Review Report

July 10, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Artist Tablets 2.5 mg, Artist Tablets 10 mg, Artist Tablets 20 mg
[Non-proprietary name]	Carvedilol (JAN*)
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	October 20, 2014
[Dosage form/Strength]	Each film-coated tablet contains 2.5 mg, 10 mg, or 20 mg of Carvedilol.
[Application classification]	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

**Japanese Accepted Name (modified INN)*

Review Results

July 10, 2015

[Brand name]	(a) Artist Tablets 2.5 mg, (b) Artist Tablets 10 mg, (c) Artist Tablets 20 mg
[Non-proprietary name]	Carvedilol
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	October 20, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with tachycardiac atrial fibrillation has been demonstrated and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]
(a) Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(b)Essential hypertension (mild to moderate)
Renal parenchymal hypertension
Angina pectoris
Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(c) Essential hypertension (mild to moderate)
Renal parenchymal hypertension
Angina pectoris
Tachycardiac atrial fibrillation

(The underline denotes added text, and the double-underline denotes altered text.)

[Dosage and administration]
(a) Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dosage should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

(The underline denotes added text, and the double-underline denotes altered text.)

(b) Essential hypertension (mild to moderate), renal parenchymal hypertension
The usual adult dosage is 10 to 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Angina pectoris
The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dose should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

(The underline denotes added text, and the double-underline denotes altered text.)

(c) Essential hypertension (mild to moderate), renal parenchymal hypertension
The usual adult dosage is 10 to 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Angina pectoris
The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

(The underline denotes added text.)

Review Report (1)

June 1, 2015

I. Product Submitted for Registration

[Brand name] (a) Artist Tablets 1.25 mg, Artist Tablets 2.5 mg,
(b) Artist Tablets 10 mg,
(c) Artist Tablets 20 mg

[Non-proprietary name] Carvedilol

[Name of applicant] Daiichi Sankyo Company, Limited

[Date of application] October 20, 2014

[Dosage form/Strength] Each film-coated tablet contains 1.25 mg, 2.5 mg, 10 mg, or 20 mg of Carvedilol in (a), (b), or (c)

[Proposed indication]

(a) Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(b) Essential hypertension (mild to moderate)
Renal parenchymal hypertension
Angina pectoris
Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(c) Essential hypertension (mild to moderate)
Renal parenchymal hypertension
Angina pectoris
Tachycardiac atrial fibrillation

(The underline denotes added text, and the double-underline denotes altered text.)

[Proposed dosage and administration]

(a) Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dose should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered

orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg and then to 20 mg in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum daily dose is 20 mg.

(The underline denotes added text, and the double-underline denotes altered text.)

(b) Essential hypertension (mild to moderate), renal parenchymal hypertension

The usual adult dosage is 10 to 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Angina pectoris

The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy

The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dose should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation

The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg and then to 20 mg in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum daily dose is 20 mg.

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Angina pectoris

The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Tachycardiac atrial fibrillation

The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg and then to 20 mg in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The

maximum daily dose is 20 mg.

(The underline denotes added text.)

II. Summary of the Submitted Data and Outline of Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

In this application, neither "Data relating to quality" nor "Non-clinical data" have been submitted for the following reasons: The application has been filed to add a new indication and a new dosage of an approved drug; heart-rate lowering effect of carvedilol can be explained by the primary pharmacodynamic data submitted in the initial application; and the proposed dosage and administration fall within the range under the approved indication.

1. Origin or history of discovery, use in foreign countries, and other information

Carvedilol is a non-selective αβ adrenergic receptor blocker developed by Boehringer Mannheim GmbH (Germany) (currently F. Hoffmann-La Roche Ltd.) and has no intrinsic sympathomimetic action. In Japan, Daiichi Pharmaceutical Co., Ltd. (currently Daiichi Sankyo Company, Limited) started the development for Artist in 1984 and obtained the approval for Artist 10 mg and 20 mg with the indication of "Essential hypertension (mild to moderate), renal parenchymal hypertension, and angina pectoris" in January 1993. Then, in October 2002, a new indication of "Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.: chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy" was added to Artist 10 mg, and Artist 1.25 mg and 2.5 mg were approved for the same indication.

Outside Japan, Artist was first approved for the indication of hypertension in Germany and Belgium in 1990, and as of April 2015, it is approved for the indications of hypertension, angina pectoris, chronic heart failure (CHF), etc., in at least 80 countries or regions, but not for the indication of atrial fibrillation in any country or region.

With respect to this application, a request for an additional indication of atrial fibrillation for Artist was submitted to the Ministry of Health, Labour and Welfare by major cardiovascular-related academic societies (Japanese Society of Electrocardiology, Japanese Circulation Society, Japanese College of Cardiology, Japanese Heart Rhythm Society, Japanese Heart Failure Society) in March 2009. Daiichi Sankyo Company, Limited conducted a Japanese clinical study in patients with atrial fibrillation and then filed a partial change application for Artist to seek approval for an additional indication of tachycardiac atrial fibrillation. In consideration of the currently proposed dosage and administration (draft) of Artist, the previous application of Artist Tablets 1.25 mg for the proposed indication was withdrawn in [redacted].

2. Clinical data

2.(i) Summary of biopharmaceutic studies and associated analytical methods

No biopharmaceutic data were submitted in this application.

2.(ii) Summary of clinical pharmacology studies

No clinical pharmacology data were submitted in this application.

2.(iii) Summary of clinical efficacy and safety

2.(iii).A Summary of the submitted data

The applicant submitted evaluation data resulting from 1 Japanese phase III study.

2.(iii).A.(1) Japanese phase III study (Protocol No. DQ2466-A-J301, Attached document 5.3.5.1-1 [July 2013 to May 2014])

A randomized, double-blind, comparative study in Japanese patients with chronic atrial fibrillation was conducted to evaluate the efficacy and safety of carvedilol orally administered once daily at 5 mg, 10

mg, and 20 mg in a dose escalating manner, or a fixed dose of 5 mg (target sample size; 40 per group, 120 in total) at 18 study centers in total in Japan.

The main inclusion criterion was outpatients aged ≥20 years with chronic (persistent or perpetual) atrial fibrillation (AF).

Subjects were randomized to receive carvedilol once daily at a fixed dose of 5 mg (5-mg fixed-dose group) or once daily at a dose of 5 mg initially and then at an escalated dose of up to 10 mg or 20 mg (10-mg dose-escalation group and 20-mg dose-escalation group, respectively) depending on the tolerability and heart rate. In the 5-mg fixed-dose group, carvedilol was administered once daily at a dose of 5 mg throughout the treatment period (Periods I, II, and III, each 2 weeks long). In the 10-mg dose-escalation group, carvedilol was administered once daily at a dose of 5 mg during Period I, and at the end of Period I or Period II, the dose of carvedilol was increased to 10 mg once daily in subjects with systolic blood pressure ≥110 mmHg who met the following criteria: (a) The resting heart rate >80 beats/min on 12-lead electrocardiogram (ECG) and (b) acceptable tolerability and safety. In the 20-mg dose-escalation group, at the end of Period I or Period II, the dose of carvedilol was increased to 10 mg once daily when the previous dose was 5 mg, or to 20 mg once daily when the previous dose was 10 mg in subjects with systolic blood pressure ≥110 mmHg who met the above (a) and (b). Subjects who did not meet the dose-escalation criteria received the same dose as that in the previous period, and subjects who had a heart rate <60 beats/min received the decreased dose. Subjects were randomized by the minimization method using "mean heart rate during 24-hour Holter monitoring at baseline" as a factor.

All of the 127 randomized subjects (42 subjects in the 5-mg fixed-dose group, 42 subjects in the 10-mg dose-escalation group, 43 subjects in the 20-mg dose-escalation group; hereinafter the numbers of subjects in these groups are described in the same order) received the study drug and were included in the safety analysis. Of these, 125 subjects (42 subjects, 42 subjects, 41 subjects) were included in the Full Analysis Set (FAS) and served as the primary efficacy analysis population. Excluded were 2 subjects who were not examined at all with a Holter monitor after randomization. The study was discontinued in 4 subjects (0 subjects, 1 subject, 3 subjects) due to subject's request (1 subject in the 10-mg dose-escalation group), adverse events (2 subjects in the 20-mg dose-escalation group), and the blood pressure meeting the discontinuation criteria (1 subject in the 20-mg dose-escalation group).

The changes in dose by dose group in the safety analysis population were as follows: (i) in the 5-mg fixed-dose group, 100% (42 of 42 subjects) received carvedilol at a dose of 5 mg/day throughout the study, that is, in Periods I, II, and III; (ii) in the 10-mg dose-escalation group, 100% (42 of 42 subjects) received carvedilol 5 mg/day during Period I, 35.7% (15 of 42 subjects) and 64.3% (27 of 42 subjects) received carvedilol 5 mg/day and 10 mg/day, respectively, during Period II, and 19.0% (8 of 42 subjects) and 81.0% (34 of 42 subjects) received carvedilol 5 mg/day and 10 mg/day, respectively, during Period III; and (iii) in the 20-mg dose-escalation group, 100% (43 of 43 subjects) received carvedilol 5 mg/day during Period I, 32.6% (14 of 43 subjects) and 60.5% (26 of 43 subjects) received carvedilol 5 mg/day and 10 mg/day, respectively, during Period II, and 25.6% (11 of 43 subjects), 20.9% (9 of 43 subjects), and 46.5% (20 of 43 subjects) received carvedilol 5 mg/day, 10 mg/day, and 20 mg/day, respectively, during Period III.

The primary efficacy endpoint was change in mean heart rate during 24-hour Holter monitoring (hereinafter, a positive figure indicates a decrease in heart rate, and a negative figure, an increase). The missing values were imputed by the last observation carried forward (LOCF) method. In consideration of the multiplicity of the study, statistical analysis was performed in the following procedure: (a) Firstly, the mean heart rate at the end of Week 2 of once-daily administration at a dose of 5 mg (based on the pooled data from the 5-mg fixed-dose group, 10-mg dose-escalation group, and 20-mg dose-escalation group) was compared with that at baseline; (b) if a significant difference was observed in (a), changes in the mean heart rate at the end of Week 6 in the 5-mg fixed-dose group, 10-mg dose-escalation group, and 20-mg dose-escalation group were tested for any dose-response relationship; (c) if a significant difference was observed in (b), the change in the mean heart rate at the end of Week 4 in the 5-mg fixed-dose group was compared with that in the pooled dose-escalation group (based on the pooled data from the 10-mg dose-escalation group and 20-mg dose-escalation group); and (d) if a significant difference

was observed in (c), changes in the mean heart rate at the end of Week 6 in the 5-mg fixed-dose group was compared with that in the 20-mg dose-escalation group.

In the procedure (a), the mean heart rate for 24 hours before the start of the study treatment (at baseline) was 96.1 ± 13.0 (mean ± standard deviation [SD]) beats/min, and that at the end of Week 2 was 89.5 ± 12.2 beats/min. The change from baseline to Week 2 was 6.6 ± 7.91 beats/min, indicating a significant heart rate lowering effect (paired t-test, $P < 0.0001$). In the procedure (b), the mean heart rate in the 5-mg fixed-dose group was 98.4 ± 15.1 beats/min at baseline and 89.9 ± 12.67 beats/min at the end of Week 6, and the change from baseline to the end of Week 6 was 7.6 [5.4, 9.8] (least squares mean [95% confidence interval (CI)]) beats/min; in the 10-mg dose-escalation group, the mean heart rate was 95.6 ± 13.45 beats/min at baseline and 86.9 ± 11.61 beats/min at the end of Week 6, and the change from baseline to the end of Week 6 was 8.9 [6.7, 11.1] beats/min; and in the 20-mg dose-escalation group, the mean heart rate was 94.3 ± 9.75 beats/min at baseline and 84.4 ± 7.12 beats/min at Week 6, and the change from baseline to the end of Week 6 was 10.6 [8.4, 12.8] beats/min. No significant dose-response relationship was observed between the escalated doses and heart rate lowering effect (analysis of covariance [ANCOVA] with the mean 24-hour heart rate at baseline as a covariate in pairwise comparisons [-1, 0, 1], $P = 0.0638$).

The secondary endpoint was defined as the percentage of subjects in whom the target mean heart rate during 24-hour Holter monitoring (≤80 beats/min) was achieved. The concerned percentage at the end of Week 6 was 21.4% (9 of 42 subjects) in the 5-mg fixed-dose group, 28.6% (12 of 42 subjects) in the 10-mg dose-escalation group, and 34.1% (14 of 41 subjects) in the 20-mg dose-escalation group.

The incidence of adverse events was 18.9% (24 of 127 subjects) during Period I. Adverse events reported by ≥2 subjects included ventricular tachycardia in 5 subjects, nasopharyngitis in 3 subjects, cardiac failure chronic in 2 subjects, and upper respiratory tract inflammation in 2 subjects. During Period II, the incidence of adverse events was 15.5% (11 of 71 subjects) of the subjects who received carvedilol 5 mg once daily during this period (5-mg dose subjects [Period II]) and 15.1% (8 of 53 subjects) of subjects who received carvedilol 10 mg once daily during this period (10-mg dose subjects [Period II]). Adverse events reported by ≥2 subjects at either dose included ventricular tachycardia in 2 of the 5-mg dose subjects (Period II) and ventricular tachycardia in 2 of the 10-mg dose subjects (Period II). During Period III, the incidence of adverse events was 11.5% (7 of 61 subjects) of the subjects who received carvedilol 5 mg once daily during this period (5-mg dose subjects [Period III]), 9.3% (4 of 43 subjects) of the subjects who received carvedilol 10 mg once daily during this period (10-mg dose subjects [Period III]), and 35.0% (7 of 20 subjects) of the subjects who received carvedilol 20 mg once daily during this period (20-mg dose subjects [Period III]). Adverse events reported by ≥2 subjects at any dose included nasopharyngitis and gamma-glutamyltransferase increased each in 2 of the 5-mg dose subjects (Period III); no applicable events in the 10-mg dose subjects (Period III); and alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased each in 2 of the 20-mg dose subjects (Period III). Adverse events assessed to be causally "related" to the study drug included cardiac failure chronic in 2 subjects, and dizziness, immune thrombocytopenic purpura, and abdominal discomfort, each in 1 subject during Period I; malaise in 1 of the 10-mg dose subjects (Period II); gamma-glutamyltransferase increased in 1 of the 5-mg dose subjects (Period III), blood lactate dehydrogenase increased in 1 of the 10-mg dose subjects (Period III), and blood lactate dehydrogenase increased/gamma-glutamyltransferase increased/alanine aminotransferase increased/aspartate aminotransferase increased/blood alkaline phosphatase increased in 1 subject and haemoglobin decreased in 1 subject of the 20-mg dose subjects (Period III).

No deaths occurred. A serious adverse event occurred in 1 subject of the 5-mg fixed-dose group (5-mg dose subject, subdural haematoma), and a causal relationship to the study drug was ruled out. Adverse events leading to study discontinuation were observed in 2 subjects of the 20-mg dose-escalation group (both of them were 5-mg dose subjects, cardiac failure chronic), and both events were assessed to be causally related to the study drug.

2.(iii).B Outline of the review by PMDA

2.(iii).B.(1) Clinical positioning of carvedilol

PMDA asked the applicant to explain the clinical positioning of carvedilol in terms of choice between carvedilol and the conventional therapies intended to control heart rate in atrial fibrillation (β blockers other than carvedilol, digitalis preparations, calcium antagonists) and concomitant use with them.

The applicant's response:

The clinical positioning of carvedilol was presented in the international standard text books (*Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. *Single Volume,* 9th ed. 2012;825-844, *Conn's current therapy.* 2014;423-427) and clinical practice guidelines for atrial fibrillation in each region, as one of the β-blockers used to control heart rate in patients with atrial fibrillation. Guidelines in Japan, the US, and Europe such as *Guidelines for Pharmacotherapy of Atrial Fibrillation* (JCS 2013 Guidelines) (2012 Joint Working Group Report, Joint Working Group: Japanese Circulation Society, Japanese College of Cardiology, Japanese Society of Electrocardiology, and Japanese Heart Rhythm Society), 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (2014 AHA/ACC/HRS Guideline) (*J Am Coll Cardiol.* 2014;64(21):e1-76), and Guidelines for the management of atrial fibrillation of the European Society of Cardiology (The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology) (ESC Guidelines) (*Eur Heart J.* 2010;(31):2369-2429) refer to β-blockers, non-dihydropyridine calcium antagonists (verapamil, diltiazem), digitalis preparations, and amiodarone hydrochloride (amiodarone) as oral drugs that slow atrioventricular nodal conduction and therefore can be used to control heart rate in chronic atrial fibrillation (AF). In Japan and overseas, β-blockers are prescribed for many AF patients to control their heart rate. In a Japanese study, Study J-RHYTHM, in which the prescribing physicians were allowed to choose drugs at their discretion (*Circ J.* 2009;73(2):242-248), β-blockers were prescribed to 51.5% of patients with paroxysmal AF and 31.0% of patients with persistent AF (*Circ J.* 2008;72 (suppl. IV):1581-1638). In the questionnaire survey for the "Treatment Guidelines for Atrial Fibrillation" in cardiologists in Japan (Atarashi H. *Prog. Med.* 2008;28(6):1577-1592), β-blockers were prescribed to 52.5% of patients with AF not complicated by heart failure (carvedilol accounted for 31.8% of the drugs) (1238 respondents), and 29.0% of patients with AF complicated by heart failure (carvedilol accounted for 77.1% of the drugs) (1236 respondents). Of the β-blockers, 3 β-blockers (carvedilol, bisoprolol fumarate [bisoprolol], and atenolol; all administered once daily) were widely used in patients with AF not complicated by heart failure; and carvedilol was by far most likely to be prescribed to patients with coexisting heart failure. In addition, the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013 Guidelines) and *Guidelines for Drug Treatment of Arrhythmias* (JCS 2009) (2008 Joint Working Group Report, Joint Working Group: Japanese Circulation Society, Japanese Society of Pediatric Cardiology and Cardiac Surgery, Japanese College of Cardiology, Japanese Society of Electrocardiology, and Japanese Heart Rhythm Society) recommend β-blockers or non-dihydropyridine calcium antagonists for persistent or permanent AF not complicated by heart failure in the absence of an accessory pathway and suggest digoxin, carvedilol, bisoprolol, or amiodarone for AF complicated by heart failure in the absence of an accessory pathway as an oral drug to slow the heart rate over a long period (all classified as "Class I" drugs, which have evidence of the efficacy or usefulness or are widely considered as such). The choice between the drugs is to be determined according to individual patient characteristics and conditions in light of properties of the drugs (pharmacokinetics, pharmacological action, safety and efficacy profiles) as well as relevant guidelines in Japan and overseas. Basically, β-blockers are used as the first-line drugs in AF patients without reduced cardiac function or accessory pathway, and if the patients respond poorly to β-blocker alone, concomitant use of calcium antagonists or digitalis preparations is potentially considered. In addition, even in AF patients who have reduced cardiac function but are active, β-blockers are used as the first-line drugs, and in patients who have been initially treated with digitalis preparations but need to have heart rate controlled during exercise or do not respond well, concomitant use of β-blockers with the digitalis preparations, or switch to β-blockers alone or in combination with calcium antagonists is potentially considered.

Carvedilol is an αβ-blocker characterized by vasodilation and a non-selective β blocking action and lowers heart rate through the β_1 receptor blocking activity. Of non-selective β-blockers, propranolol is indicated for tachycardiac atrial fibrillation but should be administered 3 times daily, and is not prescribed frequently. On the other hand, both bisoprolol and atenolol are as widely used to control heart rate in AF patients in Japan as Bisoprolol and atenolol are selective β_1 receptor blockers and are similar to carvedilol in main pharmacological mechanism for heart rate lowering action. Both drugs lack

intrinsic sympathomimetic activity and feature a long-acting pharmacokinetic property allowing a once-daily regimen. Furthermore, the JCS 2013 Guidelines recommend carvedilol and bisoprolol as drugs that can be used in patients with reduced cardiac function. Both drugs are considered be used in controlling heart rate in atrial fibrillation as β-blockers in generally the same manner (in terms of distinguished use from calcium antagonists and digitalis preparations, concomitant use with them, etc.).

In the Japanese phase III study of bisoprolol in chronic AF patients, the change (mean ± SD) in the mean heart rate from baseline after 2-week treatment of bisoprolol 2.5 mg was 12.2 ± 9.1 beats/min (*J Cardiol.* 2013;62(1):50-57), while in the Japanese phase III study of (Attached document 5.3.5.1-1), the change in the mean heart rate from baseline after 2-week treatment of carvedilol 5 mg was 6.6 ± 7.91 beats/min. Although a direct comparison between these results is not possible, the daily dose of carvedilol potentially presenting the same effect in patients with heart failure as that bisoprolol is 5- to 10-fold (2.5- to 5-fold as single dose) that of bisoprolol (*Eur J Heart Fail.* 2005;7(4):640-649, *Eur J Heart Fail.* 2011;13(6):670-680, *Am J Cardiol.* 2011;107(2):215-219). In addition, comparison studies between these drugs at the comparable doses showed that carvedilol lowered heart rate more mildly than bisoprolol did (*Eur J Heart Fail.* 2011;13(6):670-680, *Am J Cardiol.* 2011;107(2):215-219, *Int J Cardiol.* 2012;161(3):160-165.). In light of the above, carvedilol at the starting dose (5 mg) is considered to present a milder heart rate lowering effect than bisoprolol at the starting dose (2.5 mg).
As described above, carvedilol is considered to be used to control heart rate in atrial fibrillation generally in the same manner (in terms of distinguished use from calcium antagonists and digitalis preparations, concomitant use with them, etc.,) as the other β-blockers are. In addition, carvedilol is considered to present a milder heart rate lowering effect at its starting dose than bisoprolol at its starting dose, and thus carvedilol is expected to have an advantage in the safe use for patients starting heart rate control therapy, elderly patients, and patients with bradycardia concern (especially those in whom attention should be paid to worsening of nocturnal bradycardia). It is therefore considered clinically significant to make carvedilol available in the clinical setting as one of the β-blockers used to control heart rate in atrial fibrillation.

PMDA's view:
Usefulness of heart rate control therapy in AF patients has been established in Japan and overseas. It is clinically significant to make carvedilol available in the clinical setting as one of the β-blockers used to control heart rate in AF patients for the following reasons: (i) already approved bisoprolol, a long-acting β-blocker (allowing once-daily administration), as well as carvedilol and atenolol, which are not yet approved for the indication of atrial fibrillation in Japan at present, have been widely used in AF patients in clinical practice; and (ii) the Japanese phase III study has demonstrated that carvedilol has heart-rate lowering effect in Japanese AF patients [see "2.(iii).B.(3) Efficacy and dosage and administration of carvedilol"] and there were no special safety concerns [see "2.(iii).B.(4) Safety of carvedilol"]. With respect to the choice between carvedilol and the conventional therapeutic drugs used to control heart rate in AF patients (the other β-blockers, digitalis preparations, calcium antagonists, etc.) and concomitant use with them, there are no clinical studies comparing the efficacy and safety of carvedilol to those of the other comparable drugs directly or ones evaluating the efficacy and safety of concomitant use with them, but these drugs have been used in clinical practice for a long time and their mechanism of action and properties have been mostly elucidated. Based on the efficacy and safety profiles of each drug and the JCS 2013 Guidelines as well as patient's characteristics such as complications, it is necessary to select one from therapeutic drugs for atrial fibrillation including carvedilol and the conventional β-blockers for each patient. Heart failure is one of the causes of atrial fibrillation and many patients with AF are also assumed to have heart failure. Making carvedilol available for atrial fibrillation in the clinical practice is considered to have clinical significance because carvedilol, which is already approved to be indicated for patients with heart failure, potentially serves as a therapeutic option for patients with AF complicated by heart failure. Heart rate lowering actions of bisoprolol and carvedilol have not been directly compared as the applicant discussed, and it is therefore difficult to compare and explain the heart rate lowering effect and safety of the two drugs appropriately at present. In clinical practice, a suitable β-blocker at an appropriate dose is expected to be selected in consideration of its properties and according to the patient characteristics including the condition and treatment for patients complicated by heart failure.

2.(iii).B.(2) Application data package

The applicant's explanation on the application data package:

The international standard text book (*Conn's current therapy.* 2014;423-427) and foreign guidelines (2014 AHA/ACC/HRS Guideline, ESC Guidelines) refer to carvedilol as one of the β-blockers used to control heart rate in AF patients and suggest recommended dosage regimens. However, the dosage and administration of β-blockers in Japan are different from those employed overseas. A literature search[1] for the recent clinical use status of carvedilol in AF patients in Japan was conducted. As a result, of 21 reports identified as ones on management of AF not complicated by CHF, 18 reports included a description about doses of carvedilol, which ranged from 2.5 to 20 mg/day; in 94% of the reports (17 of 18 reports), the doses ≥5 mg/day were used; and in reported studies where the dose was increased depending on the tolerability and heart rate, carvedilol was administered once daily at the maximum dose of 20 mg. Thus, the applicant considered that carvedilol was mostly used at a dose of ≥5 mg/day and ≤20 mg/day to control heart rate especially in patients with AF not complicated by chronic CHF. On the other hand, the appropriateness of the dose of carvedilol has not been verified in Japanese AF patients, and thus a Japanese phase III study was to be conducted to investigate the dosage and administration in Japanese patients with persistent or permanent AF. In addition, the efficacy and safety of carvedilol in patients with tachycardiac AF were discussed covering the data on the efficacy and safety from the use-results survey in patients with hypertension (*Drugs R D.* 2011;11(2):171-190) and a special survey for long-term use in patients with hypertension (*Drugs R D.* 2011;11(2):191-205) as well as information on the efficacy and safety in patients with paroxysmal AF obtained from the literature-search-based actual use survey for carvedilol.

PMDA's view:

As explained by the applicant, the significance of carvedilol's heart rate lowering effect in AF patients has been already recognized in Japan and overseas. The optimal doses of β-blockers including carvedilol, on the other hand, differ in Japan and overseas. Therefore, the applicant's development plan is considered appropriate in which the dosage regimen was employed in the Japanese phase III study based on the use results in Japanese AF patients to investigate the heart rate lowering effect of carvedilol at doses ranging from 5 to 20 mg/day. The submitted data in this application were considered to allow, based on the following points, evaluation of the efficacy and safety of carvedilol administered to Japanese AF patients according to the proposed dosage and administration: the dosage regimen of carvedilol in the Japanese phase III study and the subsequently obtained results for the efficacy and safety [see "2.(iii).B.(3) Efficacy and dosage and administration of carvedilol" and "2.(iii).B.(4) Safety of carvedilol"]; the applicant's explanation about the efficacy and safety of the long-term administration [see "2.(iii).B.(5) Efficacy and safety of carvedilol administered for a long-term period"]; the descriptions in the guidelines in Japan and overseas; and the fact that carvedilol has been widely used in AF patients in clinical practice in Japan.

2.(iii).B.(3) Efficacy and dosage and administration of carvedilol

2.(iii).B.(3).1) Study design of the Japanese phase III study

The applicant's explanation on the study design of the Japanese phase III study:

The JCS 2013 Guidelines recommends heart rate control therapy in patients with persistent or permanent AF as Class I ("There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful."). Furthermore, calcium antagonists and β-blockers are firstly recommended for patients with adequate cardiac function over digitalis preparations. The Japanese phase III study, therefore, included patients with persistent or permanent AF presenting the mean heart rate during 24-hour Holter monitoring >80 beats/min, at which the heart rate lowering effect of carvedilol was properly evaluated. Based on the actual use in Japan, as described above, once-daily doses of 5 mg, 10 mg, and 20 mg were investigated. The study consists of the 5-mg fixed-dose group in which carvedilol was administered at a dose of 5 mg once daily as well as the 10-mg dose-escalation group and 20-mg dose-escalation group in which carvedilol was administered once daily at the starting dose of 5 mg followed by dose escalation to 10 mg or 20 mg depending on the tolerability and heart rate, and these groups were compared. The primary efficacy endpoint was the change in mean heart rate during 24-hour Holter

[1] Japan Medical Abstracts Society WEB, JAPICDOC, JMEDPlus, PubMed (search period: January 1, 2000 to May 28, 2014)
Search terms: Atrial fibrillation, atrial flutter, carvedilol
Exclusion criteria: Reports on ventricular arrhythmia, reports only on heart failure, reports on treatment in non-Japanese patients, non-original articles, or reviews

monitoring from baseline, and a relationship between the dose and heart rate lowering effect (whether the effect is intensified with the increasing dose or not) was verified in accordance with the following testing procedure: (a) Comparison of the mean heart rate at the end of Week 2 with that at baseline; (b) dose-response relationship of a change in the mean heart rate at Week 6; (c) comparison of a change in the mean heart rate at Week 4 in the 5-mg fixed-dose group with that in the pooled dose-escalation group (the pooled data from the 10-mg dose-escalation and 20-mg dose-escalation groups); and (d) comparison of a change in the mean heart rate at Week 6 in the 5-mg fixed-dose group with that in the 20-mg dose-escalation group. The duration for each period was set as 2 weeks, because the pulse rate lowering action of carvedilol reached a steady state at 2 weeks in the late phase II study in patients with mild or moderate essential hypertension. The dosing frequency was set as once daily, because in a clinical pharmacology study in patients with effort angina pectoris, the pulse rate lowering action of carvedilol lasted even 24 hours after the single dose, and mean, maximum, and minimum hourly heart rate determined by Holter monitoring remained significantly lower than baseline until 24 hours after the administration. Because patients with severe atrioventricular block or severe sinoatrial block were excluded from the Japanese phase III study, the doses lower than the starting dose of 5 mg were not employed. In the Japanese phase III study, heart rate was measured by both Holter monitoring and 12-lead ECG. Since 24-hour Holter monitoring provides stable data with little variability and reflects rest and activities of daily living, the data obtained by Holter monitoring were used to determine the mean heart rate for the analysis of the primary endpoint and secondary endpoint.

PMDA's view:
As described above, the efficacy of carvedilol in lowering heart rate in AF patients was deemed to be established based on the accumulated knowledge about the heart rate lowering effect of carvedilol in Japan and overseas as well as descriptions in the guidelines based on such knowledge in Japan and overseas. However, the optimal doses of β-blockers including carvedilol for various diseases in Japan are different from those overseas, and thus it was considered necessary to investigate if the dosage regimen generally used in Japan for other diseases than atrial fibrillation is also appropriate for Japanese AF patients, and furthermore to justify the following dosage regimen of carvedilol in the Japanese phase III study selected based on the actual use in Japan: the starting dose is ≥5 mg/day; if its efficacy is not sufficient, the dose should be increased to 10 mg/day and then to 20 mg/day in a stepwise manner. Long-acting β-blockers including carvedilol, on the other hand, have been widely used in AF patients in clinical practice in Japan, making it difficult to design a placebo-controlled study of carvedilol. Therefore the applicant conducted the study to investigate the heart rate lowering effect of carvedilol at doses ranging from 5 to 20 mg/day in Japanese AF patients, and this is considered generally appropriate. Setting the evaluation period in the Japanese phase III study based on the information at the time of previous approval was also considered appropriate. The Japanese phase III study included the AF patients presenting the resting heart rate ≥80 beats/min. PMDA considers the concerned inclusion criterion as follows: Based on the data from Study RACE II (*N Engl J Med.* 2010;362(15):1363-73), the ESC Guidelines and 2011 ACCF/AHA/HRS Focused Update (*J Am Coll Cardiol.* 2011;57(2):223-42) have changed the recommended target heart rate in control therapy from the previous target value in the ACC/AHA/ESC 2006 Guidelines (resting heart rate, 60-80 beats/min) to <110 beats/min for some patients. Study RACE II, however, included patients with the limited characteristics, and it is unclear whether the study data can be used as the rationale for setting of the target heart rate in the control therapy for overall Japanese AF patients; the JCS 2013 Guidelines in Japan indicate that the resting heart rate must be decreased to 60 to 80 beats/min in atrial fibrillation. Therefore, the inclusion criteria of the Japanese phase III study defining AF patients at the resting heart rate ≥80 beats/min is appropriate. In light of the applicant's explanation about the measurement method of the mean heart rate, it is appropriate to evaluate the efficacy of carvedilol using the mean heart rate during 24-hour Holter monitoring, which is described as a useful method in controlling heart rate in AF patients as with the exercise ECG in the foreign guideline (2011 ACCF/AHA/HRS Focused Update).

2.(iii).B.(3).2) Efficacy and dosage and administration of carvedilol in the Japanese phase III study

PMDA asked the applicant to discuss the cause for a failure in verifying the dose-response of heart rate lowering effect at Week 6 in the analysis of the primary endpoint in the Japanese phase III study the applicant planned.

The applicant's response:
The cause for the failure in verifying the dose-response and increased dose effect in the analysis of the primary endpoint is considered to be smaller differences in effect between dose groups and larger variability among subjects than assumed at the time of planning. Although the primary analysis in the FAS failed to verify the dose-response of heart rate lowering effect at Week 6, the secondary analysis in the Per-Protocol Set (PPS) presented significant dose-response (ANCOVA with the mean 24-hour heart rate at baseline as covariate in pairwise comparisons [-1, 0, 1], $P = 0.0364$). Investigation into 3 subjects who were excluded from the PPS revealed that there was 1 subject who violated the inclusion criteria (10-mg dose-escalation group) in whom sinus rhythm was found even during the run-in period. This subject was found to have both atrial fibrillation and sinus rhythm during the run-in period and at Week 2 by Holter monitoring, and have only sinus rhythm at Week 4 and Week 6. Exploratory analysis in the FAS excluding this subject showed a significant dose-response ($P = 0.0414$). In this subject, the change in heart rate (117 beats/min at baseline; 59 beats/min at Week 6; change, 58 beats/min) was markedly greater than those in the other subjects. The change at Week 6 in the 10-mg dose-escalation group of the FAS (mean ± SD) was 8.7 ± 10.14 beats/min, but the change in the same group excluding the subject was 7.5 ± 6.56 beats/min with the markedly reduced variability, resulting in P value <0.05. Based on the above, the concerned results from the analysis in the FAS are considered attributable to including the subject who did not meet the inclusion criteria for pharmacodynamic evaluation using the heart rate as the indicator, which led to the large variability in the 10-mg dose-escalation group.

PMDA's view:
The applicant explained that the failure in verification of the efficacy in the primary analysis was caused by the departure of the study results from the applicant's presumption at the time of planning. If so, it is suspected that the applicant did not sufficiently collect and investigate the relevant information in advance at the time of planning. In addition, the applicant discussed that the 10-mg dose-escalation group included 1 patient with paroxysmal AF ineligible for evaluation of the heart rate lowering action of carvedilol; and the subject was found to have both atrial fibrillation and sinus rhythm during the run-in period and at Week 2 by Holter monitoring, and have only sinus rhythm at Week 4 and Week 6, affecting the study results. Although the presence of this patient possibly affected the analysis results for the dose-response relationship of carvedilol, it is not acceptable to conclude that the discussion based on the post-hoc analysis excluding the concerned patient data succeeded in demonstrating the dose-response relationship. It was critical that evaluation of the primary endpoint in the Japanese phase III study did not provide the assumed results, and PMDA further investigated as shown below.

In the Japanese phase III study, study treatment was started at a dose of 5 mg/day and, if not effective enough then the dose was increased to 10 mg/day and 20 mg/day in a stepwise manner. To investigate the appropriateness of such a dose escalation design, PMDA asked the applicant to explain the rationale for employing the study design in which groups with the dose arbitrarily increased to low or high dose level were compared without considering their sufficiency in terms of efficacy before randomization, instead of a design in which poor responders to the low dose were randomized to the low and high dose groups to be compared.

The applicant's response:
The reason for the design in which subjects poorly responding to the lower doses (5 mg/day or 10 mg/day) were not included in evaluation at the higher doses was as follows: To investigate the effect of the increased dose of carvedilol from 10 mg/day to 20 mg/day by the parallel group comparison, the subjects meeting the dose-escalation criteria to 20 mg/day at Week 4 have to be randomized to either 10 mg/day group (10 mg/day-maintained group) or 20 mg/day group (20 mg/day-escalated group). Then, the changes in mean 24-hour heart rate from Week 4 to Week 6 have to be compared between the groups. If carvedilol 20 mg/day is administered to subjects who have poorly responded to 10 mg/day, and the change in mean 24-hour heart rate and its SD are assumed to be 2 beats/min and 5 beats/min, respectively, the number of subjects required to detect the difference between the 10 mg/day-maintained group and 20 mg/day-escalated group at the statistical power of 80% is estimated to be 100 subjects for each group. Based on the percentage of the subjects estimated to require dose-escalation to either dose, the study has to include approximately 1000 subjects in total, and it potentially takes a long term to complete the study. This development project targeting an additional indication of atrial fibrillation was based on the request from healthcare professionals in the clinical setting, and such study design was considered unrealistic. Also, more subjects are necessary if the effect of the increased dose from 5 mg/day to 10 mg/day due to

lack of the effect at 5 mg/day is to be verified in the same study in addition to verification of the effect of the increased dose from 10 mg/day to 20 mg/day due to lack of the effect at 10 mg/day by parallel group comparison. Such a study design was considered further unrealistic.

As described above, the Japanese phase III study was designed to compare the efficacy between 3 regimens (5-mg fixed-dose group, 10-mg dose-escalation group, 20-mg dose-escalation group). The analysis to investigate the effect of the increased dose, up to 10 mg/day and 20 mg/day, is designed to be based on differences in maximum dose allowed among 3 regimens. The applicant therefore considered it appropriate to investigate heart rate lowering effect for the dose-response relationship among 3 regimen groups, and then perform pairwise comparisons (5-mg fixed-dose group vs. 10-mg dose-escalation group, 5-mg fixed-dose group vs. 20-mg dose-escalation group). The "effect of the increased dose in subjects poorly responding to the lower doses," which should be primarily evaluated by parallel group comparison, was specified as a secondary endpoint to be evaluated after the pre-determined sub-group analysis in poor responders. The "comparison between the 10-mg dose-escalation group and 20-mg dose-escalation group" for the effect of the increased dose (up to 20 mg/day) was to compare the point estimates and set as a secondary endpoint.

PMDA considers that it should have been more appropriate to evaluate the effect of the increased dose of carvedilol in a study design in which the effect of the increased dose in subjects poorly responding to the lower doses was to be demonstrated, and thus such a study design was to make a more unambiguous evaluation of the effect of the increased dose, in light of the objective of the Japanese phase III study, which was to investigate the appropriateness of the following dosage and administration: treatment should be initiated at a dose of 5 mg/day; if there is a lack of efficacy, the dose may be increased to 10 mg/day and then to 20 mg/day in a stepwise manner. The applicant, on the other hand, adopted an optional titration study design. PMDA, nevertheless, considers the above applicant's policy appropriate to some extent, because it is obviously difficult to include patients in a clinical study in Japan where long-acting β-blockers including carvedilol have been widely used in AF patients in clinical practice.

Although the analysis of the primary endpoint in the Japanese phase III study did not demonstrate the linear dose-response or the effect of the increased dose, the applicant proposed the following dosage and administration: The initial dose is 5 mg of carvedilol administered orally once daily; if there is a lack of efficacy, the dose should be increased to 10 mg and then to 20 mg in a stepwise manner. PMDA asked the applicant to explain the reasons for proposing the dosage and administration as well as the rationale for expecting the effect of the increased dose from 5 mg/day to 10 mg/day and from 10 mg/day to 20 mg/day.

The applicant's response:

(a) Dose-response relationship

As described above, the failure in verifying a significant dose-response relationship in the FAS was considered attributable to including 1 ineligible subject by inclusion criteria in the data analysis, which increased the variability. In addition, changes in mean hourly heart rate over 24 hours and data on active heart rate by Holter monitoring showed that the day-time (active) heart rate markedly decreased with the increasing maximum dose among 3 groups (regimens) (Figure 1). Furthermore, the percentage of subjects in whom the mean heart rate by Holter monitoring and the resting heart rate on 12-lead ECG achieved ≤80 beats/min tended to increase in a dose-dependent manner. Actually, however, the 10-mg dose-escalation group included subjects who received carvedilol at the final dose of 5 mg/day, and the 20-mg dose-escalation group included subjects who received carvedilol at the final dose of 5 mg/day or 10 mg/day. To investigate the dose-response more accurately, post-hoc analysis was performed on the changes in mean heart rate at Week 6 for dose-response by actual final dose. As a result, the dose-response based on the actual dose was confirmed (P = 0.0359). The change in mean heart rate from baseline to Week 6 (least squares mean [95% CI]) was 7.9 [6.0, 9.7] beats/min at 5 mg/day, 9.4 [7.2, 11.6] beats/min at 10 mg/day, and 11.8 [8.6, 15.0] beats/min at 20 mg/day; the heart rate decreased with the increasing dose. Based on these results, although the pre-determined analysis failed in verifying the dose-response, it is considered appropriate to determine that the heart rate lowering effect of carvedilol has the dose-response over doses of 5 mg/day, 10 mg/day, and 20 mg/day.

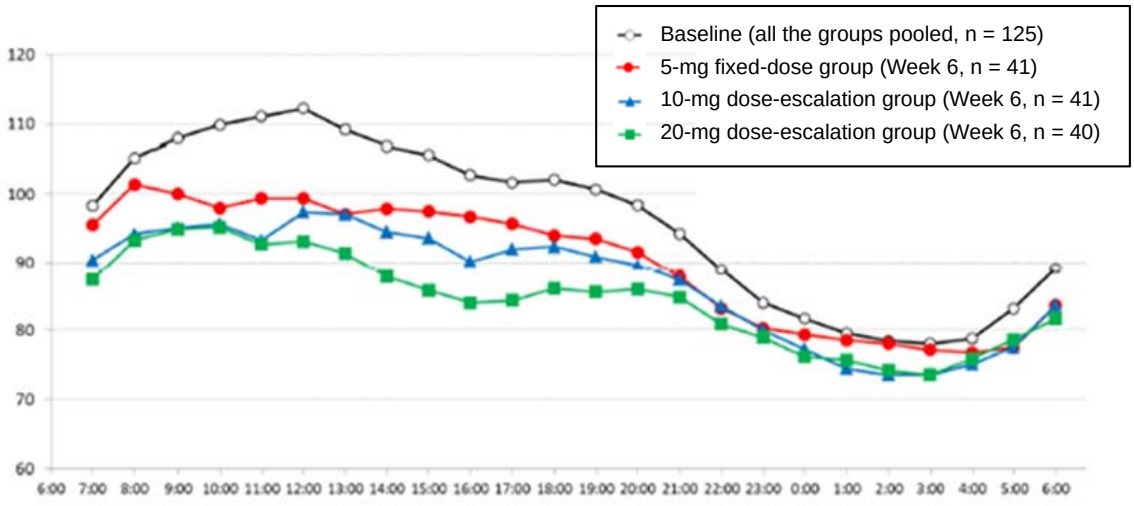

Figure 1. Changes in mean hourly heart rate by Holter monitoring at Week 6 (FAS, without LOCF) (Adapted from the submitted data)

(b) Effect of the increased dose up to 10 mg/day

The changes in mean heart rate at Week 6 did not show any significant dose-response relationship between the 5-mg fixed-dose group, 10-mg dose-escalation group, and 20-mg dose-escalation group. As reference information, however, the "effect of the increased dose based on the change in mean heart rate at Week 4 in comparison between the pooled dose-escalation groups (10-mg dose-escalation group and 20-mg dose-escalation group) and the 5-mg fixed-dose group" was investigated. In both the 10-mg dose-escalation group and 20-mg dose-escalation group, the maximum dose at Week 4 was 10 mg/day, allowing these groups to be pooled. In the 5-mg fixed-dose group in the FAS, the mean 24-hour heart rate (mean ± SD) was 98.4 ± 15.1 beats/min at baseline and 91.4 ± 13.55 beats/min at Week 4, and the change from baseline to Week 4 (least squares mean [95% CI], ANCOVA with the mean 24-hour heart rate at baseline as covariate) was 6.3 [3.8, 8.7] beats/min. In the dose-escalation group, the mean 24-hour heart rate was 95.0 ± 11.72 beats/min at baseline and 86.7 ± 10.62 beats/min at Week 4, and the change from baseline to Week 4 was 8.6 [6.9, 10.4] beats/min. The difference in change between the 5-mg fixed-dose group and dose-escalation group was 2.4 [-0.64, 5.37] beats/min. The 10-mg dose-escalation group included 1 above-mentioned ineligible subject by inclusion criteria. As a result of the post-hoc analysis of the data excluding this subject, the difference in change was 1.6 [-0.96, 4.24] beats/min. As a result of the secondary analysis in the PPS, the difference was 2.2 [-0.21, 4.62] beats/min. The failure in demonstrating the significant effect of the increased dose in a series of analyses was considered attributable to a smaller difference in heart rate lowering effect between the 5-mg fixed-dose group and dose-escalation groups (at Week 4, 10-mg dose-escalation group and 20-mg dose-escalation group combined) and larger variability among subjects than assumed. That is, the difference between the groups at the time of planning was assumed to be 3 beats/min (change in the 10-mg dose-escalation group, 10 beats/min; change in the 5-mg fixed-dose group, 7 beats/min) and the SD, 5 beats/min, but the actual difference between the groups was 2.4 beats/min and the SD was 8.01 to 10.77 beats/min, which departed from the assumption. In addition, both the 10-mg dose-escalation group and 20-mg dose-escalation group until Week 4 included not only the subjects treated with the increased dose of 10 mg/day but also the subjects on the maintenance dose of 5 mg/day. To investigate the effect of the increased dose (up to 10 mg/day) more accurately, a secondary endpoint analysis in the subjects in whom the dose escalation to 10 mg/day was judged necessary was performed by presence or absence of the subsequent dose escalation. As a result, of the subjects in whom the dose escalation was judged necessary due to the lack of efficacy at the dose of 5 mg/day, 30 subjects continued to receive carvedilol at the dose of 5 mg/day after assessment for dose-escalation. The change in mean heart rate from Week 2 to Week 4 was 0.1 [-1.86, 2.13] beats/min in these subjects. In 53 subjects in whom the dose was increased to 10 mg/day (10-mg dose-escalation group and 20-mg dose-escalation group combined), on the other hand, the change was 3.4 [0.97, 5.86] beats/min, exhibiting further heart rate lowering effect. The applicant therefore determined that the effect of the increased dose (up to 10 mg/day) was confirmed. The post-hoc analysis excluding the subject in the 10-mg dose-escalation group ineligible by inclusion criteria

presented comparable results as well. Of 53 subjects in whom the dose was increased to 10 mg/day due to the lack of efficacy at the dose of 5 mg/day, 12 subjects were judged to have no need for the dose-escalation to 20 mg/day, suggesting presence of patients sufficiently responding to the dose of 10 mg/day. The time course of changes in mean hourly heart rate over 24 hours by Holter monitoring in the subjects in whom the dose was not increased to 10 mg/day was almost comparable to that at baseline (at the time of assessment for dose-escalation) without a definite heart rate lowering effect, while the time course in the subjects in whom the dose was increased to 10 mg/day deviated from that at the time of assessment for dose-escalation and that in the subjects without dose escalation especially during the day (active), demonstrating a definite heart rate lowering effect. Similarly, the time course of changes in maximum and minimum hourly heart rates over 24 hours showed a definite heart rate lowering effect during the day (active). Data on the maximum 24-hour heart rate also showed an increasing trend of heart rate lowering effect with the increasing dose (11.6 ± 17.92 beats/min for the 5-mg fixed-dose group, 19.0 ± 21.66 beats/min for the pooled dose-escalation group). The results on the percentage of subjects in whom the mean heart rate during 24-hour Holter monitoring and the resting heart rate on 12-lead ECG achieved the target heart rate supported the effect of the increased dose (up to 10 mg/day). Based on these results, although no statistically significant effect of the increased dose was observed in the dose-escalation group at Week 4, it was considered appropriate to determine that the effect of the increased dose (up to 10 mg/day) was clinically observed.

(c) Effect of the increased dose up to 20 mg/day

The changes in mean heart rate at Week 6 did not show any significant dose-response relationship between the 5-mg fixed-dose group, 10-mg dose-escalation group, and 20-mg dose-escalation group. Only for reference information, however, the pre-determined analysis of the effect of the increased dose in the 20-mg dose-escalation group based on the change in mean heart rate at Week 6 in comparison with the 5-mg fixed-dose group showed that the change from baseline to Week 6 was 7.7 [5.7, 9.7] beats/min in the 5-mg fixed-dose group (ANCOVA with the mean 24-hour heart rate at baseline as a covariate) and 10.7 [8.6, 12.7] beats/min in the 20-mg dose-escalation group in the FAS. The between-group difference in the change was 2.9 [0.06, 5.80] beats/min. As a result of the secondary analysis in the PPS, the between-group difference in the change was 3.0 [0.15, 5.95] beats/min, which was similar to the above. The changes (least squares mean) in mean heart rate at Week 6 in the 10-mg dose-escalation group and 20-mg dose-escalation group were 8.4 beats/min and 10.2 beats/min, respectively, and even in the post-hoc analysis excluding the subject ineligible by inclusion criteria, the changes are 7.3 beats/min and 10.0 beats/min, respectively, suggesting that heart rate lowering effect was greater in the 20-mg dose-escalation group than that in the 10-mg dose-escalation group. A secondary endpoint analysis in the subjects in whom the dose escalation to 20 mg/day was judged necessary was performed by presence or absence of the subsequent dose escalation. As a result, of the subjects in whom the dose escalation was judged necessary due to the lack of efficacy at the dose of 10 mg/day, 18 subjects continued to receive carvedilol 10 mg/day after assessment for dose-escalation. The change in mean heart rate from Week 4 to Week 6 was -0.7 [-3.88, 2.43] beats/min in these subjects. In 20 subjects in whom the dose was increased to 20 mg/day, on the other hand, the change was 5.0 [0.04, 9.96] beats/min, exhibiting further heart rate lowering effect. The applicant therefore determined that the effect of the increased dose (up to 20 mg/day) was confirmed. Of 53 subjects in the 10-mg dose-escalation group and 20-mg dose-escalation group in whom the dose was increased to 10 mg/day due to the lack of efficacy at the dose of 5 mg/day, 38 subjects were judged to have a need for the dose-escalation to 20 mg/day due to the lack of efficacy at the dose of 10 mg/day, suggesting the presence of patients who have to receive carvedilol at the dose of 20 mg/day clinically. The time course of changes in mean hourly heart rate over 24 hours by Holter monitoring in the subjects in whom the dose was increased to 20 mg/day deviated from that at the time of assessment for dose-escalation and that in the subjects (10 mg/day) without dose escalation especially during the day (active), showing a definite heart rate lowering effect. Similarly, the changes in maximum and minimum hourly heart rates over 24 hours showed a definite heart rate lowering effect. The percentages of subjects in whom the target mean heart rate by Holter monitoring and resting heart rate on 12-lead ECG were achieved supported the clinical significance of the increased dose to 20 mg/day.

As described above, although the analysis of the primary endpoint did not demonstrate statistically significant dose-response or the effect of the increased dose, the applicant considered the dose-response over doses of 5 mg/day, 10 mg/day, and 20 mg/day as well as the increasing heart rate lowering effect with the increasing dose to be clinically justified, and thus determined that the following proposed

dosage and administration were appropriate: the initial dose is 5 mg of carvedilol administered orally once daily; if there is a lack of efficacy, the dose should be increased to 10 mg/day and then to 20 mg/day in a stepwise manner.

PMDA's view:
In the Japanese phase III study, the mean heart rate during 24-hour Holter monitoring was 96.1 ± 13.00 beats/min at baseline and 89.5 ± 12.20 beats/min at Week 2 in the FAS. Although the period effect has to be considered, 2-week treatment at the dose of 5 mg/day decreased the heart rate by 6.6 ± 7.91 beats/min with a statistical significance. Of 124 subjects, a total of 16 subjects did not need the dose increase throughout the treatment period, indicating that a certain number of patients successfully control heart rate at the dose of 5 mg/day. Carvedilol 5 mg/day is suggested to have a clinically significant heart rate lowering effect. Furthermore, in terms of the safety, no adverse events potentially attributable to an excessive heart rate lowering effect of carvedilol occurred following start of the treatment at 5 mg/day. It is therefore considered possible to set the starting dose at 5 mg/day.

The primary analysis of the primary endpoint in the Japanese phase III study did not verify the linear dose-response or the effect of the increased dose. The primary data from the Japanese phase III study alone therefore hardly justify the dose increments in the dose escalation regimen proposed by the applicant. As described above, however, it should be noted for the interpretation of the concerned study data that the Japanese phase III study, in the first place, had no choice but to be designed in consideration of its feasibility. In the Japanese phase III study, the results on point estimates for the changes in mean heart rate during 24-hour Holter monitoring, the primary endpoint, suggested a dose-dependent heart rate lowering effect; and the percentages of subjects in whom the target mean heart rate during 24-hour Holter monitoring and resting heart rate on 12-lead ECG at Week 6, the secondary endpoint and another endpoint, were achieved tended to increase in the order of the 5-mg fixed-dose group, 10-mg dose-escalation group, and 20-mg dose-escalation group. In the evaluation based on the actual doses, the changes in mean heart rate from baseline to Week 6 by final dose showed the heart rate decreased with the increasing dose, although the results have to be carefully interpreted, because the evaluation was performed as a post-hoc subgroup analysis, and the results were not derived from a randomized between-group comparison. Furthermore, an analysis in the subjects in whom the dose escalation to 10 mg/day was judged necessary was performed by presence or absence of the dose escalation. As a result, heart rate lowering effect was observed in response to the dose increase from 5 mg/day to 10 mg/day; of 53 subjects in whom the dose was increased to 10 mg/day due to the lack of efficacy at the dose of 5 mg/day, 12 subjects were judged to have no need for the dose-escalation to 20 mg/day, indicating that a certain number of patients successfully control heart rate at the dose of 10 mg/day. In addition, the subjects in whom the dose escalation was judged necessary due to the lack of efficacy at the dose of 10 mg/day and actually made to 20 mg/day showed further heart rate lowering effect. In light of the above, the results from the concerned study have suggested the efficacy of carvedilol administered according to the dosage regimen (the proposed dosage and administration) based on the actual clinical status (the gradually increasing heart rate lowering effect with the increasing doses of 5, 10, and 20 mg/day). At the same time, an additional clinical study is not considered necessary to re-evaluate the carvedilol's effect of the increased dose, up to 10 mg/day and 20 mg/day, taking into account that the guidelines in Japan and overseas refer carvedilol to a drug for controlling heart rate in atrial fibrillation and that carvedilol has been widely used as one of the standard therapeutic drugs for AF patients already in Japan.

No adverse events attributable to an excessive heart rate lowering effect of carvedilol occurred in any dose group, and the dose should be adjusted within a range from 5 to 20 mg/day from the viewpoint of the safety [see "2.(iii).B.(4) Safety of carvedilol"]. The safety of carvedilol at a dose >20 mg/day was not investigated in the Japanese phase III study and the upper limit dose of carvedilol should be set at 20 mg/day.

In clinical practice, the dose of has to be adjusted to achieve the target heart rate, which is set for each patient, taking account of the patient characteristics including therapeutic target and the severity of the symptoms associated with the blood pressure, cardiac function, and atrial fibrillation.

Although the following dosage and administration of carvedilol for atrial fibrillation are considered appropriate, a final decision on the matter will be made, taking account of comments raised in the Expert Discussion.

[Dosage and administration]
The usual initial dosage for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

2.(iii).B.(4) Safety of carvedilol

2.(iii).B.(4).1) Safety of carvedilol in the Japanese phase III study

The applicant's explanation on the safety of carvedilol:
All the adverse drug reactions (adverse events assessed to be causally "related" to the study drug) reported in the Japanese phase III study were known reactions for carvedilol, and the incidence in this study was 7.9% (10 of 127 subjects). At the approval of the indications for essential hypertension, renal parenchymal hypertension, and angina pectoris, and at the completion of the re-examination, the incidence of adverse drug reactions was 6.2% (82 of 1329 subjects) and 5.0% (328 of 6572 subjects), respectively. At the approval of the indication for chronic heart failure and the completion of the re-examination, the incidence was 40.2% (104 of 259 subjects) and 14.9% (296 of 1991 subjects), respectively. The incidence of adverse drug reactions in the Japanese phase III study did not markedly exceed those at the approval of the indications above or at the completion of the re-examination. A similar trend was also observed in the incidences of individual adverse drug reactions. Neither new adverse drug reactions nor increased incidence of the known adverse drug reactions was observed following carvedilol treatment of patients with atrial fibrillation (AF). Of the main adverse events possibly attributable to the pharmacologic action of carvedilol, hypotension, light-headed feeling, and dizziness/vertigo, all classified into cardiac or vascular disorders, were investigated. Events reported by ≥2 subjects throughout the study period included ventricular tachycardia (8.7%, 11 of 127 subjects), dizziness (2.4%, 3 of 127 subjects), and cardiac failure chronic (1.6%, 2 of 127 subjects). All the events of ventricular tachycardia were nonsustained ventricular tachycardia identified by Holter monitoring and were no clinically significant. Adverse events assessed to be related to the study drug included cardiac failure chronic in 2 subjects (1.6%) and dizziness in 1 subject (0.8%). The cardiac failure chronic in 2 subjects occurred at the dose of 5 mg during Period I. Of the adverse events possibly attributable to the pharmacologic action of carvedilol, No events showed the increasing incidence with the increasing dose.

PMDA's view:
Dizziness and orthostatic hypotension occurred in 3 subjects and 1 subject, respectively, in the Japanese phase III study, and events such as bradycardia have been reported in literature on routine clinical use of carvedilol in AF patients in Japan. When carvedilol is used for atrial fibrillation in routine clinical practice, attention should be paid to development of excessive bradycardia and hypotension through physical examination and by 24-hour Holter monitoring periodically. The current package insert of carvedilol includes the following precautions: dose-reduction or discontinuation of carvedilol should be taken depending on the incidence of adverse drug reactions; and a cardiac function test should be periodically performed. At present, it is unnecessary to add new precautions to the current precautions.

2.(iii).B.(4).2) Risk of cardiac failure aggravated by carvedilol

PMDA asked the applicant to explain a risk of cardiac failure aggravated by carvedilol in consideration of the finding that cardiac failure chronic aggravated occurred in 2 of 20 subjects with atrial fibrillation (AF) complicated by CHF in the Japanese phase III study as well as the use-results survey of carvedilol and literature on routine clinical use of carvedilol in AF patients in Japan. In addition, PMDA asked the applicant to specifically explain the risk of cardiac failure aggravated following administration of carvedilol in patients with AF complicated by heart failure of Class II or higher according to the New York Heart Association (NYHA) Functional Classification based on the currently available information in consideration that patients with heart failure of NYHA Functional Class II or higher were excluded from the Japanese phase III study; and then to explain whether the dosage and administration for chronic heart failure adequately ensures the safety in patients with AF complicated by CHF.

The applicant's response:
Of 20 subjects with AF complicated by CHF of NYHA Functional Class I included in the Japanese phase III study, 2 subjects experienced chronic cardiac failure aggravated. Of the 2 subjects, 1 subject

who had complications of CHF (NYHA Functional Class I), hypertension, hypertrophic cardiomyopathy, and nonsustained ventricular tachycardia experienced acute on chronic heart failure on Day 8 of treatment with carvedilol 5 mg, and then experienced body weight gain and foot oedema on Day 14 (the scheduled visit at Week 2). The carvedilol treatment was thus discontinued. For the treatment, the dose of furosemide was increased from 20 mg to 40 mg, and digoxin was started. On 22 days after onset of the adverse events, recovery was confirmed with reduced body weight as well as resolution of shortness of breath on effort and oedema. These events were assessed to be causally related to the study drug. The other subject who had complications of CHF (NYHA Functional Class I), diabetes mellitus, nonsustained ventricular tachycardia, and chronic hepatitis C experienced acute on chronic heart failure on Day 2 of treatment with carvedilol 5 mg and then made an unscheduled visit on Day 4, because of marked leg oedema. On the same day, carvedilol was discontinued, and furosemide and digoxin were started for the treatment. On 24 days after onset of the adverse events, recovery was confirmed with reduced body weight and alleviated leg oedema. These events were assessed to be causally related to the study drug. These events were mild or moderate in severity. All of them were complicated cardiac failure chronic (NYHA Functional Class I) aggravated and developed during an early phase of the treatment (Period I at a dose of 5 mg) in the 20-mg dose-escalation group. The approved dosage and administration for chronic heart failure specify that the starting dose of 1.25 mg of carvedilol is administered twice daily, suggesting that the starting dose of 5 mg is not suitable for some patients with CHF.

To investigate the risk of onset of heart failure in patients with AF complicated by CHF during treatment with carvedilol, the incidence of adverse drug reactions in data from the use-results survey and special survey of carvedilol in patients with CHF were analyzed by presence or absence of complication of AF. In these surveys, carvedilol was administered in accordance with the dosage and administration for chronic heart failure in the package insert. The use-results survey (survey period, January 2003 to June 2005) included 1732 patients for the safety evaluation as follows by NYHA Functional Class: 24.1% (418 of 1732 patients) in Class I; 54.9% (951 of 1732 patients) in Class II; 18.1% (314 of 1732 patients) in Class III; 2.1% (37 of 1732 patients) in Class IV; and 0.7% (12 of 1732 patients) in unknown class. In the 1302 patients in Class II or higher, the incidence of adverse drug reactions was 11.6% (106 of 912 patients) in patients not complicated by AF and 12.9% (50 of 387 patients) in patients complicated by AF. Patients who experienced “cardiac failure,” “cardiac failure acute,” or “cardiac failure congestive” (events related to cardiac failure aggravated), accounted for 4.4% (40 of 912 patients) of patients not complicated by AF and 4.1% (16 of 387 patients) of patients complicated by AF; there was no difference in the incidence of cardiac failure aggravated between patients with and without AF complication. The special survey (survey period, January 2003 to June 2005) included 497 patients for the safety evaluation as follows by NYHA Functional Class: 11.5% (57 of 497 patients) in Class I; 61.2% (304 of 497 patients) in Class II; 22.9% (114 of 497 patients) in Class III; 2.0% (10 of 497 patients) in Class IV; and 2.4% (12 of 497 patients) in unknown class. In the 428 patients in Class II or higher, the incidence of adverse drug reactions was 10.1% (33 of 327 patients) in patients not complicated by AF and 14.1% (14 of 99 patients) in patients complicated by AF. Patients who experienced any of “cardiac failure,” “cardiac failure acute,” or “cardiac failure congestive” accounted for 4.0% (13 of 327 patients) of patients not complicated by AF and 4.0% (4 of 99 patients) of patients complicated by AF; there was no difference in the incidence of cardiac failure aggravated between patients not complicated by AF and patients complicated. As described above, both use-results survey and special survey showed that the incidence of cardiac failure aggravated in patients with CHF of NYHA Functional Class II or higher complicated by AF and received carvedilol in accordance with the dosage and administration for chronic heart failure was not higher than that in those not complicated by AF.

Events related to cardiac failure aggravated were investigated by presence or absence of complication of AF in the data from the late phase II study, which was conducted for the partial change application for the additional indication of chronic heart failure. This late phase II study was conducted as a randomized, double-blind, placebo-controlled study in patients with CHF based on dilated cardiomyopathy and ischemic cardiomyopathy of NYHA Functional Class II or Class III who had a left ventricular ejection fraction ≤40%. During the trial period of this study, carvedilol was started at a dose of 2.5 mg/day (1.25 mg twice daily for 1-2 weeks). Patients in whom carvedilol 5 mg/day (2.5 mg twice daily for ≥2 weeks) was well tolerated were randomized to receive carvedilol at a dose of 2.5 mg twice daily (5-mg group); to receive carvedilol twice daily at an increasing dose of 2.5 to 10 mg up to 20 mg/day (dose-escalation up-to-20-mg group) depending on the tolerability during the dose-finding

period subsequent to the trial period; or to receive the corresponding placebo. In subjects complicated by AF who received carvedilol, events related to cardiac failure aggravated (hospitalization or re-hospitalization, discontinuation of medication, increased dose of a concomitant drug, additional concomitant drug for heart failure) did not occur in the 5-mg group. The incidence of these events was 2.7% (1 of 37 subjects) in the dose-escalation up-to-20-mg group during the dose-finding period (after randomization), in which the dose was increased to the maximum tolerated dose depending on the tolerability, 5.4% (2 of 37 subjects) in the dose-escalation up-to-20-mg group during the fixed-dose period from Week 25 to the study completion. In subjects not complicated by AF who received carvedilol, the incidence of these events was 1.3% (1 of 79 subjects) in the 5-mg group during a period from the start of the fixed-dose period to Week 12 and 1.3% (1 of 79 subjects) in the 5-mg group during the fixed-dose period from Week 25 to the completion. In the subjects who received the placebo, the incidence of events related to cardiac failure aggravated was 22.2% (2 of 9 subjects) in subjects complicated by AF and 18.9% (7 of 37 subjects) in subjects not complicated by AF throughout the study period. In both the placebo group and carvedilol group, the incidence of the events related to cardiac failure aggravated tended to be higher in subjects complicated by AF than subjects not complicated. Irrespective of presence or absence of complication of AF, carvedilol suppressed the onset of these events compared with placebo (presence of complication, 22.2% [2 of 9 subjects] in the placebo group vs 8.1% [3 of 37 subjects] in the carvedilol group; absence of complication, 18.9% [7 of 37 subjects] in the placebo group vs 2.5% [2 of 79 subjects] in the carvedilol group).

Of recent reports identified in the literature search[1] for actual clinical use of carvedilol in AF patients in Japan, 13 reports describe treatment for atrial fibrillation in patients with heart failure complicated by AF. Of these, 1 case report describes discontinuation of carvedilol (10 mg/day) due to development of cardiac failure congestive (*Kongetsu no chiryo.* 2004;12(10):3-10), but none of the others report cardiac failure aggravated by carvedilol.

As described above, the results from the use-results survey, special survey, and late phase II study in patients with CHF showed that carvedilol did not largely increase the incidence of aggravation of CHF even in patients with CHF of NYHA Functional Class II or higher irrespective of presence or absence of complication of AF. In patients with AF complicated by CHF, administration of carvedilol in accordance with the dosage and administration for chronic heart failure is considered to ensure the safety. In addition, as described in the draft package insert, it is considered necessary to provide cautions to ensure that patients are carefully monitored for clinical symptoms by means such as cardiac function test.

PMDA's view:
In the Japanese phase III study in which patients with heart failure of NYHA Functional Class II or higher were excluded, subjects with AF complicated by heart failure of NYHA Functional Class I experienced cardiac failure aggravated soon after start of the treatment with carvedilol at the starting dose of 5 mg/day. From the viewpoint of the safety, treatment with carvedilol should be started at <5 mg/day for patients with AF complicated by heart failure, irrespective of the severity, including patients complicated by mild heart failure of Class I.

The late phase II study, which was conducted for the partial change application for the additional indication of chronic heart failure, suggested that carvedilol tends to suppress onset of events related to cardiac failure aggravated compared with the placebo group in CHF patients of NYHA Functional Class II and Class III with or without atrial fibrillation, although the underlying diseases were limited to dilated cardiomyopathy and ischemic cardiomyopathy. When carvedilol is administered to patients with AF complicated by CHF of NYHA Functional Class II or higher, the dosage and administration for chronic heart failure is considered to ensure the safety. The use-results survey and special survey in patients with CHF and literature thereof suggested that the dosage and administration of carvedilol for chronic heart failure enables the administration to patients with AF complicated by heart failure without largely increasing the risk of cardiac failure chronic aggravated. Based on the above, it is considered appropriate, from the viewpoint of the safety, to start the treatment with carvedilol 1.25 mg twice daily, the starting dose in the dosage and administration for chronic heart failure (CHF), in patients with CHF irrespective of the NYHA Functional Classification. The following caution statement under the "Precautions for dosage and administration" section in the draft package insert was considered appropriate: for patients with atrial fibrillation complicated by chronic heart failure, carvedilol should be administered in accordance with the dosage and administration for chronic heart failure.

In addition, in patients with AF complicated by heart failure, attention should be paid to a risk of cardiac failure aggravated especially at the beginning of the treatment with carvedilol or at the time of dose increase. The applicant included the following precaution under the "Important precautions" section in the draft package insert: Heart failure may worsen after treatment with carvedilol in patients with tachycardiac atrial fibrillation complicated by heart failure; the patient should be carefully monitored for clinical symptoms by means such as cardiac function tests (pulse rate, blood pressure, ECG, X-ray, etc.). PMDA concluded that appropriate measures are taken.

2.(iii).B.(5) Efficacy and safety of carvedilol administered for a long-term period

PMDA asked the applicant to explain the safety and efficacy of carvedilol administered to AF patients for a long-term period based on the currently available findings.

The applicant's response:

The use-results survey of carvedilol in patients with hypertension, an approved indication, showed that, in patients receiving carvedilol for ≥12 weeks, no adverse drug reaction occurred in 40 patients with hypertension complicated by AF and the incidence of adverse drug reactions was 1.59% (55 of 3451 subjects) in 3451 patients with hypertension not complicated by AF. No adverse drug reaction occurred in 6 patients with hypertension complicated by AF who received carvedilol for ≥24 weeks. With respect to heart rate lowering effect in patients who received carvedilol for ≥12 weeks, the mean pulse rate (SD) in 22 patients with hypertension complicated by AF was 68.2 (7.6) beats/min at Week 12, which was decreased from 74.0 (12.2) beats/min at baseline. The special survey for long-term use of carvedilol in patients with hypertension showed that no adverse drug reaction occurred in 4 patients with hypertension complicated by AF who received carvedilol for 18 months, the standard observation period, while the incidence of adverse drug reactions was 5.16% (18 of 349 subjects) in patients with hypertension not complicated by AF.

Of recent reports identified in the literature search[1] for actual clinical use of carvedilol in AF patients in Japan, 34 reports described treatment for atrial fibrillation in patients with AF not complicated by CHF and patients with heart failure complicated by AF in Japan. Of these, 24 reports provided the treatment period. Of the 24 reports, 46% (11 of 24 reports) and 29% (7 of 24 reports) described the treatment with carvedilol for ≥6 months and ≥1 year, respectively. One report (*J Cardiovasc Pharmacol.* 2013;61(1):77-82) evaluated the safety in patients who received carvedilol for ≥6 months. In this report, adverse events in subjects who received carvedilol at a dose of 5 to 20 mg (14.5 mg/day on average) for 3 years included cerebral infarction in 1 subject, transient ischaemic attack in 1 subject, cardiac failure in 2 subjects, and bradycardia in 2 subjects. These adverse events are known adverse drug reactions of carvedilol, and the safety profile was not largely different from those for the approved indications.

The efficacy of carvedilol was investigated in the reports covering ≥6 month treatments. In the above study in which carvedilol was administered for 3 years, the longest period among the reports investigated, the mean heart rate in subjects treated with carvedilol significantly decreased from 72 beats/min at baseline to 64 beats/min after 1 month of treatment, and the rate was maintained at approximately the same level until 3 years after the start of treatment. A clinical study conducted in 11 patients with permanent atrial fibrillation to investigate the antitachycardia action of carvedilol (initially at a dose of 10 mg/day followed by dose-escalation to 20 mg/day) (*J Arrhythmia.* 2013;29 Suppl:229-230) was a long-term treatment, and the treatment period was 12 months. The mean heart rate was 89.0 beats/min at baseline, 77.3 beats/min after 6 months of treatment, and 76.8 beats/min after 12 months of treatment; and the mean maximum heart rate was 177.7 beats/min at baseline, 148.5 beats/min after 6 months of treatment, and 146.5 beats/min after 12 months of treatment. The mean heart rate and the mean maximum heart rate significantly decreased after 6 and 12 months of treatment compared with those at baseline.

These results showed that the safety profile in AF patients who received carvedilol for a long-term period was not largely different from those in patients receiving carvedilol for the approved indications, demonstrating the continuous efficacy of carvedilol in controlling heart rate in AF patients.

PMDA's view:

Although no clinical studies have been conducted to evaluate the safety and efficacy of carvedilol treatment in AF patients for a long-term period, the results from the use-results survey, special survey, clinical reports in Japan, etc., for the approved indications of carvedilol allow to conclude the stable

efficacy of carvedilol can be expected even in the long-term treatment. In consideration of the pharmacologic action of carvedilol and findings of bradycardia and cardiac failure in clinical reports in Japan, attention should be paid to excessive bradycardia and cardiac failure not only at the time of dose increase but also during the period at maintenance dose in the long-term treatment with carvedilol, and appropriate measures such as dose reduction or discontinuation of carvedilol should be taken if these adverse events are observed. The current package insert of carvedilol recommends that the cardiac function test be performed periodically, and measures such as dose reduction and treatment discontinuation be taken at the onset of bradycardia or hypotension when carvedilol is administered for a long-term period. Thus, the current precautions in the package insert are appropriate.

2.(iii).B.(6) Indications and intended population

The applicant's rationale for the proposed indication:

The proposed indication was established based on the results from the Japanese phase III study in patients with persistent or permanent AF and the drug utilization survey in Japan. The study showed that carvedilol is useful in controlling heart rate. The study did not include patients with paroxysmal AF, some of whom need controlling their heart rate. The foreign guidelines recommend heart rate control therapy not only for patients with persistent or permanent chronic AF but also for patients with paroxysmal AF, and include recommended dosage regimen of carvedilol as one of the drugs for controlling heart rate. The main pharmacological mechanism of carvedilol in controlling heart rate is based on suppression of the atrioventricular conducting system in the atrioventricular nodal cells that resulted from suppression of calcium ion current through β_1 receptor blocking action. This mechanism is not different from those of the other β-blockers such as bisoprolol, which is approved for the indication of tachycardiac atrial fibrillation including paroxysmal atrial fibrillation. Of the recent reports identified in the literature search[1] for drug utilization of carvedilol in AF patients in Japan, 22 reports describe treatment for paroxysmal AF in Japan (including reports about prevention of postoperative atrial fibrillation). Of the 22 reports, 17 describe the doses of carvedilol, and only 1 of them concluded that carvedilol alone or in combination with antiarrhythmia drugs did not have sufficient efficacy. The remaining 16 reports demonstrated that the treatment with carvedilol had efficacy in controlling heart rate or preventing onset of postoperative AF in patients with paroxysmal AF. These drug utilization studies are considered to support the efficacy of carvedilol in patients with paroxysmal AF. In the reports evaluating the safety, all the adverse events were known adverse drug reactions of carvedilol. Based on the above, it is considered appropriate to specify "tachycardiac atrial fibrillation" as the indication to be added in this application.

PMDA's view:

From the submitted data in this application, it has been concluded that carvedilol has significant efficacy and acceptable safety in AF patients. Although the Japanese phase III study was conducted in patients with persistent or permanent AF, it is considered appropriate to indicate carvedilol for patients with atrial fibrillation presenting tachycardia for the following reasons: heart rate control is needed during tachycardia in paroxysmal AF; the pharmacological mechanism of heart rate control for chronic AF is not different from that for paroxysmal AF; and the ESC Guidelines also recommend carvedilol for controlling heart rate in patients with paroxysmal AF. Although it is considered appropriate to specify "tachycardiac atrial fibrillation" as the indication related to atrial fibrillation, a final decision on the matter will be made, taking account of comments raised in the Expert Discussion.

2.(iii).B.(7) Post-marketing investigations

PMDA asked the applicant to explain whether information on the safety and efficacy of carvedilol should be additionally collected in response to the additional indication of atrial fibrillation for carvedilol.

The applicant's response:

It is considered possible to evaluate the safety of carvedilol in AF patients based on the existing information, because the safety information in patients receiving carvedilol for hypertension, angina pectoris, and chronic heart failure (approved indications), which coexist frequently with atrial fibrillation, has been sufficiently collected; and the safety profile in AF patients is not largely different from that in patients with the approved indications. The use-results survey and the special survey for long-term use of carvedilol in patients with hypertension showed that the occurrence of adverse drug reactions (incidence and details of reactions) in patients with hypertension complicated by arrhythmia

or AF was not largely different from that in patients with hypertension without the complications. Even in the clinical study, use-results survey, and special survey in patients with CHF, the occurrence of adverse drug reactions in patients with CHF complicated by AF was not largely different from that in patients with CHF not complicated. All the reported adverse events in the literature-search-based drug utilization survey were known events for the approved indications, and the safety profile in AF patients was not largely different from that in patients with the approved indications. Based on the above, it is considered unnecessary to collect the safety information from AF patients additionally. For heart rate control therapy in AF patients, international standard, text books and guidelines for AF management in Japan and overseas recommend β-blockers, and carvedilol is positioned as one of the β-blockers used for heart rate control therapy, and thus consensus has been established for carvedilol among medical and pharmaceutical professionals. The efficacy of carvedilol is potentially expected, including when used for a long-term period, based on the following: (a) the data from the Japanese phase III study; (b) changes in pulse rate before and after administration of carvedilol to patients complicated by arrhythmia or AF in the use-results survey and special survey for long-term use in patients with hypertension; and (c) the results from the literature-search-based drug utilization survey. In conclusion, there is no information that should be collected through additional post-marketing surveillance in AF patients.

PMDA's view:
In Japan, carvedilol has already been widely used in patients with tachycardiac atrial fibrillation in clinical practice, and no additional concerns have been found in clinical studies or in information collected from AF patients monitored in post-marketing surveillance for the approved indications. Therefore, the following applicant's conclusion is acceptable: there is no information that should be collected through an additional survey after addition of the indication of tachycardiac atrial fibrillation. Furthermore, it is unnecessary to conduct additional post-marketing surveillance for this application. Neither additional pharmacovigilance activities nor risk minimization activities are necessary in the risk management plan for this application at present.

III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application. The inspection and assessment revealed no particular problems. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application (5.3.5.1-1). The inspection revealed the clinical study was conducted in accordance with the GCP as a whole. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. PMDA notified the applicant (sponsor) of the following observed finding regarding the sponsor requiring improvement, although it does not largely affect the overall evaluation of the study.

Finding requiring improvement
Sponsor

- Serious unexpected adverse drug reactions etc., were not fully reported to the investigator or head of the medical institution immediately.

IV. Overall Evaluation

Based on the submitted data, the efficacy of carvedilol in controlling heart rate in patients with tachycardiac atrial fibrillation has been demonstrated, and its safety is acceptable in view of its expected benefits. Carvedilol is therefore considered to have clinical significance as an option of therapeutic drugs used to control heart rate in tachycardiac atrial fibrillation.

This application may be approved if Carvedilol is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 10, 2015

I. Product Submitted for Registration

[Brand name]	Artist Tablets 2.5 mg, Artist Tablets 10 mg, Artist Tablets 20 mg
[Non-proprietary name]	Carvedilol
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	October 20, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Clinical positioning of carvedilol

PMDA has concluded that carvedilol has clinical significance as one of the β-blockers used to control heart rate in patients with atrial fibrillation (AF) for the following reasons: The usefulness of heart rate control therapy in patients with AF is established in Japan and overseas; carvedilol has been widely used in AF patients in clinical practice in Japan; and the Japanese phase III study suggested carvedilol has heart rate lowering effect and no additional safety concerns were observed. PMDA has also concluded that therapeutic drugs for atrial fibrillation including carvedilol should be selected based on their efficacy and safety profiles and guidelines in Japan and overseas as well as each patient's characteristics such as complications and treatment goal. The above conclusion of PMDA was supported by the expert advisors.

(2) Study design of the Japanese phase III study

From the existing information in Japan and overseas, PMDA has considered that the heart rate lowering effect of carvedilol in AF patients is demonstrated and that optimal doses of β-blockers including carvedilol differ from Japan to overseas. PMDA thus has concluded it appropriate for the applicant to have conducted the Japanese phase III study in Japanese AF patients to investigate the heart rate lowering effect at the doses of 5 to 20 mg/day, already used in clinical practice, in this development. The above conclusion of PMDA was supported by the expert advisors.

(3) Efficacy and dosage and administration

The Japanese phase III study suggested a clinically significant heart rate lowering effect at a dose of 5 mg/day, and no adverse events potentially attributable to an excessive heart rate lowering effect of carvedilol occurred after treatment was started at 5 mg/day. In terms of the efficacy, the primary analysis of the primary endpoint of the Japanese phase III study did not verify the linear dose-response or increased dose effect. However, carvedilol has already been widely used in AF patients in Japan, and it all the more restricted the study scale. Taking account of the above, the following endpoints were comprehensively evaluated as well: (i) the results on point estimates for changes in mean heart rate during 24-hour Holter monitoring, the primary endpoint; (ii) the percentage of subjects in whom the mean heart rate during 24-hour Holter monitoring and the resting heart rate on 12-lead ECG at Week 6, the secondary endpoint and another endpoint, achieved the target heart rate; and (iii) the results of the evaluation based on the doses actually used in clinical practice. As a result, PMDA has concluded that the gradually increasing heart rate lowering effect of carvedilol was suggested with its increasing doses of 5, 10, and 20 mg/day. No adverse events attributable to an excessive heart rate lowering effect occurred. Based on the above, PMDA has concluded that the following dosage and administration of the proposed product is appropriate: The usual initial dosage for adults is 5 mg of carvedilol administered

orally once daily; if there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner; the dose may be adjusted according to the patient's age and symptoms; the maximum dose is 20 mg once daily. The following comments were raised from the expert advisors: The conclusion of PMDA is appropriate; this study failed in verification on the primary endpoint, and although no clear differences are observed among groups, the increased dose effect is expected in the detailed investigation on the study data including those on the secondary endpoint, and thus the conclusion of PMDA for the dosage and administration of carvedilol is understandable. The above conclusion of PMDA was supported by the expert advisors.

(4) Safety

Based on the data from the Japanese phase III study, PMDA has concluded that the following precautions in the current package insert are also applicable to the proposed indication: During use of carvedilol, examinations such as 24-hour Holter monitoring should be periodically performed, and attention should be paid to the onset of excessive bradycardia or sinus arrest; appropriate measures such as dose reduction or discontinuation of carvedilol should be taken depending on the occurrence of adverse drug reactions; and cardiac function test should be periodically performed. Cardiac failure aggravated occurred in patients with AF complicated by heart failure at the beginning of the treatment in the Japanese phase III study. For patients with AF complicated by heart failure, therefore, it is considered appropriate, from the viewpoint of safety, to start the treatment with carvedilol 1.25 mg twice daily irrespective of the severity of heart failure, which is the dosage and administration for chronic heart failure. The following caution statement therefore should be included in the "Precautions for dosage and administration" section in the draft package insert: Patients with tachycardiac atrial fibrillation complicated by chronic heart failure should receive carvedilol in accordance with the dosage and administration for chronic heart failure. PMDA has concluded that the above applicant's action is appropriate. In addition, the package insert should include a caution statement that heart failure may worsen after treatment with carvedilol in patients with atrial fibrillation complicated by heart failure and these patients should be carefully monitored by cardiac function tests while taking carvedilol. PMDA has concluded that the above applicant's action is appropriate. The above conclusion of PMDA was supported by the expert advisors.

(5) Indication

Based on the following consideration, PMDA has concluded that it is appropriate to specify the indication as "tachycardiac atrial fibrillation": Although the Japanese phase III study included patients with persistent or permanent atrial fibrillation, it is considered appropriate to indicate carvedilol tablets for patients with atrial fibrillation presenting tachycardia because heart rate should be controlled during tachycardia in paroxysmal atrial fibrillation; the pharmacological mechanism of heart rate control for chronic atrial fibrillation is not different from that for paroxysmal atrial fibrillation; and the ESC Guidelines also recommend carvedilol for controlling heart rate in patients with paroxysmal atrial fibrillation. The above conclusion of PMDA was supported by the expert advisors.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below.

[Indication]

(a) Artist Tablets 2.5 mg
Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(b) Artist Tablets 10 mg
Essential hypertension (mild to moderate)
Renal parenchymal hypertension

Angina pectoris
Patients with the following conditions who are receiving basic treatment with angiotensin-converting enzyme inhibitors, diuretics, digitalis preparations, etc.
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
Tachycardiac atrial fibrillation

(c) Artist Tablets 20 mg
Essential hypertension (mild to moderate)
Renal parenchymal hypertension
Angina pectoris
Tachycardiac atrial fibrillation

(The underline denotes added text, and the double-underline denotes altered text.)

[Dosage and administration] (a) Artist Tablets 2.5 mg
Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dose should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

(The underline denotes added text, and the double-underline denotes altered text.)

(b) Artist Tablets 10 mg
Essential hypertension (mild to moderate), renal parenchymal hypertension
The usual adult dosage is 10 to 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Angina pectoris
The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Chronic heart failure caused by ischemic heart disease or dilated cardiomyopathy
The usual initial dose for adults is 1.25 mg of Carvedilol administered orally twice daily after meals. If the dose of 1.25 mg twice daily is tolerated, the dose should be increased in a stepwise manner at an

interval of 1 week or longer depending on tolerability. If not tolerated, the dose should be reduced. The dose should be adjusted in a stepwise manner only; a dose should be 1.25 mg, 2.5 mg, 5 mg, or 10 mg, and Carvedilol should be administered orally twice daily after meals at any dose. The usual maintenance dose is 2.5 to 10 mg of Carvedilol administered orally twice daily after meals.

A lower initial dose may be used according to the patient's age and symptoms. Depending on the patient's response to Carvedilol, the maintenance dose may be adjusted.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

(The underline denotes added text, and the double-underline denotes altered text.)

(c) Artist Tablets 20 mg

Essential hypertension (mild to moderate), renal parenchymal hypertension
The usual adult dosage is 10 to 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Angina pectoris
The usual adult dosage is 20 mg of Carvedilol administered orally once daily. The dose may be adjusted according to the patient's age and symptoms.

Tachycardiac atrial fibrillation
The usual initial dose for adults is 5 mg of Carvedilol administered orally once daily. If there is a lack of efficacy, the dose should be increased to 10 mg once daily and then to 20 mg once daily in a stepwise manner. The dose may be adjusted according to the patient's age and symptoms. The maximum dose is 20 mg once daily.

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