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Report on Investigation Results

February 1, 2024

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Carvedilol
[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 animal studies, etc. in the “Proper Use Promotion Project for Pregnant and Lactating Women,”[1] and it has been conducting activities to promote the reflection of information about administration of drugs to pregnant and lactating women 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 carvedilol (hereinafter referred to as “this drug”) to “pregnant women or women who may be pregnant” is contraindicated. It was decided not to administer this drug to pregnant women or women who may be pregnant at the marketing approval of the brand-name product (February, 1993) for the following reasons: A decrease in the corpus luteum count and an increase in skeletal anomalies (shortening of 13th ribs) have been reported at

[1] Webpage of the MHLW (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/ninshin_00002.html) (only in Japanese) (accessed on September 26, 2023)

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approximately 900-fold the clinical dose (300 mg/kg) in studies in rats before pregnancy and in early pregnancy; the safety of administration during pregnancy has not been established in humans.

Recently, 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; Appendix 2 is not included in this document. See the Japanese original report.) was prepared considering that this drug is indicated for chronic cardiac failure due to ischaemic heart disease or dilated cardiomyopathy and the use of this drug for rapid atrial fibrillation or cardiac failure accompanied by systolic failure is recommended among β-blockers (including α/β-blockers). 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, etc. under the “Notification on Request of Investigation Related to the Safety of Drugs, etc.” (PSEHB/PSD 0731 No.2, dated July 31, 2023). The PMDA accordingly conducted an investigation based on 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 this drug.

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. Descriptions in overseas product labeling	7. Appropriateness of lifting the contraindications
4. Animal study	8. Proposed revision of package inserts

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

Reproductive toxicity studies at the time of approval of the brand-name product of this drug were evaluated by the WG (Refer to "4. Animal study" in the WG report).

In addition to the evaluation by the WG, articles concerning reproductive toxicity of this drug published after marketing approval were searched[2] by the marketing authorization holder of the brand-name product (Daiichi Sankyo Co., Ltd.). However, no relevant published articles were found.

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

2-1. Published literature

Published articles concerning this drug and pregnancy were searched and 6 reports (5 reports of epidemiological studies, 1 report of case report) were retrieved by the WG (searched on January 15, 2021, additionally searched on March 23, 2023). (Refer to "5. Reports on clinical uses" in the WG report.)

Of the 5 reports of epidemiological studies, 3 reports evaluated the effects of exposure during the first trimester of pregnancy (reference 2, 3, and 4 in the WG report), 2 reports evaluated the exposure from the second trimester of pregnancy onward (reference 1, 3 in the WG report), and the timing of exposure is uncertain for 1 report (reference 6 in the WG report). (Duplicated reports are included.) The summary is as shown below.

Among the 3 study reports in which the effects of exposure during the first trimester of pregnancy were evaluated, 1 study report showed a significantly increased risk of cardiac malformation among infants in the group exposed to β-blockers in early pregnancy (778 patients using β-blockers only, 9 patients using this drug) compared with the population not exposed to β-blockers (reference 2 in the WG report). One study report showed no increased

[2] Search database (Embase 1980 to 2023 August 18, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to August 18, 2023), search conditions (carvedilol, pregnancy, teratogenicity, reproductive toxicity, teratogenic effect, fetus, gestational), target period (from January 19, 1993 to July 31, 2023)

risk for overall congenital anomalies (for any specific type of congenital anomaly) and various congenital anomalies including cardiac malformations in the group exposed to β-blockers (the name of the drugs unknown) during the first trimester of pregnancy compared with the group not exposed to β-blockers (reference 3 in the WG report). One study report showed a significantly increased risk of congenital heart disease in the group exposed to β-blockers during the first trimester of pregnancy (the number of patients using this drug unknown) compared with the unexposed group. However, no increased risk of congenital heart disease was observed after adjusting for maternal age, maternal body mass index, maternal comorbidities, etc. (reference 4 in the WG report).

Among the 2 study reports in which the effects of exposure from the second trimester of pregnancy onward were evaluated, one study report showed a significantly increased risk of respiratory failure, hypoglycaemia, perinatal jaundice, digestive system disorders, and feeding problems in infants in the group exposed to β-blockers (the name of the drugs unknown) during the third trimester of pregnancy compared with the unexposed group (reference 3 in the WG report). One study report showed a significant increase in foetal growth restriction in the group exposed to β-blockers (the name of the drugs unknown) for at least 2 weeks before delivery compared with the unexposed group, although no increase in foetal growth restriction was noted in the group exposed to this drug compared with the unexposed group (reference 1 in the WG report).

One study report for which the timing of maternal exposure is unknown showed that neonatal hypoglycaemia significantly increased in the group exposed to carvedilol compared with the unexposed group and that small for gestational age (SGA) was observed significantly more frequently in the group exposed to β-blockers compared with the unexposed group or the group exposed to carvedilol, although no significant increase of congenital heart disease was observed in the group exposed to β-blockers and the group exposed to carvedilol (reference 6 in the WG report).

Refer to the WG report for the case report (reference 5 in the WG report).

2-2. 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 is shown in Appendix 3 with a total of 11 events in 11 reports (excluding duplicate cases) (data lock:

August 31, 2023).

The events for which 2 or more events were reported were 3 events of maternal exposure during pregnancy and 2 events each of oligohydramnios and neonatal hypoglycaemia.

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

3-1. Descriptions concerning the use of this drug in pregnant women in the guidelines

The WG investigated the descriptions concerning the use of this drug in pregnant women in Japanese and overseas guidelines (Refer to "6. Japanese and overseas guidelines" in the WG report.).

After the preparation of the WG report, "Guideline for Obstetrical Practice in Japan (2020) " was updated to "Guideline for Obstetrical Practice in Japan (2023)" among the Japanese guidelines described in the WG report. The descriptions concerning the use of this drug in pregnant women in the "Guideline for Obstetrical Practice in Japan (2023)" are as follows.

(1) Guideline for Obstetrical Practice in Japan (2023) (Japan Society of Obstetrics and Gynecology/Japan Association of Obstetricians and Gynecologists)

CQ104-3. Table 3 lists "carvedilol, bisoprolol (note that, similarly to other β-blockers, they may pose a risk of foetal growth restriction and neonatal beta-blocking symptoms after 14 weeks of pregnancy)" as "the drugs which can be considered as bringing no clinically significant effects on foetus in case they are used only during the first trimester of pregnancy, among drugs which are so called contraindicated drugs in the package insert."

In addition, its explanation states that "it is unlikely that carvedilol and bisoprolol are teratogenic or foetally toxic during the first trimester of pregnancy, although they may pose a risk of foetal growth restriction and neonatal beta-blocking symptoms from the second trimester of pregnancy onward."

3-2. Descriptions concerning clinical positioning of this drug in the guidelines

In addition to the evaluation by the WG, the PMDA investigated the Japanese guidelines concerning clinical positioning of this drug for the indicated diseases.

(1) Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure (2017 edition) (Joint Guidelines of the Japanese Circulation Society and the Japanese

Heart Failure Society)

For the cardiac failure with decreased left ventricular ejection fraction (LVEF), administration of β-blockers is recommended to improve the prognosis of symptomatic patients. Among β-blockers, this drug and bisoprolol for which improvement of life prognosis and reduction in mortality rate are shown in large-scale studies in patients with chronic cardiac failure are recommended.

(2) Guideline on Pharmacotherapy of Cardiac Arrhythmias (2020 edition) (Joint Guidelines of the Japanese Circulation Society and Japanese Heart Rhythm Society)

As a pharmacotherapy used for heart rate control therapy in rapid atrial fibrillation (AF), heart rate control using long-term β-blockers (this drug, bisoprolol) for rapid AF with reduced cardiac function or with preserved cardiac function are recommended.

(3) Guidelines for the Management of Hypertension 2019 (the Japanese Society of Hyper tension)

β-blockers (including α/β-blockers) are considered to be one of the major antihypertensive drugs and are preferentially used in patients with concomitant heart failure with decreased LVEF, tachycardia, and angina pectoris and those with post-myocardial infarction. Regarding this drug, the guideline states that “β-blockers are used as basic drugs in the treatment of heart failure with reduced ejection fraction regardless of the presence or absence of hypertension. In Japan, carvedilol and bisoprolol are covered by health insurance based on the evidence.”

(4) JCS 2022 Guideline Focused Update on Diagnosis and Treatment in Patients with Stable Coronary Artery Disease (Joint Guidelines of the Japanese Circulation Society, Japan Radiological Society, Japanese Society of Nuclear Medicine, the Japanese Coronary Association, the Japanese Association for Thoracic Surgery, Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Cardiovascular Surgery, and Japanese College of Cardiology)

β-blockers are recommended as one of the first-line drugs of anti-anginal medications to be used for relieving symptoms in patients with stable coronary artery disease.

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

1. Decision on the administration to pregnant women

Based on the WG report and the results of "IV. Investigation by the PMDA," the PMDA considers, for the following reasons, that "pregnant women 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.

- Regarding chronic cardiac failure, taking into account the clinical positioning of this drug or β-blockers in the Japanese guidelines, a clinical need of this drug or β-blockers in pregnant women with chronic cardiac failure is considered to exist, and the need is increasing due to reasons such as increased cases of delayed child-bearing and improvement of prognosis of the patients with congenital heart disease. However, β-blockers which can be administered to pregnant women at present (atenolol, propranolol, labetalol, etc.) are not indicated for chronic cardiac failure, and the drugs meeting these needs are not sufficient in the current situation. (Refer to "7. Appropriateness of lifting the contraindications" in the WG report and "IV. 3-2 Descriptions concerning clinical positioning of this drug in guidelines" in this report.)
- Also, regarding each indication of this drug other than chronic cardiac failure (rapid AF, essential hypertension, renal parenchymal hypertension, angina pectoris), the clinical need of this drug in pregnant women is also considered to exist, and the need is increasing as it is for chronic cardiac failure. (Refer to "7. Appropriateness of lifting the contraindications" in the WG report and "IV. 3-2 Descriptions concerning clinical positioning of this drug in guidelines" in this report.)
- Concerning the use of this drug in pregnant women, the Japanese guideline states that "it is unlikely that carvedilol and bisoprolol are teratogenic or foetally toxic during the first trimester of pregnancy, although they may pose a risk of foetal growth restriction and neonatal beta-blocking symptoms from the second trimester of pregnancy onward." (Refer to "IV. 3-1. Descriptions concerning the use of this drug in pregnant women in guidelines" in this report.) In addition, concerning the use of β-blockers in pregnant women, the Japanese guidelines state that "it is probably safe" when there are any related descriptions, and the guidelines in Europe and the US state that it is safe (generally safe/a favorable safety profile). (Refer to "6. Japanese and overseas

guidelines" in the WG report and "IV. 3-1. Descriptions concerning the use of this drug in pregnant women in guidelines" in this report.)

- Concerning skeletal abnormalities and corpus luteum-related events which are the reasons for setting contraindications in pregnant women, no epidemiological study results suggesting these risks in humans have been obtained (refer to "5. Reports on clinical uses" in the WG report).
- In overseas product labeling (the US, the UK, Canada, and Australia), the use of this drug in pregnant women is not contraindicated, and it is stated that this drug should be administered if the potential therapeutic benefits are considered to outweigh the potential risks. (Refer to the "3. Descriptions in overseas product labeling" in the WG report.)

In addition to skeletal anomalies and corpus luteum-related events, which are the reasons for setting the current contraindications for pregnant women, the WG's literature search results, etc. include reports suggesting foetal/neonatal toxicity (hypoglycaemia, feeding intolerance, bradycardia, etc.) and teratogenicity (heart malformation). (Refer to "5. Reports on clinical uses" in the WG report and "3. Descriptions in overseas product labeling" as well as "IV. 2-2. Adverse reaction report" in this report.) The PMDA decided that there is little need to separately add a contraindication for pregnant women on the basis of these findings at this time for the following reasons. However, the PMDA will continue to conduct pharmacovigilance activities such as collecting case reports of adverse reactions and published articles and to take measures as necessary.

- There have been reports suggesting foetal/neonatal toxicities (hypoglycaemia, feeding intolerance, bradycardia, etc.). However, they are clinically manageable by observing the mother and the foetus and taking appropriate measures.
- There have been reports suggesting a teratogenic (heart malformation) risk. However, no consensus has been obtained concerning a teratogenic (heart malformation) risk because of other conflicting literature reports.

2. Proposed revision

Concerning the proposed revision of the package insert, similarly to the opinions of the WG, the PMDA considers it necessary to issue a precaution stating that appropriate measures should be taken if any abnormalities are observed, with mothers, foetuses, and

neonates monitored when the drug is administered, in addition to the provision of information regarding the events reported in the literature and adverse reaction reports. For the provision of information regarding the events reported in the literature, etc., the PMDA will consider the necessity of describing events such as bradycardia, taking also account of comments raised in the Expert Discussion.

Ⅵ. Expert discussion

1. Decision on administration to pregnant women

The 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 supported by all the expert advisors.

2. Proposed revision

Concerning the proposed revision of the package insert, the PMDA decided that it was necessary to issue a precaution stating that appropriate measures should be taken if any abnormalities are observed, with mothers, foetuses, and neonates monitored when the drug is administered, in addition to a precaution 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,” and to provide information regarding the events reported in the literature and adverse reaction reports. The decision was generally supported by expert advisors with the following opinions expressed:

・Precautions should be described separately for foetuses and neonates since treatments for foetues and neonates are different.

・The effects of β-blockers on neonates should be fully considered. It is appropriate for the PMDA to decide to include bradycardia, which is described in Japanese and overseas guidelines and overseas product labeling, etc., in specific examples of adverse events observed in neonates, in addition to hypoglycaemia and feeding intolerance proposed by the WG.

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.)

Appendix 1

Summary of drug products investigated (as of December 1, 2023)

No.	Brand name	Marketing authorization holder	Indications/dosage and administration
1	Artist Tablets 1.25 mg, 2.5 mg, 10 mg, 20 mg	Daiichi Sankyo Co., Ltd.	·Tablets 10 mg, 20 mg <Essential hypertension (mild to moderate), renal parenchymal hypertension> The usual daily dose for adults is 10 to 20 mg of carvedilol once daily administered orally. The dose should be adjusted depending on the age or symptoms of the patients. ·Tablets 10 mg, 20 mg <Angina pectoris> The usual daily dose for adults is 20 mg of carvedilol once daily administered orally. The dose should be adjusted depending on the age or symptoms of the patients. ·Tablets 1.25 mg, 2.5 mg, 10 mg <Patients with the following disease who receive basic treatment with angiotensin converting enzyme inhibitors, diuretics, digitalis preparations, etc.: Chronic cardiac failure due to ischaemic heart disease or dilated cardiomyopathy> The usual starting dose for adults is 1.25 mg of carvedilol twice daily administered orally after a meal. If a dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner over intervals of at least 1 week, based on tolerability. If not tolerated, the dose should be decreased. The dose should be increased or decreased in a stepwise manner at a dose of 1.25, 2.5, 5, or 10 mg. At
2	Carvedilol Tablets 1.25 mg “Amel,” 2.5 mg “Amel,” 10 mg “Amel,” 20 mg “Amel”	Kyowa Pharmaceutical Industry Co., Ltd.	
3	Carvedilol Tablets 1.25 mg “Sawai,” 2.5 mg “Sawai,” 10 mg “Sawai,” 20 mg “Sawai”	Sawai Pharmaceutical Co., Ltd.	
4	Carvedilol Tablets 1.25 mg “Tanabe,” 2.5 mg “Tanabe,” 10 mg “Tanabe,” 20 mg “Tanabe”	Nipro ES Pharma co., Ltd.	
5	Carvedilol Tablets 1.25 mg “Towa,” 2.5 mg “Towa,” 10 mg “Towa,” 20 mg “Towa”	Towa Pharmaceutical Co., Ltd.	
6	Carvedilol Tablets 1.25 mg “Nipro,” 2.5 mg “Nipro,” 10 mg “Nipro,” 20 mg “Nipro”	Nipro ES Pharma co., Ltd.	
7	Carvedilol Tablets 1.25 mg “DSEP,” 2.5 mg “DSEP,” 10 mg “DSEP,” 20 mg “DSEP”	Daiichi Sankyo Espha Co., Ltd.	
8	Carvedilol Tablets 1.25 mg “JG,” 2.5 mg “JG,” 10 mg “JG,” 20 mg “JG”	Nihon Generic Co., Ltd.	
9	Carvedilol Tablets 1.25 mg “Me,” 2.5 mg “Me,” 10 mg “Me,” 20 mg	Meiji Seika Pharma Co., Ltd.	

	“Me”		any doses, the drug should be administered orally after a meal twice daily. The usual maintenance dose is 2.5 to 10 mg of carvedilol twice daily administered orally after a meal. A lower starting dose may be used depending on the age or symptoms of the patients. The maintenance dose should be adjusted depending on the responsiveness of the patients to this drug. ·Tablets 2.5 mg, 10 mg, 20 mg <Rapid atrial fibrillation> The usual starting dose for adults is 5 mg of carvedilol administered orally once daily. The dose should be increased to 10 mg once daily, and then to 20 mg once daily in a stepwise manner in patients who are not sufficiently responsive. The dose should be adjusted depending on the age or symptoms of the patients, but the maximum daily dose should not exceed 20 mg once daily.
10	Carvedilol Tab. 1.25 mg “NIG,” 2.5 mg “NIG,” 10 mg “NIG,” 20 mg “NIG”	Nichi-Iko Gifu Plant Co., Ltd.	
11	Carvedilol Tablets 1.25 mg “TCK,” 2.5 mg “TCK,” 10 mg “TCK,” 20 mg “TCK”	Tatsumi Kagaku Co., Ltd.	
12	Carvedilol Tablets 1.25 mg “VTRS,” 2.5 mg “VTRS,” 10 mg “VTRS,” 20 mg “VTRS”	Viatris Healthcare G.K.	

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Appendix 3

Occurrence of events related to pregnancy and neonates note 1)

Event (PT)	Number of events
Neonatal disorders (SMQ)	
Hypoglycaemia neonatal	2
Premature baby	1
Small for dates baby	1
Foetal disorders (SMQ)	
Foetal growth restriction	1
Oligohydramnios	2
Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)	
Premature delivery	1
Maternal exposure during pregnancy	3

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)”