuses were investigated when propofol was administered as the induction agent for general anesthesia during cesarean section. Propofol 1 mg/kg and remifentanil 1 μg/kg were administered as the induction agent for general anesthesia, and propofol 3 mg/kg/hour and remifentanil 7 μg/kg/hour were administered as the maintenance agent. Induction of anesthesia was initiated after disinfection of the surgical field in group I, and induction of anesthesia was initiated before disinfection of the surgical field in group II (20 patients per group). The time from induction of anesthesia to delivery (hereinafter, "I-D time", mean ± SD) was 6.9 ± 1.2 minutes in group I and 18.0 ± 1.9 minutes in group II. The ratio of neonates with the Apgar score of ≤ 7 was 35 % (7/20 neonates) in group I and 30 % (6/20 neonates) in group II at 1 minute after birth, and 0 % (0/20 neonates) in group I and 5.0 % (1/20 neonates) in group II at 5 minutes after birth. The Apgar score recovered to 10 in all neonates in both groups by 10 minutes after birth. Of them, respiratory depression was observed in 5 neonates in group I and 4 neonates in group II, and spontaneous respiration recovered by mask ventilation. No neonate required endotracheal intubation. The plasma concentration of propofol in maternal artery and umbilical vein is as shown in Table 2, indicating that group II tended to have a greater ratio of plasma concentration of propofol in umbilical vein to plasma concentration of propofol in maternal artery. The results of umbilical blood gas measurement are as shown in Table 3, and there was no significant difference between the groups in any measurement.

Table 2 Plasma concentration of propofol

	Group I (20 patients)	Group II (20 patients)
Plasma concentration of propofol in maternal artery (μg/mL)	1.91 ± 0.46	1.57 ± 0.30
Plasma concentration of propofol in umbilical vein (μg/mL)	1.17 ± 0.29	1.07 ± 0.19
Plasma concentration of propofol in umbilical vein/ Plasma concentration of propofol in maternal artery	0.63 ± 0.09	0.69 ± 0.07

Mean ± SD

Table 3 Results of umbilical blood gas measurement

		Group I (20 patients) (Mean ± SD)	Group II (20 patients) (Mean ± SD)	p value (t test)
Umbilical arterial blood	pH	7.26 ± 0.03	7.28 ± 0.04	0.35
	Partial pressure O2 (mmHg)	21.1 ± 3.7	22.5 ± 5.0	0.41
	Partial pressure of carbon dioxide (mmHg)	56.5 ± 6.3	57.1 ± 4.9	0.77
	Base excess(mmoL/L)	-2.8 ± 1.3	-2.2 ± 1.1	0.23
Umbilical venous blood	pH	7.29 ± 0.05	7.32 ± 0.04	0.15
	Partial pressure O2 (mmHg)	37.5 ± 8.4	38.2 ± 8.1	0.84
	Partial pressure of carbon dioxide (mmHg)	49.1 ± 6.6	48.4 ± 5.1	0.73
	Base excess(mmoL/L)	-2.2 ± 1.3	-2.6 ± 1.8	0.50

3.4 Actual use status in Japan

Results of national questionnaire survey on the current status of anesthesia for cesarean section (Journal of Japan Society for Clinical Anesthesia 2013; 33: 411-420)

A questionnaire survey on the mode of anesthesia during cesarean section was conducted among 121 university hospitals and obstetric and pediatric hospitals in Japan in June 2011. The response rate of the questionnaire was 66.1% (80 institutions). Of them, 77 institutions excluding 3 institutions without intraoperative care by an anesthesiologist were included in the analysis. For the mode of anesthesia used as the first-line drug during routine scheduled cesarean section, 75% of the institutions selected combined spinal-epidural anesthesia and 25% of the institutions selected spinal anesthesia. Epidural or general anesthesia was selected when these modes of anesthesia were not applicable. Regarding use of the induction agent for general anesthesia, 67% of the institutions use thiopental or thiamylal, and 33% of the institutions use propofol.

4. Accumulation status of adverse reaction reports in Japan

There were 9 adverse reactions in 6 fetuses or neonates when propofol was administered to pregnant women reported by November 1, 2017. The reported adverse reactions included 3 cases of “neonatal asphyxia”, 2 cases of “neonatal hypoxia”, and 1 case of “foetal heart rate decreased”, “neonatal respiratory depression”, “neonatal respiratory distress syndrome”, and “hyperthermia malignant”, respectively. There was no adverse reaction report of malformation in fetuses or neonates (Appendix 3).

5. Research reports and foreign action reports

There were 31 research reports related to propofol reported by November 1, 2017, and of them, there was no research report related to administration to pregnant women such as teratogenicity. There were 17 foreign action reports related to propofol reported by November

1, 2017, and of them, there were 5 action reports related to administration to pregnant women. All of the reports described that the United States package insert was revised and the following content was added.

- It is described in the sections of Warnings and Precautions that although the significance in clinical use is unknown, apoptosis of the neurons is observed in the fetuses or juvenile animals when general anesthetics or sedatives are administered for 3 hours or longer, suggesting an association with long-term cognitive disorder in non-clinical studies in pregnant animals or juvenile animal studies.

6. Overview of investigation by PMDA

Based on the descriptions in foreign package inserts, Japanese and foreign guidelines, textbooks, publications, and accumulation of adverse reaction reports in Japan, PMDA considers as follows.

Surgery for pregnant women is recommended to be performed after delivery if the disease permits postponement of the procedure. Regional anesthesia is preferable to select whenever possible even if emergency surgery is performed by necessity (Perinatal anesthesia, Kokuseido Shuppan, 2012). However, general anesthesia is required for surgery when regional anesthesia is not applicable due to necessity of general management during surgery because of complications or spinal diseases. General anesthetics include inhalation anesthetic such as isoflurane, and drugs administered intravenously such as thiopental. In Japanese guidelines, it is described that inhalation anesthetics may cause atonic hemorrhage due to its muscle relaxant effect of the uterus. In the meantime, it also describes that there is no report of uterine contraction by propofol in the clinical settings. It is considered that propofol is used since it has been reported that thiopental cannot obtain substantial sedation after induction of anesthesia compared to propofol (Journal of Obstetrics and Anesthesia 2013; 90: 14-17) (3.4).

Based on the above considerations, PMDA considered that it is acceptable to revise Contraindications of propofol for pregnant women, replaced by precaution that propofol should be administered if the expected therapeutic benefits outweigh the possible risks associated with treatment to call attention for the following reasons.

- Although propofol is transferred to the fetuses, protocol has considerable clinical experience (3.4), and all cases of the respiratory depression observed in the neonates in adverse reaction reports in Japan resolved by appropriate treatment and there is no case with serious outcome.
- Propofol is an option for general anesthetics for cesarean section and nonobstetric surgery and sedatives during artificial ventilation in intensive care during pregnancy in Japanese guidelines.
- Propofol is an option for general anesthetics for cesarean section in the guidelines in the United States and representative foreign textbooks related to anesthesia.
- In published literature, there is no significant difference in the Apgar score of the neonates between the propofol group and the thiopental/isoflurane group that are not listed in Contraindications for pregnant women in use as general anesthesia during cesarean section in Japanese package inserts (3.3.1, 3.3.2). There is no clinically problematic tendency in the measurements of umbilical blood gas (3.3.2, 3.3.3).
- No teratogenicity was observed in the reproductive and developmental toxicity studies submitted at the application of the initial approval, and there has been no teratogenic finding of propofol to date.

The expert advisors presented the following opinions regarding the PMDA's conclusion in the above, and PMDA's conclusion was supported by the expert advisors.

- Cesarean section with general anesthesia is often an extreme emergency surgery, and in such a case, it is recommended to use familiar agents used in routine general anesthesia. Although inhalation anesthetics are useful for maintenance of anesthesia, it is not usually used as the induction agent. Propofol is more commonly used than barbiturates, because of (1) complications that contraindicate administration of barbiturates (severe bronchial asthma etc.), (2) concerned tissue injury in case of extravascular leakage, (3) concerned turbidity and precipitation by mixing with muscle relaxants and obstruction of the intravenous route, and (4) barbiturates require preparation beforehand and take time for preparation in an emergency. Therefore, revision of Contraindications for propofol in pregnant women will be a great benefit.

The following opinions were presented by the expert advisors.

- Artificial ventilation management in intensive care is rarely required in pregnant women; however, the necessity of propofol administration should be examined in consideration of the effects of continuous administration on the fetuses when it is administered. It is unknown whether propofol syndrome occurs in the fetuses[5]; however, there is a possibility considering the facts that propofol is transferred to the fetuses when it is administered to pregnant women, and although it is rare, propofol syndrome may occur in infants and young children. It is considered that limiting the administration time to a certain length of time should be taken into account when propofol is administered.

PMDA considers as follows regarding the opinions by the expert advisors.

Since there has been no adverse reaction report or publication related to propofol syndrome in the fetuses due to transplacental exposure to propofol, and no information that supports the establishment of the period of use when propofol is used for artificial ventilation management in intensive care in pregnant women at this point, it is considered that no rationale for calling attention in the package insert regarding the period of use when propofol is administered to pregnant women has been obtained. However, PMDA will monitor future adverse reaction reports and publications and respond appropriately.

IV. Overall assessment

PMDA concluded that it is acceptable to revise the precautions of the package inserts as follows.

[5]Pathology caused by (1) and (2) observed when propofol is administered intravenously (Paediatr Anaesth 1998; 8: 491-99)
(1) The occurrence of idiopathic or relatively idiopathic refractory bradycardia that progresses to asystole
(2) Includes at least one of the following
・The occurrence of dyslipidemia
・Hepatomegaly or fatty infiltration of the liver by autopsy
・Metabolic acidosis with base excess (≤ -10 mEq/L)
・Muscular symptoms associated with rhabdomyolysis or myoglobinuria

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[Proposed revision] Propofol

Underlined language added, struck-out language deleted

Current version	Proposed revision
[Contraindications] (Propofol is contraindicated in the following patients) 1. Patients with a history of hypersensitivity to propofol or any ingredient of propofol ~~2. Pregnant women (Refer to the section of "Use in pregnant, parturient and breast-feeding women")~~ 3. Children (sedation during artificial ventilation in intensive care) (Refer to the section of "Pediatric Use.")	[Contraindications] (Propofol is contraindicated in the following patients) 1. Patients with a history of hypersensitivity to propofol or any ingredient of propofol 2. Children (sedation during artificial ventilation in intensive care) (Refer to the section of "Pediatric Use.")
Use during Pregnancy, Delivery, or Lactation 1. ~~Propofol is contraindicated in pregnant women since~~ transfer to human fetuses has been reported.	Use in Pregnant, Parturient and Breast-feeding Women 1. <u>This drug should be administered to pregnant women or women who may be pregnant only if the potential benefits outweigh the risks (as this drug is transferred to the fetus, symptoms such as neonatal respiratory depression may occur).</u>

Appendix 1

List of pharmaceutical products investigated

Propofol

Brand name	Approval holder	INDICATIONS	DOSAGE AND ADMINISTRATION
1% Diprivan Injection	Aspen Japan K.K.	Induction and maintenance of general anesthesia Sedation during artificial ventilation in intensive care	1. Induction and maintenance of general anesthesia (1) Induction The usual adult dose of Diprivan for intravenous use is 0.05 mL/Kg at the rate of 10 seconds (0.5 mg/kg/10 seconds of propofol) through monitoring of the patient's general condition until sleep is obtained. Diprivan should be administered at a slower rate in patients with ASA III or IV. Usually, sleep can be obtained by the adult dose of Diprivan of 0.20 to 0.25 mL/kg (2.0 to 2.5 mg/kg of propofol). Sleep may be obtained by a smaller dose in the elderly. Diprivan should be additionally administered after sleep is obtained according to need. (2) Maintenance Usually, Diprivan is administered intravenously in combination with oxygen or oxygen and nitrous oxide mixture. Rate of administration should be adjusted through monitoring the patient's general condition to obtain the appropriate anesthetic depth. Usually, the appropriate anesthetic depth can be obtained at the rate of administration of Diprivan of 0.4 to 1.0 mL/kg (4 to 10 mg/kg of propofol) in adults. Diprivan should be used in combination with an analgesic (narcotic analgesic, local anesthetic). The appropriate anesthetic depth can be obtained by a lower dose in combination with a local anesthetic. 2. Sedation during artificial ventilation in intensive care In adults, Diprivan should be administered at a dose of 0.03 mL/kg/hour (0.3 mg/kg/hour of propofol). Intravenous administration should be initiated by continuous infusion and the rate of administration should be adjusted through monitoring of the patient's general condition to obtain the appropriate anesthetic depth. Usually, the appropriate sedative depth can be obtained at the rate of administration of 0.03 to 0.30 mL/kg/hour (0.3 to 3.0 mg/kg/hour of propofol) in adults. The rate of administered should be adjusted according to the required sedative depth in consideration of the disease types and severity of the symptoms. Analgesics should be used in combination where necessary.

1% Diprivan Injection - Kit			1. Induction and maintenance of general anesthesia (1) Mode of administration without Diprifusor TCI system 1)Induction The usual adult dose of Diprivan for intravenous use is 0.05 mL/Kg at the rate of 10 seconds (0.5 mg/kg/10 seconds of propofol) through monitoring of the patient's general condition until sleep is obtained. Diprivan should be administered at a slower rate in patients with ASA III or IV. Usually, sleep can be obtained by the adult dose of Diprivan of 0.20 to 0.25 mL/kg (2.0 to 2.5 mg/kg of propofol). Sleep may be obtained by a smaller dose in the elderly. Diprivan should be additionally administered after sleep is obtained according to need. 2)Maintenance Usually, Diprivan is administered intravenously in combination with oxygen or oxygen and nitrous oxide mixture. The rate of administration should be adjusted through monitoring the patient's general condition to obtain the appropriate anesthetic depth. Usually, the appropriate anesthetic depth can be obtained at the rate of administration of Diprivan of 0.4 to 1.0 mL/kg (4 to 10 mg/kg of propofol) in adults. Diprivan should be used in combination with an analgesic (narcotic analgesic, local anesthetic). The appropriate anesthetic depth can be obtained by a lower dose in combination with a local anesthetic. (2) Mode of administration with Diprifusor TCI system 1)Induction Usually, intravenous administration should be initiated with the target blood concentration of 3.0 μg/mL, and the target blood concentration should be increased by 1.0 to 2.0 μg/mL per minute when sleep cannot be obtained in 3 minutes after initiation of administration in adults. Usually, sleep can be obtained within 1 to 3 minutes after initiation of administration with the target blood concentration of 3.0 to 6.0 μg/mL. Administration should be initiated with a lower target blood concentration in the elderly and patients with ASA III and IV. 2)Maintenance Usually, Diprivan is administered intravenously in combination with oxygen or oxygen and nitrous oxide mixture. The target blood concentration should be adjusted through monitoring the patient's general condition to obtain the appropriate anesthetic depth. Usually, the appropriate anesthetic depth can be obtained with the target blood concentration of 2.0 to 5.0 μg/mL in adults. Diprivan should be used in combination with an analgesic (narcotic analgesic, local anesthetic). 2. Sedation during artificial ventilation in intensive care In adults, Diprivan should be administered at a dose of 0.03 mL/kg/hour (0.3 mg/kg/hour of propofol). Intravenous administration should be initiated by continuous infusion and the rate of administration should be adjusted through monitoring of the patient's general condition to obtain the appropriate anesthetic depth. Usually, the appropriate sedative depth can be obtained at the rate of administration of 0.03 to 0.30 mL/kg/hour (0.3 to 3.0 mg/kg/hour of propofol) in adults. The rate of administered should be adjusted according to the required sedative depth in consideration of the disease types and severity of the symptoms. Analgesics should be used in combination where necessary.

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Propofol 1% Intravenous Injection “Pfizer” 20 mL, 50 mL, 100 mL	Mylan Pharmaceutical Co., Ltd.		Same as 1% Diprivan Injection
Propofol Intravenous 1% Injection “Nichi-Iko” 20 mL, 50 mL, 100 mL	Nichi-Iko Pharmaceutical Co., Ltd.		
Propofol 1% Injection “F” (20 mL), (50 mL), (100 mL)	Fuji Pharma Co., Ltd.		
Propofol Intravenous Injection 1%“FK” 20 mg, 50 mg, 100 mg	Fresenius Kabi Japan K.K.		
1% Propofol Injection “Maruishi”, 2% Propofol Injection “Maruishi”	Maruishi Pharmaceutical Co., Ltd.		

Appendix 2

Descriptions in foreign package inserts

<table>
<tr><th>United States Package Insert (April 2017 version)</th><th>British Summary of Product characteristics (February 2017 version)</th></tr>
<tr><td>

INDICATIONS AND USAGE:

DIPRIVAN is an IV general anesthetic and sedation drug that can be used as described in the table below.

<table>
<tr><th>Indication</th><th>Approved Patient Population</th></tr>
<tr><td>Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation</td><td>Adults only</td></tr>
<tr><td>Combined sedation and regional anesthesia</td><td>Adults only (see PRECAUTIONS)</td></tr>
<tr><td>Induction of General Anesthesia</td><td>Patients greater than or equal to 3 years of age</td></tr>
<tr><td>Maintenance of General Anesthesia</td><td>Patients greater than or equal to 2 months of age</td></tr>
<tr><td>Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients</td><td>Adults only</td></tr>
</table>

Safety, effectiveness and dosing guidelines for DIPRIVAN have not been established for MAC Sedation in the pediatric population; therefore, it is not recommended for this use (see PRECAUTIONS, Pediatric Use).

DIPRIVAN is not recommended for induction of anesthesia below

</td><td>

4.1 Therapeutic indications

Diprivan 1% is a short-acting intravenous general anaesthetic for:

- Induction and maintenance of general anaesthesia in adults and children >1 month.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children >1 month.
- Sedation of ventilated patients >16 years of age in the intensive care unit.

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</table>

the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations. In the Intensive Care Unit (ICU), DIPRIVAN can be administered to intubated, mechanically ventilated adult patients to provide continuous sedation and control of stress responses only by persons skilled in the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management. DIPRIVAN is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established (see PRECAUTIONS, Pediatric Use). DIPRIVAN is not recommended for obstetrics, including Cesarean section deliveries. DIPRIVAN crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN may be associated with neonatal depression (see PRECAUTIONS). DIPRIVAN is not recommended for use in nursing mothers because propofol has been reported to be excreted in human milk, and the effects of oral absorption of small amounts of propofol are not known (see PRECAUTIONS).	
CONTRAINDICATIONS: DIPRIVAN is contraindicated in patients with a known hypersensitivity to propofol or any of the DIPRIVAN components. DIPRIVAN is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products.	**4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Diprivan 1% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya. Diprivan 1% must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

Precautions: **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Long-term studies in animals have not been performed to evaluate the carcinogenic potential of propofol. Mutagenesis Propofol was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. Propofol was not mutagenic in either the gene mutation/gene conversion test using *Saccharomyces cerevisiae*, or *in vitro* cytogenetic studies in Chinese hamsters. In the *in vivo* mouse micronucleus assay with Chinese Hamsters propofol administration did not produce chromosome aberrations. Impairment of Fertility Female Wistar rats administered either 0, 10, or 15 mg/kg/day propofol intravenously from 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility (0.65 and 1 times the human induction dose of 2.5 mg/kg based on body surface area). Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy** Risk Summary There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, decreased pup survival concurrent with increased maternal mortality was observed with intravenous administration of propofol to pregnant rats either prior to	**4.6 Fertility, pregnancy and lactation** Pregnancy The safety of Diprivan 1% during pregnancy has not been established. Diprivan 1% should not be given to pregnant women except when absolutely necessary. Diprivan 1% can, however, be used during an induced abortion. Obstetrics Diprivan 1% crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

mating and during early gestation or during late gestation and early lactation at exposures less than the human induction dose of 2.5 mg/kg. In pregnant rats administered 15 mg/kg/day intravenous propofol (equivalent to the human induction dose) from two weeks prior to mating to early in gestation (Gestation Day 7), offspring that were allowed to mate had increased postimplantation losses. The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans [See Data]. The estimated 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 U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. <u>Data</u> <u>Animal Data</u> Pregnant rats were administered propofol intravenously at 0, 5, 10, and 15 mg/kg/day (0.3, 0.65, and 1 times the human induction dose of 2.5 mg/kg based on body surface area) during organogenesis (Gestational Days 6-15). Propofol did not cause adverse effects to	

the fetus at exposures up to 1 times the human induction dose despite evidence of maternal toxicity (decreased weight gain in all groups). Pregnant rabbits were administered propofol intravenously at 0, 5, 10, and 15 mg/kg/day (0.65, 1.3, 2 times the human induction dose of 2.5 mg/kg based on body surface area comparison) during organogenesis (Gestation Days 6-18). Propofol treatment decreased total numbers of corpora lutea in all treatment groups but did not cause fetal malformations at any dose despite maternal toxicity (one maternal death from anesthesia-related respiratory depression in the high dose group). Pregnant rats were administered propofol intravenously at 0, 10, and 15 mg/kg/day (0.65 and 1 times the human induction dose of 2.5 mg/kg based on body surface area) from late gestation through lactation (Gestation Day 16 to Lactation Day 22). Decreased pup survival was noted at all doses in the presence of maternal toxicity (deaths from anesthesia- induced respiratory depression). This study did not evaluate neurobehavioral function including learning and memory in the pups. Pregnant rats were administered propofol intravenously at 0, 10, or 15 mg/kg/day (0.3 and 1 times the human induction dose of 2.5 mg/kg based on body surface area) from 2 weeks prior to mating to Gestational Day 7. Pup (F1) survival was decreased on Day 15 and 22 of lactation at maternally toxic doses of 10 and 15 mg/kg/day. When F1 offspring were allowed to mate, postimplantation losses were increased in the 15 mg/kg/day treatment group. In a published study in primates, administration of an anesthetic	

dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits (see WARNINGS; Pediatric Neurotoxicity, PRECAUTIONS; Pediatric Use, and ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY). Labor and Delivery DIPRIVAN is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN may be associated with neonatal depression.	

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix 3

Accumulation status of adverse reactions in Japan

No.	Reporting year	Age	Sex	PT for adverse reactions	Route of administration	Outcome	Reason for use
1	2005	Week 35	Unknown	Foetal heart rate decreased	Transplacental	Recovered	General anesthesia in open reduction of maternal fractures
2	2006	Day 0	Male	Hyperthermia malignant	Intravenous (Maternal route of administration)	Recovering/Resolving	General anesthesia during cesarean section
3	2014	Unknown	Male	Neonatal asphyxia	Transplacental	Recovering/Resolving	Sedation in detailed examination for subarachnoid haemorrhage
				Neonatal hypoxia	Transplacental	Recovering/Resolving	
4	2014	Neonate	Unknown	Neonatal asphyxia	Transplacental	Recovered	General anesthesia during cesarean section
5	2015	Neonate	Unknown	Neonatal respiratory depression	Intravenous (Maternal route of administration)	Recovered	General anesthesia during cesarean section
				Neonatal respiratory distress syndrome			
				Neonatal hypoxia			
6	2017	Neonate	Male	Neonatal asphyxia	Transplacental	Recovering/Resolving	General anesthesia during cesarean section

* Extracted cases exposed to propofol from (1) reports of transplacental adverse reactions as the route of administration or (2) reports of adverse reactions in patients aged below 0 years