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Report on Investigation Results

November 8, 2022

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Amlodipine besilate
[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 amlodipine besilate (hereinafter referred to as “this drug”) to “pregnant women or women who may be pregnant” is contraindicated because prolongation of both the gestational period and the duration of labor was observed from administration to rats in late pregnancy, which was evaluated at the initial application for market approval of the brand name product.

[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)

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 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 based 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 or women who may be pregnant" in the package insert.

Table 1 Table of contents of 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
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 clinical uses (Refer to “5. Reports on clinical uses” in the WG report.)

1-1. Published literature

Published articles concerning calcium channel blockers and pregnancy were retrieved by the WG (searched on August 7, 2018). Seven retrieved reports (excluding those on nifedipine alone) 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.) Prolongation of both the gestational period and the duration of labor was not evaluated, as it occurs in routine practice and it was considered possible to be treated with reference to Japanese guidelines, etc.

Among the 8 reports, 7 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 the 7 reports referring to risk estimation indexes, 6 reports (including 2 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, 7, and 8 in the WG report). In the 1 remaining report, although 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 5 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 6 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 using similar search conditions as for the WG report[2] (searched on June 3, 2022). One report (article a), shown below), among the 8 retrieved articles, evaluated the relationship between calcium channel blockers and

[2] Refer to p.22 in the WG report.

teratogenicity, showing that exposure to amlodipine in the first trimester 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 (4.2%) 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).

1-2. Adverse reaction report

The number of case reports of adverse reaction for this drug in Japan concerning pregnancy and neonates in the PMDA's database for adverse reactions, etc. reports[3] is shown in Appendix 3 with a total of 35 events in 20 reports (data lock: May 31, 2022). No events of prolongation of both the gestational period and the duration of labor, for which concerns were raised based on the study results in rats, have been reported. As events related to congenital anomalies, left ventricle outflow tract obstruction, ventricular septal defect, atrial septal defect, congenital anomalies, congenital inguinal hernia, arteriovenous malformation, hypospadias, and hypertrophic cardiomyopathy (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.

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 or women

[3] Cases which fell under Standardized MedDRA Query (SMQ) "pregnancy and neonatal topics" were retrieved.

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.

- 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.)
- There have been no reports of adverse reactions related to prolongation of both the gestational period and the duration of labor, for which concerns were raised based on the study results in rats. In the WG report, it is judged that prolongation of both the gestational period and the duration of labor can be treated with reference to "Guideline for Obstetrical Practice in Japan (2020)," etc. as it occurs in routine practice. (Refer to "7. Appropriateness of lifting the contraindications" in the WG report.)
- No Japanese and overseas guidelines identified any particular safety concerns regarding administration of this drug to pregnant women. (Refer to "6. Japanese and overseas guidelines" in the WG report.)
- According to foreign package inserts (the US, the UK, Canada, and Australia), administration of this drug to pregnant women is not contraindicated in any of the countries. (Refer to "3. Description in overseas package insert" in the WG report.)
- Although there is a report that use of calcium channel blockers increased the risk of congenital anomalies of upper gastrointestinal tract, another report showed that administration of this drug did not increase the risk of congenital anomalies. In addition, multiple studies reported that use of calcium channel blockers did not show an increased risk of congenital anomalies. (The use of this drug is mentioned in 2 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-1-1. Published literature" in this report.)

VI. Expert discussion

PMDA decided that “pregnant women 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 generally supported by expert advisors with the following opinions expressed:

- Calcium channel blockers or nifedipine is listed as the recommended drugs in international guidelines. It is basically considered that nifedipine is used as a first-line drug. There is a concern that clinical data for this drug may not be as sufficient as those for nifedipine.
- Setting contraindications only in Japan based on concerns (prolongation of both the gestational period and the duration of labor that were observed in nonclinical study results), which can be treated with clinical care, is considered to be an excessive measure.

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	Amlodin Tablets 2.5 mg, 5 mg, 10 mg, Amlodin OD Tablets 2.5 mg, 5 mg, 10 mg	Sumitomo Pharma Co., Ltd.	**<Tablets 2.5 mg, 5 mg, OD Tablets 2.5 mg, 5 mg>** **・Hypertension** The usual daily dose for adults is 2.5-5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. The dose may be increased up to 10 mg once a day in cases which are not adequately responsive. The usual daily dose for children of 6 years old and older is 2.5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the age, body weight, or symptoms of the patients. **・Angina pectoris** The usual daily dose for adults is 5 mg of amlodipine
2	Norvasc Tablets 2.5 mg, 5 mg, 10 mg, Norvasc OD Tablets 2.5 mg, 5 mg, 10 mg	Viatris Pharmaceuticals Japan Inc.	
3	Amlodipine Tablets 2.5 mg “Meiji,” 5 mg “Meiji,” 10 mg “Meiji,” Amlodipine OD Tablets 2.5 mg “Meiji,” 5 mg “Meiji,” 10 mg “Meiji”	Meiji Seika Pharma Co., Ltd.	
4	Amlodipine Tablets 2.5 mg "Aska," 5 mg "Aska," 10 mg "Aska," Amlodipine OD Tablets 2.5 mg "Aska," 5 mg "Aska," 10 mg "Aska"	Aska Pharmaceutical Co., Ltd.	
5	Amlodipine Tab. 2.5 mg "EMEC," 5 mg "EMEC," 10 mg "EMEC," Amlodipine OD Tab. 2.5 mg "EMEC," 5 mg "EMEC," 10 mg "EMEC"	Elmed Co., Ltd.	
6	Amlodipine Tablets 2.5 mg "Kyorin," 5 mg "Kyorin," 10 mg "Kyorin," Amlodipine OD Tablets 2.5 mg "Kyorin," 5 mg "Kyorin," 10 mg "Kyorin"	KYORIN Rimedio Co., Ltd.	
7	Amlodipine Tablets 2.5 mg "Isei," 5 mg "Isei," 10 mg "Isei,"	KOA ISEI CO., LTD.	

	Amlodipine OD Tablets 2.5 mg "Isei," 5 mg "Isei," 10 mg "Isei"		once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **<Tablets 10 mg, OD Tablets 10 mg>** **・Hypertension** The usual daily dose for adults is 2.5-5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. The dose may be increased up to 10 mg once a day in cases which are not adequately responsive. **・Angina pectoris** The usual daily dose for adults is 5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. **<OD Film 2.5 mg, 5 mg>**
8	Amlodipine Tablets 2.5 mg "TYK," 5 mg "TYK," 10 mg "TYK"	KOA BIOTECH BAY CO., LTD.	
9	Amlodipine Tablets 2.5 mg [Sandoz], 5 mg [Sandoz], Amlodipine OD Tablets 2.5 mg [Sandoz], 5 mg [Sandoz], 10 mg [Sandoz]	Sandoz K.K.	
10	Amlodipine Tab. 2.5 mg "Fuso," 5 mg "Fuso," 10 mg "Fuso," Amlodipine OD Tab. 2.5 mg "Fuso," 5 mg "Fuso," 10 mg "Fuso"	Shiono Chemical Co., Ltd.	
11	Amlodipine Besilate Tab. 2.5 mg "Kaken," 5 mg "Kaken," 10 mg "Kaken"	Daito Pharmaceutical Co., Ltd.	
12	Amlodipine Tablets 2.5 mg "Tanabe," 5 mg "Tanabe," 10 mg "Tanabe"	Nipro ES Pharma co.,Ltd.	
13	Amlodipine Tab. 2.5 mg "NP," 5 mg "NP," 10 mg "NP," Amlodipine OD Tab. 2.5 mg "NP," 5 mg "NP," 10 mg "NP"	Nipro Corporation	
14	Amlodipine Tablets 2.5 mg [Pfizer], 5 mg [Pfizer], 10 mg [Pfizer], Amlodipine OD Tablets 2.5 mg [Pfizer], 5 mg [Pfizer], 10 mg [Pfizer]	Pfizer UPJ G.K.	
15	Amlodipine Tab. 2.5 mg "YD," 5 mg "YD," 10 mg "YD," Amlodipine OD Tab. 2.5 mg "YD," 5 mg "YD," 10 mg "YD"	Yoshindo Inc.	
16	Amlodipine Tablets 2.5 mg "Amel," 5 mg "Amel," 10 mg "Amel," Amlodipine OD Tablets 2.5 mg "Amel," 5 mg "Amel," 10 mg "Amel"	Kyowa Pharmaceutical Industry Co., Ltd.	

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17	Amlodipine Tablets 2.5 mg "Kunihiro," 5 mg "Kunihiro," 10 mg "Kunihiro"	Kokando Pharmaceutical Co., Ltd.	**・Hypertension** The usual daily dose for adults is 2.5-5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients. The dose may be increased up to 10 mg once a day in cases which are not adequately responsive. The usual daily dose for children of 6 years old and older is 2.5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the age, body weight, or symptoms of the patients. **・Angina pectoris** The usual daily dose for adults is 5 mg of amlodipine once a day administered orally. The dose should be adjusted depending on the symptoms of the patients.
18	Amlodipine Tablets 2.5 mg "Takata," 5 mg "Takata," 10 mg "Takata," Amlodipine OD Tablets 2.5 mg "Takata," 5 mg "Takata," 10 mg "Takata"	TAKATA Pharmaceutical Co., Ltd.	
19	Amlodipine Tab. 2.5 mg "KN," 5 mg "KN," 10 mg "KN," Amlodipine OD Tab. 2.5 mg "KN," 5 mg "KN," 10 mg "KN"	Kobayashi Kako co.,Ltd	
20	Amlodipine OD Tablets 2.5 mg "ZE," 5 mg "ZE," 10 mg "ZE"	Zensei Pharmaceutical Co., Ltd.	
21	Amlodipine Tablets 2.5 mg "Taiyo," 5 mg "Taiyo," 10 mg "Taiyo," Amlodipine Besilate O.D. Tab. 2.5 mg "Kaken," 5 mg "Kaken," 10 mg "Kaken"	Daiko Pharmaceutical Co., Ltd.	
22	Amlodipine Tablets 2.5 mg "Ohara," 5 mg "Ohara," 10 mg "Ohara"	Ohara Pharmaceutical Co., Ltd.	
23	Amlodipine Tablets 2.5 mg "DSEP," 5 mg "DSEP," 10 mg "DSEP"	Daiichi Sankyo Espha Co., Ltd.	
24	Amlodipine Tablets 2.5 mg "Sawai," 5 mg "Sawai," 10 mg "Sawai," Amlodipine OD Tablets 2.5 mg "Sawai," 5 mg "Sawai," 10 mg "Sawai"	Sawai Pharmaceutical Co., Ltd.	

25	Amlodipine Tab. 2.5 mg "TCK," 5 mg "TCK," 10 mg "TCK," Amlodipine OD Tab. 2.5 mg "TCK," 5 mg "TCK," 10 mg "TCK"	Tatsumi Kagaku Co., Ltd.	
26	Amlodipine Tab. 2.5 mg "CH," 5 mg "CH," 10 mg "CH," Amlodipine OD Tab. 2.5 mg "CH," 5 mg "CH," 10 mg "CH"	Choseido Pharmaceutical Co.,Ltd.	
27	Amlodipine Tablets 2.5 mg "Tsuruhara," 5 mg "Tsuruhara," 10 mg "Tsuruhara"	Tsuruhara Pharmaceutical Co., Ltd.	
28	Amlodipine Tablets 2.5 mg "Nichi-Iko," 5 mg "Nichi-Iko," 10 mg "Nichi-Iko," Amlodipine OD Tablets 2.5 mg "Nichi-Iko," 5 mg "Nichi-Iko," 10 mg "Nichi-Iko"	Nichi-Iko Pharmaceutical Co., Ltd.	
29	Amlodipine Tab. 2.5 mg "NS," 5 mg "NS," 10 mg "NS," Amlodipine OD Tab. 2.5 mg "NS," 5 mg "NS," 10 mg "NS"	Nissin Pharmaceutical Co., Ltd.	
30	Amlodipine Tab. 2.5 mg "JG," 5 mg "JG," 10 mg "JG," Amlodipine OD Tab. 2.5 mg "JG," 5 mg "JG," 10 mg "JG"	Nihon Generic Co., Ltd.	
31	Amlodipine Tablets 2.5 mg "Chemiphar," 5 mg "Chemiphar," 10 mg "Chemiphar," Amlodipine OD Tablets 2.5 mg "Chemiphar," 5 mg "Chemiphar," 10 mg "Chemiphar"	Nihon Pharmaceutical Industry Co., Ltd.	
32	Amlodipine Besilate Tablets 2.5 mg "F," 5 mg "F"	Fuji Pharma Co., Ltd.	
33	Amlodipine OD Tab. 2.5 mg "Takeda Teva," 5 mg "Takeda Teva," 10 mg "Takeda Teva"	Teva Takeda Pharma Ltd.	

34	Amlodipine Tab. 2.5 mg "QQ," 5 mg "QQ," 10 mg "QQ," Amlodipine OD Film 2.5 mg "QQ," 5 mg "QQ"	Kyukyu Pharmaceutical Co.,Ltd.	

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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
Disseminated intravascular coagulation in newborn	1
Premature baby	3
Low birth weight baby	4
Small for dates baby	1
Congenital, familial and genetic disorders (SMQ)	
Left ventricle outflow tract obstruction	1
Ventricular septal defect	1
Atrial septal defect	1
Congenital anomaly	1
Congenital inguinal hernia	1
Arteriovenous malformation	1
Hypospadias	1
Hypertrophic cardiomyopathy	1
Foetal disorders (SMQ)	
Foetal Bradycardia	1
Foetal growth restriction	4
Oligohydramnios	3
Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)	
HELLP syndrome	1
Premature labour	1
Gestational hypertension	1
Foetal exposure during pregnancy	1
Maternal exposure during pregnancy	3
Termination of pregnancy and risk of abortion (SMQ)	
Abortions spontaneous	1
Abortion early	1

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)”