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Report on Investigation Results

November 8, 2022

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Nifedipine
[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

The Ministry of Health, Labour and Welfare (hereinafter referred to as "MHLW") has established the Information Provision Working Group (hereinafter referred to as the "WG") composed of physicians, pharmacists, experts in reproductive toxicity, etc. in the "Proper Use Promotion Project for Pregnant and Lactating Women,"[1] and it has been conducting the activities to promote the reflection of information about administration of drugs to pregnant and lactating women (hereinafter referred to as "pregnant women, etc.") to package inserts through organizing and evaluating the information accumulated at the Japan Drug Information Institute in Pregnancy in the National Center for Child Health and Development.

Administration of nifedipine (hereinafter referred to as "this drug") to "pregnant women or women who may be pregnant" has been contraindicated since the market approval of the brand name product, due to teratogenicity observed in toxicity studies using rats, mice, etc. As a result of reviewing the contraindications in 2011, the language was revised to "pregnant

[1]Pharmaceuticals and Medical Devices Safety Information No. 355 (issued by Pharmaceutical Safety and Environmental Health Bureau)
https://www.mhlw.go.jp/content/11120000/000307752.pdf (in Japanese) (accessed on September 15, 2022)
https://www.pmda.go.jp/files/000225335.pdf (in English)

women (less than 20 weeks of pregnancy) or women who may be pregnant."[2]

Recently, given the increasing need in clinical settings for strict blood pressure control during the entire gestational age, the appropriateness of contraindicating this drug to "pregnant women (less than 20 weeks of pregnancy) or women who may be pregnant" in the package insert was investigated by the WG, and a report (hereinafter referred to as the "WG report") (Appendix 2) was prepared, taking into account that this drug has a high prescription rate in clinical settings among calcium channel blockers, which are considered as the first-line drugs for hypertension without compelling indications. (Appendix 2 is not included in this document. See the Japanese original report.) In response to the WG report, the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW requested the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") to conduct an investigation on the revision of Precautions of this drug regarding administration to pregnant women/nursing mothers under the "Notification on Request of Investigation Related to the Safety of Drugs, etc." (PSEHB/PSD 0513 No.4, dated May 13, 2022). PMDA accordingly conducted an investigation on the request and discussed the necessity of revision of the package insert.

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 (less than 20 weeks of pregnancy) or women who may be pregnant" in the package insert.

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. Description in overseas package insert	7. Appropriateness of lifting the contraindications

[2] Material 1 for the 2011 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (2nd meeting) (https://www.mhlw.go.jp/stf/shingi/2r9852000001hbq8.html) (accessed on September 15, 2022)

4. Animal study	8. Proposed revision of the package insert

IV. Investigation by PMDA

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

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

1-1. Published literature

Articles concerning teratogenicity of this drug in nonclinical studies were searched by the WG (searched on May 14, 2019). No more information was obtained than the knowledge evaluated at the application for marketing authorization of the brand name product and at the review of contraindications of this drug in 2011.

Articles concerning teratogenicity of this drug in nonclinical studies, which were published after the search date for the WG report, were retrieved by the marketing authorization holder of the brand name product (Bayer Yakuhin Ltd.) using similar search conditions[3] as for the WG report (searched on June 1, 2022). As a result of evaluating 17 retrieved reports, no reports on teratogenicity of this drug were found.

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

2-1. Published literature

Articles concerning calcium channel blockers and pregnancy were retrieved by the WG (searched on August 7, 2018). A total of 11 reports including 10 retrieved reports and 1 identified by handsearching were found to be investigations on teratogenicity in clinical uses. (Refer to "5. Reports on Clinical uses" in the WG report.) Of note, 3 of the 11 reports had been evaluated at the review of contraindications of this drug in 2011 (reference 1, 3, and 4 in the WG report).

Among the 11 reports, 10 study reports referred to risk estimation indexes (risk ratio, odds ratio, etc.) for congenital anomalies and the remaining 1 report did not include those indexes. Of 10 reports on controlled studies, 6 reports (including 3 reports describing the use of this drug) showed that administration of calcium channel blockers in the first trimester of pregnancy did not increase the risk of congenital anomalies (reference 1 to 4, 8, and 10 in

[3] Refer to p.25 in the WG report.

the WG report). In 1 report, administration of this drug did not increase the risk of oesophageal obstruction, although it is unknown whether or not this drug was used in the first trimester of pregnancy (reference 11 in the WG report). In another report, while administration of calcium channel blockers in the first trimester of pregnancy did not increase the risk of overall congenital anomalies (for any specific type of congenital anomaly), an increased risk of congenital anomalies of upper gastrointestinal tract was observed in the evaluation by the type of congenital anomaly (reference 6 in the WG report). There were 2 reports, with no information on whether or not this drug was used in the first trimester of pregnancy, that showed increased risks by the use of this drug, one on the risk of craniofacial malformation, and the other on the risk of right-sided obstructive defects of the heart (reference 5 and 9 in the WG report). In 1 study report with no description of risk estimation indexes, 8 females, who had been exposed to calcium channel blockers at the time of detection of pregnancy, were followed up, and all of them delivered healthy offspring (reference 7 in the WG report).

Articles concerning calcium channel blockers including this drug and pregnancy, which were published after the search date for the WG report, were retrieved by the marketing authorization holder of the brand name product (Bayer Yakuhin Ltd.) using similar search conditions[4] as for the WG report (searched on June 3, 2022). One report (article a), shown below), among the 8 retrieved articles, evaluated the relationship between calcium channel blockers and teratogenicity, showing that exposure to amlodipine in the first trimester of pregnancy did not increase the risk of congenital anomalies.

a) Safety of Amlodipine in Early Pregnancy (J Am Heart Assoc. 2019; 8: e012093.)

A total of 231 women with chronic hypertension, including those who received amlodipine or other antihypertensives during early pregnancy, were recruited, and frequencies of morphologic abnormalities in their 231 offspring born between April 2008 and July 2016 were investigated. 48 neonates exposed to amlodipine in the first trimester (amlodipine group), 54 neonates exposed to antihypertensives other than amlodipine (other antihypertensive group), and 129 neonates not exposed to antihypertensives (no-antihypertensive group) were evaluated. The incidence of morphologic abnormalities of offspring in each group was 2/48

[4] Refer to p.25 in the WG report.

(4.2%) in amlodipine group, 3/54 (5.6%) in other antihypertensive group, and 6/129 (4.7%) in no-antihypertensive group. The odds ratio comparing amlodipine group and other antihypertensive group was 0.74 (95% CI: 0.118–4.621), and that comparing amlodipine group and no-antihypertensive group was 0.89 (95% CI: 0.174–4.575).

2-2. Adverse reaction report

The number of case reports of adverse reaction for this drug concerning pregnancy and neonates in Japan in the PMDA's database for adverse reactions, etc. reports[5] is shown in Appendix 3 with a total of 211 events in 126 reports (data lock: May 31, 2022).

There were no reports related to limb anomalies, for which a potential increased risk is indicated in nonclinical studies. As events related to congenital anomalies, atrial septal defect (2 events), myotonic dystrophy, cardiac septal defect, congenital cystic kidney disease, congenital pulmonary valve stenosis, and coarctation of the aorta (1 event each) have been reported. However, it is possible that primary diseases, etc., which were treated with drugs, might have affected the occurrence of each event.

A total of 9 events related to foetal death, including late abortion (1 event), foetal death (7 events), and stillbirth (1 event), have been reported. The causal relationship between this drug and the reported 9 events are as follows: 1 event of foetal death was ruled out by the reporter (author of the literature) after obtaining additional information; 1 event of foetal death was considered by the reporter (physician) as “possibly unlikely”; information on the 7 other events was not reported by the reporters (physicians or authors). It is possible that primary diseases, etc., which were treated with drugs, might have affected the occurrence of each event.

V. PMDA’s judgment based on the WG report and “IV. Investigation by PMDA”

Based on the WG report, the results of “IV. Investigation by PMDA,” and the clinical need for this drug, PMDA considers, for the following reasons, that “pregnant women (less than 20 weeks of pregnancy) or women who may be pregnant” may be deleted from the CONTRAINDICATIONS section in the package insert for this drug and that this drug may be administered to pregnant women or women who may be pregnant if the potential therapeutic benefits are considered to outweigh the potential risks.

[5] Cases which fell under Standardized MedDRA Query (SMQ) “pregnancy and neonatal topics” were retrieved.

- The Japanese Society of Hypertension Guidelines for the Management of Hypertension state that the initial antihypertensive drug (first-line drugs) should be selected from calcium channel blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors and diuretics in hypertensive patients without compelling indications. (Refer to “2. Background” in the WG report.)
- This drug is recommended as first-line or second-line antihypertensive drugs during pregnancy including the first trimester of pregnancy in Japanese and overseas guidelines. (Refer to “6. Japanese and overseas guidelines” in the WG report.)
- In the published literature on clinical use, there have been reports of an increased risk of congenital anomalies of upper gastrointestinal tract with the use of calcium channel blockers in the first trimester of pregnancy and craniofacial malformation or right-sided obstructive defects of the heart with the use of this drug, although it is unknown whether this drug was used in the first trimester. On the other hand, there has been a report that administration of this drug did not increase the risk of oesophageal obstruction which is one of the congenital anomalies of upper gastrointestinal tract, although it is unknown whether or not this drug was used in the first trimester of pregnancy. In addition, there have been multiple reports that use of calcium channel blockers in the first trimester of pregnancy did not increase the risk of congenital anomalies. (The use of this drug is mentioned in 3 reports among 6 reports.) Taking these results into account, no consensus has been reached on whether or not the administration of this drug increases the risk of congenital anomalies. (Refer to “5. Reports on clinical uses” in the WG report and “IV-2-1. Published literature” in this report.)
- Regarding the overseas package inserts (the US, the UK, Canada, Australia), while administration of this drug to pregnant women is contraindicated in the package inserts of Canada and Australia since teratogenicity was observed in nonclinical studies, it is not contraindicated in the US and the UK, and the use of this drug is allowed by weighing the potential benefits and risks. Thus, there is no uniformity among countries in contraindicating this drug to pregnant women. (Refer to “3. Description in overseas package insert” in the WG report.)

VI. Expert discussion

PMDA decided that “pregnant women (less than 20 weeks of pregnancy) or women who

may be pregnant" may be deleted from the CONTRAINDICATIONS section in the package insert and that this drug may be administered to pregnant women or women who may be pregnant if the potential therapeutic benefits are considered to outweigh the potential risks, and the decision was supported by all the expert advisors.

VII. Overall evaluation

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 the Detailed information on revisions of PRECAUTIONS.)

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Appendix 1

Summary of drug products investigated (as of September 1, 2022)

No.	Brand name	Marketing authorization holder	Indications/dosage and administration
1	Adalat-L10, L20, CR10, CR20, CR40	Bayer Yakuhin Ltd.	**<L Tablets 10 mg, 20 mg>** **·Essential hypertension, renal hypertension** The usual daily dose for adults is 10-20 mg of nifedipine twice a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **·Angina pectoris** The usual daily dose for adults is 20 mg of nifedipine twice a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **<CR Tablets 10 mg, 20 mg, 40 mg>** **·Hypertension** The usual daily dose for adults is 20-40 mg of nifedipine once a day administered orally. The administration should be started at daily dose of 10-20 mg. The dose may be titrated up as necessary. The dose may be increased up to 40 mg twice a day in cases which are not adequately responsive with administration of 40 mg/day. **·Renal parenchymal hypertension, renovascular hypertension**
2	Sepamit-R Capsules 10, 20, Sepamit-R Fine Granules 2%, Sepamit Fine Granules 1%	Nihon Generic Co., Ltd.	
3	Nifedipine L Tablets 10 mg “Kyorin,” 20 mg “Kyorin”	KYORIN Rimedio Co., Ltd.	
4	Nifedipine CR Tablets 10 mg “NP,” 20 mg “NP,” 40 mg “NP”	Nipro Corporation	
5	Nifedipine L Tablets 10 mg “Sanwa,” 20 mg “Sanwa,” Nifedipine CR Tablets 10 mg “Sanwa,” 20 mg “Sanwa,” 40 mg “Sanwa”	Sanwa Kagaku Kenkyusho Co., Ltd.	
6	Nifedipine L Tablets 10 mg	Kyoto	

	"KPI," 20 mg "KPI"	Pharmaceutical Industries Co., Ltd.	The usual daily dose for adults is 20-40 mg of nifedipine once a day administered orally. The administration should be started at daily dose of 10-20 mg. The dose may be titrated up as necessary. **·Angina pectoris, variant angina** The usual daily dose for adults is 40 mg of nifedipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. The maximum daily dose should be 60 mg once a day. **<R Capsules 10, 20>** **·Essential hypertension, renal hypertension** The usual daily dose for adults is 10-20 mg of nifedipine twice a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **·Angina pectoris** The usual daily dose for adults is 20 mg of nifedipine twice a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **<R Fine Granules 2%>** **·Essential hypertension** The usual daily dose for adults is 10-20 mg of nifedipine twice a day administered orally after a meal. The dose should be adjusted depending on the symptoms of the patients.
7	Nifedipine L Tablets 10 mg "ZE," 20 mg "ZE," Nifedipine CR Tablets 10 mg "ZE," 20 mg "ZE," 40 mg "ZE"	Zensei Pharmaceutical Co., Ltd.	
8	Nifedipine L Tablets 10 mg "Sawai," 20 mg "Sawai," Nifedipine CR Tablets 10 mg "Sawai," 20 mg "Sawai," 40 mg "Sawai," Nifedipine Capsules 5 mg "Sawai," 10mg "Sawai"	Sawai Pharmaceutical Co., Ltd.	
9	Nifedipine L Tablets 10 mg "Tsuruhara," 20 mg "Tsuruhara," Nifedipine Capsules 5 mg "Tsuruhara," Nifedipine Tablets 10 mg "Tsuruhara," Nifedipine Fine Granules 1% "Tsuruhara"	Tsuruhara Pharmaceutical Co., Ltd.	

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E-mail: safety.info@pmda.go.jp

10	Nifedipine L Tablets 10 mg "Towa," 20 mg "Towa," Nifedipine CR Tablets 10 mg "Towa," 20 mg "Towa," 40 mg "Towa"	Towa Pharmaceutical Co., Ltd.	**·Angina pectoris** The usual daily dose for adults is 20 mg of nifedipine twice a day administered orally after a meal. The dose should be adjusted depending on the symptoms of the patients. **<Fine Granules 1%>** **Sepamit Fine Granules** ·Essential hypertension, renal hypertension, angina pectoris The daily dose is 10 mg of nifedipine 3 times a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **Nifedipine Fine Granules "Tsuruhara"** ·Essential hypertension, renal hypertension, angina pectoris The usual daily dose for adults is 10 mg of nifedipine 3 times a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **<Capsules 5 mg, 10 mg*, Tablets 10mg, Fine granules 1%>** **·Essential hypertension, renal hypertension, angina pectoris** The usual daily dose for adults is 10 mg of nifedipine 3 times a day administered orally. The dose should be adjusted depending on the symptoms of the patients. *The dosage and administration for Nifedipine Capsules 10 mg "Sawai" is as follows: "The daily dose
11	Nifedipine L Tablets 10 mg "Nichi-Iko," 20 mg "Nichi-Iko," Nifedipine CR Tablets 10 mg "Nichi-Iko," 20 mg "Nichi-Iko," 40 mg "Nichi-Iko"	Nichi-Iko Pharmaceutical Co., Ltd.	
12	Nifedipine Capsules 5 mg "Teva," 10mg "Teva"	Teva Takeda Yakuhin Ltd.	

			is 1 capsule 3 times a day administered orally. The dose should be adjusted depending on the 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 disorder (SMQ)	
Apgar score low	1
Poor sucking reflex	1
Transient tachypnoea of the newborn	2
Neonatal asphyxia	1
Neonatal respiratory distress syndrome	6
Neonatal respiratory distress	1
Hyperbilirubinaemia neonatal	1
Neonatal hypoxia	1
Premature baby	31
Low birth weight baby	35
Small for dates baby	1
Retinopathy of prematurity	1
Congenital, familial and genetic disorders (SMQ)	
Myotonic dystrophy	1
Cardiac septal defect	1
Atrial septal defect	2
Congenital cystic kidney disease	1
Pulmonary valve stenosis congenital	1
Coarctation of the aorta	1
Foetal disorders (SMQ)	
Intrauterine infection	1
Foetal distress syndrome	2
Foetal heart rate deceleration abnormality	2
Nonreassuring foetal heart rate pattern	3
Bradycardia foetal	3
Foetal disorder	1
Foetal heart rate disorder	1
Baseline foetal heart rate variability disorder	3
Foetal growth restriction	16
Oligohydramnios	2
Amniotic fluid volume decreased	1
Umbilical cord vascular disorder	2
Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)	
HELLP syndrome	3
Uterine rupture	2
Pre-eclampsia	4
Foetal exposure timing unspecified	2
Peripartum cardiomyopathy	3

Premature labour	4
Premature rupture of membranes	2
Premature delivery	19
Placental insufficiency	2
Retroplacental haematoma	1
Placental disorder	1
Premature separation of placenta	3
Caesarean section	20
Gestational hypertension	4
Exposure during pregnancy	3
Obstructed labour	1
Benign hydatidiform mole	1
Subchorionic haematoma	1
Termination of pregnancy and risk of abortion (SMQ)	
Abortion late	1
Stillbirth	1
Foetal death	7

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