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Report on Investigation Results

March 27, 2025

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Domperidone
[Brand name]	See Appendix 1.
[Marketing authorization holder]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Administration of domperidone to “pregnant women or women who may be pregnant” is contraindicated. It was decided at the approval of the brand-name product of domperidone (June 1982) that domperidone should not be administered to pregnant women or women who may be pregnant, based on the teratogenicity, such as visceral/skeletal anomalies, in rat foetuses at approximately 65 times the clinical dose (200 mg/kg) reported in a study on administration during the organogenesis period of rat foetuses, which was conducted during the development phase of domperidone.

Recently, the Information Provision Working Group (hereinafter referred to as the “WG”) in the “Proper Use Promotion Project for Pregnant and Lactating Women[1]” of the MHLW reviewed the appropriateness of the contraindication for “pregnant women or women who may be pregnant” in the package insert for the drug products shown in Appendix 1, and an evaluation report on the revision of PRECAUTIONS for domperidon (hereinafter referred to as the “WG report”) (Appendix 2; Appendix 2 is not included in this document. See the Japanese original report.) was prepared. Domperidone is indicated for diseases including

[1] Web page of the MHLW (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/ninshin_00002.html) (accessed on January 24, 2025) (only in Japanese)

chronic gastritis and gastroptosis and for gastrointestinal symptoms including nausea/vomiting when receiving a drug. Because of the similarity between the symptoms of hyperemesis gravidarum and the gastrointestinal symptoms for which domperidone is indicated, there are a certain number of cases that result in prescribing domperidone to pregnant women who are unaware of their pregnancy, according to the WG report. The WG report pointed out that women may become anxious about continuing their pregnancy in such cases when they notice the fact that domperidone is contraindicated for pregnant women after recognizing their pregnancy, and that they may choose to undergo an elective abortion. In response to the WG report, the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, MHLW requested the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) to conduct an investigation into the revision of PRECAUTIONS of domperidone regarding administration to pregnant women/nursing mothers, under the “Notification on Request of Investigation Related to the Safety of Drugs, etc.” (PSB/PSD 0122 No.1, dated January 22, 2025). The PMDA accordingly conducted an investigation into the request and discussed the necessity of revision of the package insert.

The PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Investigation by the WG

The WG report (Appendix 2), containing the items shown in Table 1, was prepared on the appropriateness of the precautions concerning “pregnant women or women who may be pregnant” in the package insert of domperidone.

Table 1 Table of Contents in the WG report

1. Summary of drug	5. Reports on clinical uses
2 Background	6. Japanese and overseas guidelines
3. Descriptions in overseas product labeling	7. Appropriateness of lifting the contraindications
4. Animal study	8. Proposed revision of package insert by the WG

IV. Investigation by the PMDA

Taking account of the WG report, the PMDA conducted the following review.

1. Information based on nonclinical studies (Refer to "4. Animal study" in the WG report.)

1-1. Published literature

The WG evaluated reproductive and developmental toxicity studies, which were conducted during the development phase of domperidone, as well as those described in overseas product labeling. The contraindications for domperidone are based on teratogenicity observed in rat foetuses, which was reported at a dose of 200 mg/kg/day (corresponding to 65 times the maximum recommended clinical dose). While maternal toxicity and mild foetal toxicity were noted at a dose of 70 mg/kg/day (corresponding to 23 times the maximum recommended clinical dose), no teratogenic toxicity in rat foetuses was observed. In the most recent version of the Guidelines for Evaluation of Reproductive and Developmental Toxicity of Drugs[2], it is stated that concerns regarding clinical use are small if the toxic effects are exhibited only at an exposure level that exceeds 25 times the exposure level for the maximum recommended clinical dose. (Refer to "4. Animal study" in the WG report.)

In addition, although literature published after market approval of the brand-name product of domperidone was searched, no articles were retrieved concerning the reproductive and developmental toxicity of domperidone. (Refer to "4. Animal study" in the WG report.)

2. Information based on clinical uses (Refer to "5. Reports on clinical uses" in the WG report.)

2-1. Published literature

The WG searched for published literature on domperidone and pregnancy, retrieving 4 epidemiological studies (searched on October 8, 2024). (Refer to "5. Reports on clinical uses" in the WG report.)

Effects of exposures to domperidone in the first trimester of pregnancy were evaluated in each of the retrieved 4 epidemiological studies, revealing no increase in the risk of congenital anomaly by the use of domperidone in the first trimester of pregnancy (references 1 to 4 in the WG report).

[2] PSB/PSD 0129 No.8 dated January 29, 2021, "The Guidelines for Evaluation of Reproductive and Developmental Toxicity of Drugs"

2-2. Adverse reaction report

The number of case reports of adverse reaction for domperidone in Japan concerning pregnancy and neonates in the PMDA's database for adverse reactions, etc. report is shown in Appendix 3, with a total of 36 events in 27 cases that fell under Standardized MedDRA Query (SMQ (broad)) “pregnancy and neonatal topics” (data lock: January 24, 2025).

The events (PT) for which 2 or more events have been reported included 7 events of spontaneous abortion, 4 events of lactation disorder, 2 events each of low birth weight baby, ventricular septal defect, and stillbirth. It is described in the current package insert that an increase in the risk of “teratogenic effects, such as skeletal or visceral anomaly,” has been indicated in an animal study (rats). Regarding events possibly related to “teratogenic effects, such as skeletal or visceral anomaly,” 2 events of ventricular septal defect, 1 event each of Fallot's tetralogy, motor developmental delay, duodenal obstruction, cardiac disorder, meningocele, congenital genital malformation, congenital aortic anomaly, congenital deafness, congenital skin dimples, congenital dacryostenosis, intellectual disability, cerebral ventricle dilatation, and Fanconi syndrome have been reported. Every report lacked information, such as maternal primary diseases, dose and duration of domperidone administration, presence or absence of concomitant drugs, and clinical courses, making the assessment of a causal relationship difficult.

3. Guidelines (Refer to “6. Japanese and overseas guidelines” in the WG report.)

3-1. Descriptions in the guidelines regarding the use of domperidone in pregnant women

The WG reviewed descriptions in Japanese and overseas guidelines regarding the use of domperidone in pregnant women and the clinical positioning of domperidone concerning the indicated diseases. (Refer to “6. Japanese and overseas guidelines” in the WG report.)

A description about domperidone as “a drug considered not to inflict a foetal impact of clinical significance when it is used only in the first trimester of pregnancy” was found in “Guideline for Obstetrical Practice in Japan (2023) (edited and supervised by Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists).” In a standard textbook[3] on which the description in the guideline is based, it is stated as

[3] Masahiro Hayashi, Kodo Sato, and Hiroaki Kitagawa. Drugs in Pregnancy (2nd edition), 2010, published by JIHO (Tokyo)

follows: It is not considered that frequency or risk of malformation may be increased by administration of domperidone, since no risk of malformation from domperidone use is indicated in an epidemiological study[4] or pregnancy outcomes reported in consulted cases at Toranomon hospital.

4. Descriptions in overseas product labeling (Refer to "3. Descriptions in overseas product labeling" in the WG report.)

The WG reviewed descriptions in overseas product labeling (the UK, Canada, Australia, France, and Germany). Of note, domperidone is not marketed in the US. (Refer to "3. Descriptions in overseas product labeling" in the WG report.) In the product labeling in these countries, administration of domperidone to pregnant women is not contraindicated, and it is stated that domperidone should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks.

V. PMDA's judgment based on the WG report and "IV. Investigation by the PMDA"

1. Decision on administration to pregnant women

Based on the WG report and the results of "IV. Investigation by the PMDA," the PMDA considered that "pregnant women or women who may be pregnant" may be deleted from the CONTRAINDICATIONS section in the package insert for domperidone for the following reasons.

- The epidemiological studies of pregnant women administered domperidone in the first trimester of pregnancy showed no results that indicated an association between domperidone and an increased frequency of congenital anomalies. (Refer to "5. Reports on clinical uses" in the WG report.) Regarding the administration of domperidone to pregnant women, domperidone is included in a list of drugs that are considered not to inflict a foetal impact of clinical significance when it is used only in the first trimester of pregnancy, which is described in a Japanese guideline. (Refer to "6. Japanese and overseas guidelines" in the WG report.)
- In overseas product labeling (the UK, Canada, Australia, France, and Germany), the use of domperidone in pregnant women is not contraindicated, and it is stated that domperidone should be administered only if the potential therapeutic benefits are

[4] Choi JS, et al. Foetal and neonatal outcomes in women taking domperidone during pregnancy (ABS). Birth Defects Research (part A) .

considered to outweigh the potential risks. (Refer to “3. Descriptions in overseas product labeling” in the WG report.)

2. Proposed revision

The PMDA considered that the package insert of domperidone may be revised as follows: “Pregnant women or women who may be pregnant” may be deleted from 2. CONTRAINDICATIONS; a statement that “pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” may be added to the 9.5 Pregnant Women section in 9. PRECAUTIONS CONCERNING PERSONS WITH SPECIFIC BACKGROUNDS, based on the descriptions in the overseas product labeling. Regarding the description in the current package insert that teratogenicity in rats has been reported, it is a result at a high dose which is approximately 65 times the clinical dose based on body surface area conversion, although the correlation between the doses and exposures in the non-clinical studies is not clear. (Refer to “4. Animal study” and “8. Proposed revision of package insert by the WG” in the WG report.) Therefore, it was considered to be appropriate that the ratio of the dose in the animal study to the clinical dose be provided in the package insert as information for users to assess the risk.

VI. Expert Discussion

The PMDA decided that “pregnant women or women who may be pregnant” may be deleted from 2. CONTRAINDICATIONS, and a statement that “pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” may be added to the 9.5 Pregnant Women section in 9. PRECAUTIONS CONCERNING PERSONS WITH SPECIFIC BACKGROUNDS, and the decision and the proposed revision were supported by all the expert advisors. Of note, the following opinions were expressed by expert advisors concerning the adverse reaction reports of spontaneous abortion and congenital anomalies associated with domperidone. (Refer to “2-2. Adverse reaction report” in this report.)

- Seven cases of spontaneous abortion have been reported in the adverse reaction reports for domperidone. (Refer to “2-2. Adverse reaction report” in this report.) However, taking into account a description in “Guideline for Obstetrical Practice in Japan (2023)” that 15% of clinically confirmed pregnancies result in abortions, these

events are not considered to be specific to domperidone.

- Regarding congenital anomalies reported for domperidone, assessing a causal relationship with the use of domperidone is difficult in each case. The number of cases for each event is also small with 1 or 2 cases, and no events of interest are noted at this point.

VII. Overall evaluation

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 4 based on the above discussions. (Appendix 4 is not included in this document. See “Detailed information on revisions of PRECAUTIONS” on the PMDA’s website.)

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Appendix 1

Summary of investigated drug products (as of January 24, 2025)

No.	Brand name	Marketing authorization holder	Indications/dosage and administration
1	Nauzelin Tablets 5, 10 Nauzelin OD tablets 5, 10	Kyowa Kirin Co., Ltd.	The following diseases and gastrointestinal symptoms (nausea, vomiting, inappetence, abdominal distension, upper abdominal discomfort, abdominal pain, heartburn, eructation) Adults: Chronic gastritis, gastroptosis, post gastrectomy syndrome When antineoplastic agents or levodopa preparations are administered Children: Cyclic vomiting syndrome, upper respiratory tract infection When antineoplastic agents are administered Adults: The usual daily dose is 10 mg of domperidone orally administered 3 times a day before meals. Note that the dose is 5 to 10 mg of domperidone 3 times a day administered orally before meals when levodopa preparations are administered. The dose should be adjusted depending on the age or symptoms of the patients. Children: The usual daily dose is 1.0 to 2.0 mg/kg of domperidone orally administered 3 times a day in divided doses before meals. The dose should be adjusted depending on the age, body weight, or symptoms of the patients. Note that the maximum daily dose should not exceed 30 mg of domperidone. In addition, the maximum daily dose should be 1.0 mg/kg of domperidone for children aged 6 years or older.
2	Domperidone Tablets 5mg "Kyorin," 10 mg "Kyorin"	KYORIN Rimedio Co., Ltd.	
3	Domperidone Tablets 5 mg "Sawai," 10 mg "Sawai"	Sawai Pharmaceutical Co., Ltd.	
4	Domperidone Tablets 5 mg "Tsuruhara," 10 mg "Tsuruhara"	Tsuruhara Pharmaceutical Co., Ltd.	
5	Domperidone Tablets 5 mg "Towa," 10 mg "Towa"	Towa Pharmaceutical Co., Ltd.	
6	Domperidone Tablets 5 mg "Nichi-iko," 10 mg "Nichi-iko"	Nichi-Iko Pharmaceutical Co., Ltd.	
7	Domperidone Tablets 5mg "Nissin," 10 mg "Nissin"	Nissin Pharmaceutical Co., Ltd.	
8	Domperidone Tablets 5mg "JG," 10 mg "JG"	Choseido Pharmaceutical Co., Ltd.	
9	Domperidone Tablets 5 mg "NIG," 10 mg "NIG"	Nichi-Iko Gifu Plant Co., Ltd.	
10	Domperidone Tablets 5 mg "YD," 10 mg "YD"	Yoshindo Inc.	
11	Domperidone tab. 5mg "EMEC," 10 mg "EMEC"	Alfresa Pharma Corporation	

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No.	Brand name	Marketing authorization holder	Indications/dosage and administration
12	Nauzelin Dry Syrup 1%	Kyowa Kirin Co., Ltd.	The following diseases and gastrointestinal symptoms (nausea, vomiting, inappetence, abdominal distension, abdominal pain) Children: Cyclic vomiting syndrome, pediatric diarrhoea, upper respiratory infection When antineoplastic agents are administered Children: Usually, 1.0 to 2.0 mg/kg of domperidone should be suspended in water when used, and it should be orally administered in 3 divided doses before meals. The dose should be adjusted depending on the age, body weight, or symptoms of the patients. Note that the daily dose should not exceed 30 mg of domperidone. The maximum daily dose should be 1.0 mg/kg of domperidone for children aged 6 years and older.
13	Domperidone DS for Pediatric 1% “Sawai”	Sawai Pharmaceutical Co., Ltd.	
14	Nauzelin Suppository 10, 30, 60	Kyowa Kirin Co., Ltd.	•Suppository 60 mg Adults: The following diseases and gastrointestinal symptoms (nausea, vomiting, inappetence, abdominal distension, upper abdominal discomfort, heartburn) After gastric and duodenal surgery When antineoplastic agents are administered Adults: The usual daily dose is 60 mg of domperidone twice a day administered rectally. The dose should be adjusted depending on the age or symptoms of the patients. •Suppository 10 mg, 30 mg Children: The following diseases and gastrointestinal symptoms
15	Domperidone Suppositories 10 mg “Takata,” 30 mg “Takata”	TAKATA Pharmaceutical Co., Ltd.	
16	Domperidone Suppositories 10 mg “JG,” 30 mg “JG”	Choseido Pharmaceutical Co., Ltd.	
17	Domperidone Suppositories 10mg “Nissin,” 30mg “Nissin”	Nissin Pharmaceutical Co., Ltd.	

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No.	Brand name	Marketing authorization holder	Indications/dosage and administration
			(nausea, vomiting, inappetence, abdominal distension, abdominal pain) Cyclic vomiting syndrome, pediatric diarrhoea, upper respiratory infection When antineoplastic agents are administered Children: The usual daily dose is 10 mg of domperidone administered rectally twice or 3 times a day for patients aged less than 3 years. The usual daily dose is 30 mg of domperidone administered rectally twice or 3 times a day for patients aged 3 years or older. The dose should be adjusted depending on the age, body weight, or symptoms of the patients.

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Appendix 3

Occurrence of events related to pregnancy and neonates note 1)

Event (PT)	Number of events
Neonatal disorders (SMQ)	
Irritability	1
Neonatal respiratory depression	1
Low birth weight baby	2
Congenital, familial and genetic disorders (SMQ)	
Fallot's tetralogy	1
Motor developmental delay	1
Duodenal obstruction	1
Ventricular septal defect	2
Cardiac disorder	1
Meningocele	1
Congenital genital malformation	1
Congenital aortic anomaly	1
Deafness congenital	1
Congenital skin dimples	1
Dacryostenosis congenital	1
Intellectual disability	1
Cerebral ventricle dilatation	1
Fanconi syndrome	1
Lactation related topics (incl neonatal exposure through breast milk) (SMQ)	
Hyperprolactinaemia	1
Lactation disorder	4
Breast swelling	1
Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)	
Threatened labour	1
Termination of pregnancy and risk of abortion (SMQ)	
Stillbirth	2
Abortion spontaneous	7
Abortion	1

Note 1) Events were retrieved by using Standardized MedDRA Query (SMQ (broad)) “Pregnancy and neonatal topics.” “Pregnancy and neonatal topics (SMQ (broad))” includes the following SMQs: “Congenital, familial and genetic disorders (SMQ (broad)),” “Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ (broad)),” “Foetal disorders (SMQ (broad)),” “Lactation related topics (incl neonatal exposure through breast milk) (SMQ (broad)),” “Neonatal disorders (SMQ(broad)),” “Termination of pregnancy and risk of abortion (SMQ(broad)),” and “Normal pregnancy conditions and outcomes (SMQ(broad))” (MedDRA version 27.1).