PRIDE

Assessment of the efficacy, adherence and tolerability of the single pill combination bisoprolol/PerindopRil In patients with previous myocardial infraction with arterial hypertension in the Daily clinical practicE

Protocol №: №IC4-05150-065-RUS

NCT04656847

10 March 2020

INN: bisoprolol + perindopril

Dosages:

bisoprolol 2.5 mg + perindopril 2.5 mg 1 time per day (1/2 tablet 5+5)
bisoprolol 5 mg + perindopril 5 mg once daily

bisoprolol 5 mg + perindopril 10 mg once daily

bisoprolol 10 mg + perindopril 5 mg once daily

bisoprolol 10 mg + perindopril 10 mg once daily

Presentation: film-coated tablet.

National coordinator: *Professor Kobalava Z.D. MD, PhD*

Confidential

This document is classified by Servier as confidential and is intended only for instructions during the observational period.

The contents of this document should not be disclosed to any persons or institutions not participating in this study without the prior written consent of Servier.

Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ADR	adverse drug reaction
AE	adverse event
BP	blood pressure
CAD	coronary artery disease
CCS	canadian cardiovascular sosiety
CI	confidence interval
CRF	case report form
DBP	diastolic blood pressure
ECG	Electrocardiography
HCP	health care professional
HR	heart rate
HTN	(arterial) hypertension
ISH	isolated systolic hypertension
MI	myocardial infarction
NYHA	New York Heart Association
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
SD	standard deviations
SOC	System-Organ-Class
SPC	single pill combination
SMBP	self-monitoring of blood pressure

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Contents

1 Introduction and aims

Introduction

A blood pressure (BP) lowering in the treatment of arterial hypertension (HTN) is associated with a reduction in the risk of cardiovascular mortality and the rate of complications (1,2). When prescribing antihypertensive drugs, the choice depends largely on the presence of concomitant diseases and associated conditions. The prevalence of HTN in patients with coronary artery disease (CAD) exceeds 80% (3). The BP control in patients with HTN and CAD is important, as the risk of recurring coronary events depends mostly on the BP level (4). For patients with HTN who have had a recent myocardial infarction (MI), it is recommended to use beta$_1$-adrenoceptor blocking agents and renin-angiotensin-aldosterone system (RAAS) inhibitors (5).

Monotherapy often does not contribute to achieving the target BP levels. The combination of two agents from any two classes of antihypertensive drugs is much more effective than monotherapy even at the maximum dose of the agent chosen for monotherapy (1,2). In addition to the higher efficacy, combination therapy provides a more potent organ-protective effect and has a better tolerance (by minimizing adverse effects and due to the ability to use lower doses) (2,6). The use of combination therapy increases patient adherence to treatment. A meta-analysis performed by Bangalore S et al. (2007) with the inclusion of data from 68 clinical trials assessing the single pill combinations (SPCs) and antihypertensive agents of various groups has demonstrated that antihypertensive SPCs increase treatment adherence by 24%, compared with free combinations in equivalent doses, and, therefore, provide better control of hypertension (7).

The studied efficacy and safety of perindopril and bisoprolol both in monotherapy and in free combination became the basis for the creation of Prestilol® medicine - a fixed combination of these active substances. Bisoprolol, a component of Prestilol®, is one of the long-acting beta$_1$-blockers with the highest selectivity. Bisoprolol reduces adrenergic stimulation of the heart muscle and pacemakers, which leads to a decrease in stroke volume and heart rate (HR), as well as the inhibition of renin secretion by the kidneys (3,6,8). In the BRIGHT study, 96.4% of 2161 patients with essential HTN showed significant reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR after 12 weeks of bisoprolol monotherapy. Bisoprolol has demonstrated a marked BP-lowering effect and good tolerance. Moderate adverse events (AEs) were observed in only 1.9% of patients, and no serious AEs or drug withdrawals were reported (9).

Perindopril is a highly lipophilic angiotensin-converting-enzyme (ACE) inhibitor, which has a proven organ-protective effect and is able to improve outcome in HTN, CAD, and cerebrovascular diseases. Like other ACE inhibitors, perindopril inhibits the RAAS by reduction in the formation of angiotensin II. The latter is accompanied by a decrease in total peripheral vascular resistance, formation of aldosterone and, therefore, sodium and water retention, with a reduction in circulating blood volume (6). The EUROPA study assessed the efficacy of perindopril on the top of standard therapy with β_1-blocker in CAD patients (67% of them had a history of MI, and one third had

concomitant HTN). Combination treatment with perindopril and β-blocker reduced the relative risk of the primary endpoint (cardiovascular death, nonfatal MI, and resuscitated cardiac arrest) by 24% compared with β-blocker monotherapy (HR, 0.76; 95% CI, 0.64-0.91; P = 0.002). Addition of perindopril also reduced fatal or nonfatal MI by 28% (HR, 0.72; 95% CI, 0.59-0.88; P = 0.001) and hospitalization for heart failure by 45% (HR, 0.55; 95% CI, 0.33-0.93; P = 0.025) (10,11). There are other published data from several studies of the bisoprolol/perindopril SPC efficacy in hypertensive patients with CAD.

Korennova O.Yu. et al. (2019) evaluated the efficacy of bisoprolol/perindopril SPC in patients with recent acute coronary syndrome (ACS) who underwent endovascular coronary intervention. The study has demonstrated an efficient and optimal in time (within the first 4 weeks) achievement of target levels of SBP, DBP and HR, as well as persistence of the effects after 12 weeks of treatment. Clinical benefits of bisoprolol/perindopril SPC included a significant reduction in the severity and rates of manifestations of chronic heart failure and/or angina pectoris (3).

The data of PRESTOL (2019) study examined the efficacy of bisoprolol/perindopril SPC in 2394 hypertensive patients with CAD and showed significant reductions in HR (target HR ≤70 beats per minute was achieved in 84.9% of patients) and BP (target BP ≤140/90 mm Hg was achieved in 86.9% of patients). The treatment was associated with a reduction in the number of angina attacks (from 4.4 to 2.6 per week) and an improvement in the treatment adherence level (up to 66.5% of patients) (8).

SPC of bisoprolol/perindopril with several doses of 5/5, 5/10, and 10/10 mg in one tablet makes possible to individualize therapy and increase treatment compliance, while breakable tablets of 5/5, 5/10 mg combinations provide additional options for dose titration (12).

Aim

This non-interventional, ambispective study was aimed at describing effectiveness, safety, and tolerability of bisoprolol and perindopril SPC in patients with HTN and previous myocardial infarction treated with the SPC for 12 weeks in the real clinical practice. SPC will be used according to the approved instruction for medical use of the medicine.

Primary objectives

- To describe antihypertensive effectiveness (SBP and DBP reduction) of bisoprolol/perindopril SPC in hypertensive patients with previous MI at week 12 of prospective observation.

Secondary objectives

- To describe antianginal effectiveness of bisoprolol/perindopril SPC in hypertensive patients with a history of MI at week 12 of prospective observation.
- To describe a proportion of patients achieving target systolic and diastolic BP levels among hypertensive patients with previous MI during 12 weeks of prospective observation with bisoprolol/perindopril SPC according to the age (as stated in the guidelines “2”)

- To describe mean change in resting HR from BL among study patients at week 12 of prospective observation.
- To describe a proportion of patients who achieved resting HR less than 60 bpm at week 12 of prospective observation.
- To estimate association between the resting HR and achievement of target level of BP at week 12 of prospective observation.
- To describe adherence to the treatment with bisoprolol / perindopril in hypertensive patients with previous MI during the prospective observational period of 12 weeks.
- To describe the tolerability of treatment with bisoprolol / perindopril in hypertensive patients with previous MI during 12 week prospective observation.

Outcome measures

Primary outcome measure:

- Change in the mean systolic and diastolic BP levels at week 12 of prospective observation compared to baseline among patients included in the study.

Secondary outcome measures:

- Change in mean systolic and diastolic BP levels at week 4 of prospective observation compared with baseline.
- Change in number of angina attacks per week at week 4 of prospective observation compared with baseline.
- Change in number of angina attacks per week at week 12 of prospective observation compared with baseline.
- Proportion of patients who were taking lipid lowering therapy (LLT) at week 12 of prospective observation.
- Proportion of patients receiving LLT who achieved target levels of LDL C at week 12 of prospective observation.
- Proportion of patients who achieved SBP ≤140 mm Hg and DBP ≤90 mm Hg at week 4 of prospective observation.
- Proportion of patients who achieved SBP ≤140 mm Hg and DBP ≤90 mm Hg at week 12 of prospective observation.
- Proportion of patients younger than 65 who achieved SBP ≤130 mm Hg and DBP ≤80 mm Hg at week 4 of prospective observation .
- Proportion of patients younger than 65 who achieved SBP ≤130 mm Hg and DBP ≤80 mm Hg at week 12 of prospective observation.
- Proportion of patients older than 65 years who achieved SBP≤140 mm Hg and DBP ≤90 mm Hg at week 4 of prospective observation.

- Proportion of patients older than 65 years who achieved SBP≤140 mm Hg and DBP ≤90 mm Hg at week 12 of prospective observation .
- Changes in the mean heart rate (HR) at week 4 of prospective observation compared with baseline.
- Changes in the mean heart rate (HR) at week 12 of prospective observation compared with baseline.
- Proportion of patients who achieved target level of resting HR (55-60 bpm) at week 4 of prospective observation.
- Proportion of patients who achieved target level of resting HR (55-60 bpm) at week 12 of prospective observation.
- Correlation between the resting HR values stratified by groups and achievement of BP targets at week 12 of prospective observation .
- Proportions of patients with high, medium or low adherence to the treatment with SPC of bisoprolol/perindopril, assessed by MMAS-8 self-reporting questionnaire at week 4 of prospective observation.
- Proportions of patients with high, medium or low adherence to the treatment with SPC of bisoprolol/perindopril, assessed by MMAS-8 self-reporting questionnaire at week 12 of prospective observation.
- Incidence rate of adverse events/ adverse drug reactions and special situations during 12 week observational period of the study.

2 Methods and documentation

Study design and definitions

This is a multi-centre, observational, incomparative, ambispective study, which will retrospectively and prospectively collect clinical and socio-demographic data from medical records of patients with HTN and previous MI initiated with bisoprolol/perindopril SPC in real clinical settings.

Baseline data will be collected retrospectively from medical records of patients with HTN and a history of MI. Baseline data are defined as clinical parameters of interest available in medical records at the nearest date before or at the date of the initiation of SPC with Bisoprolol/ Perindopril.

To be included in the study for further prospective observation a patient should have been administered bisoprolol/ perindopril SPC within first three months before the Index Date. *(Fig.1)*.

The Index date is a date when a decision to include a patient in the study for further 12 week prospective observation made by a treating physician after evaluation of recorded data to confirm patient's eligibility for the study.

Therefore, criteria for non-inclusion or inclusion of patients in the study are to be retrospectively evaluated by the treating physician using recorded clinical data available from medical records. Once a treating physician makes decision to include a patient in the study and, in particular, on the prospective observation for 3 months, a visit 0 (inclusion visit) to the clinic for obtaining signed patient's consent to participate in the study should be appointed and made within 1 month from the Index Date.

Retrospective screening and evaluation of patient's eligibility to inclusion/ exclusion criteria for entering the study allows mitigating a potential risk of deliberative medicine administration within the observational program. Such studies are carried out in case of observational programs when the studied drug is administered in line with indications according to the instruction for its medical use.

Several multicenter, non-interventional, open, incomparable studies have been performed with bisoprolol/perindopril SPC in patients with HTN and coronary heart disease (3,8,13,14). A total of 70 general practitioners and cardiologists from primary care facilities will participate in the program. Each doctor will include about 7-8 patients. In total, it is planned to include at least 500 patients.

Calculation of the sample size

As the present research has an exploratory nature, the study is not intended to prove any hypothesis. In this case, a formal calculation of the sample size is not performed. Moreover, all statistical tests will be performed at a level of statistical significance of 0.05 and a power of 80%.

Given that the study will include patients with any grade HTN, the variability of SBP and DBP levels may be high enough. However, assuming that standard deviations (SDs) at baseline does not exceed 50 mm Hg, a sample of 500 patients will allow achieving a statistically significant difference in BP reduction after 3 months of treatment with bisoprolol/perindopril SPC compared with baseline levels, providing it is 6.3 mm Hg or more.

This non-interventional study has an exploratory nature, so the sample size is not a strict parameter and is recommendatory in nature.

Therefore, in order to obtain a representative population of patients with this particular disease and taking into account the practical aspects of conducting research in daily everyday routine practice, the total sample should consist of at least 500 patients.

Selection of doctors

A total of 70 general practitioners and outpatient cardiologists will participate in this non-interventional study.

Selection of patients

Inclusion criteria

1. Age from 18 to 79 years.
2. Signed informed consent to participate in the study.
3. Stable arterial hypertension with concomitant
   stable angina pectoris of class I-III according to the Canadian Cardiovascular Society (CCS) classification and a history of myocardial infarction not earlier than 3 months before inclusion in the study
4. Bisoprolol/perindopril SPC prescription 1-3 months before screening
5. Bisoprolol/perindopril SPC prescription in accordance with Russian SmPC, based on necessity in treatment with bisoprolol/perindopril SPC and separated from the decision to include the patient in the study
6. Clinical parameters of interest (Resting HR; SBP and DBP; freaquency of angina attacks per week) are available in medical records for the nearest date before or at the date of the initiation of SPC with Bisoprolol/ Perindopril.

Non-inclusion criteria

1. Hypersensitivity to bisoprolol, perindopril, excipients of the medicine, or other ACE inhibitors.

2. Any contraindication for bisoprolol/perindopril's SPC according to the instruction for medical use

3. CAD, angina pectoris of functional class IV according to the CCS classification (Appendix 1).

4. Chronic heart failure of class III-IV according to the New York Heart Association (NYHA) functional classification of heart failure (Appendix 3).
5. Cerebrovascular diseases (ischemic, haemorrhagic stroke, or transient ischemic attack) within the past 6 months prior to inclusion in the study.
6. A history of revascularization procedure within 3 months prior to inclusion in the study.
7. Hypertrophic obstructive cardiomyopathy.
8. Office BP ≥ 180/110 mm Hg on treatment
9. Type 1 diabetes mellitus and decompensated type 2 diabetes mellitus.
10. Bradycardia with a heart rate of less than 60 beats per minute.
11. Atrioventricular block (II-III degree), sinoatrial block, or sick sinus syndrome.
12. Severe bronchial asthma or severe chronic obstructive pulmonary disease.
13. Arterial hypotension (BP less than 100/70 mm Hg).
14. Pregnancy, breastfeeding.
15. Secondary hypertension.
16. Severe decompensated diseases of organs and systems requiring continuous treatment.
17. Current participation in another clinical trial and within 30 days prior to signing informed consent.

Treatment during the study

Treatment with the studied drug

bisoprolol 5 mg + perindopril 5 mg once daily
bisoprolol 5 mg + perindopril 10 mg once daily
bisoprolol 10 mg + perindopril 5 mg once daily
bisoprolol 10 mg + perindopril 10 mg once daily

A minimum dosage may also be prescribed:

bisoprolol 2.5 mg + perindopril 2.5 mg 1 time per day (1/2 tablet of bisoprolol 5 mg + perindopril 5 mg)

If the dose adjustment is required, the treating physician can correct the dosage of the drug at any time after the treatment start. The decision on the need to correct the dosage lives upon the treating physician.

In renal failure, it is necessary to adjust the dose depending on the degree of impaired renal function (creatinine clearance).

Concomitant drugs

Due to the non-interventional design of the study, it is allowed to use any concomitant treatment or drugs if it is considered necessary by the treating physician and not contraindicated according to the approved instruction for use. This treatment will be appropriately reflected in the study documentation.

Duration of non-interventional study

It is planned to complete enrolment of patients in this non-intervention study within 6 month.

Follow-up period for each patient will be 3 months.

First patient in is scheduled for Q1 2021

Last patient in is scheduled for Q3 2021

Last patient last visit Q4 2021

Data base lock is scheduled for Q1 2022

Statistical analysis is scheduled for Q2 2022

Clinical study report is scheduled for Q2 2022

Documentation during the non-intervention study

2.7.1. Documentation folder

Each doctor will be provided with a documentation folder containing a complete set of documents for 7-8 patients + 2 extra sets in case of lost or damage of study documentsincluding:

- One protocol of the observation plan;
- Documents for 7-8 patients (*Patient Informed Consent Form*, *Case report form (CRF)* with 7-8 *Adverse event/adverse drug reaction/special situation reporting forms*).
- 2 extra sets in case of lost or damage of study documents (*Patient Informed Consent Form*, *CRF; Adverse event/adverse drug reaction/special situation reporting forms)*

2.7.2 Study schedule

According to the design of multicentre, non-intervention , open-label, incomparative, ambispective study in patients with HTN and CAD treated with a bisoprolol/perindopril SPC, three visits will be enough to include patients, evaluate the treatment effectiveness and safety, as well as to adjust the dose of the study drug* (3,8).

The following visits are scheduled:

1. Screening period: will be retrospectively performed to ensure each patient fulfills inclusion/ non-inclusion criteria

2. Inclusion visit (V0): month 0;

3. Follow-up visit (V1): at 1 month after the V0 visit;

4. Final visit (V2): at month 3 after the visit V0 or in case of perindopril/ bisoprolol SPC treatment withdrawal.

* *In renal impairment, it is necessary to adjust the dose depending on the degree of impaired renal function (creatinine clearance)*

2.7.3. Methods and measurements of clinical parametrs

Measurement of the clinical BP by Korotkov's method in the sitting position in the doctor's office at the regular visit. BP will be measured on the same arm of the patient after 5 minutes of the rest. BP and HR will be measured thrice with an interval of 1-2 min; the average value of the last two measurements will be considered as the BP value measured at the visit; if the differences between two consecutive measurements of SBP are ≥ 15 mm Hg, it is necessary to perform the repeated BP measurement.

2.7.4 Study procedures and data collection

The plan at each visit during the study is presented in Table 1.

Patients will be provided with the self-observation diaries where they will record the BP values self-measured at home, the number of anginal attacks and the need to use short-acting nitrates.

Table 1 – Plan of visits during the study

Procedures	**Screening period (retrospective)**	**V0 Inclusion visit (month 0)**	**V1 Follow-up visit (month 1)**	**V2 Final visit (month 3)**
Obtaining patient informed consent		×		
Inclusion/ non-inclusion criteria	×	×		
Demographic data		×		
Risk factors and lifestyle		×		
Medical history		×		
Medical records on Resting HR; SBP and DBP; freaquency of angina attacks per week for the nearest date before or at the date of the initiation of SPC with Bisoprolol/ Perindopril		×		
Physical examination and vital signs (rest heart rate and BP) at the office visit		×	×	×
Current symptoms and the use of short-acting nitrates		×	×	×
Number of angina attacks per week		×	×	×
Current use of antianginal agents		×	×	×
Current use of other cardiovascular drugs		×	×	×
Current use of other drugs		×	×	×
Treatment adherence assessed by the patient (Morisky Medication Adherence Scale)		×	×	×
Current use of bisoprolol/perindopril SPC and reasons for discontinuation/ disruption of the treatment (if applicable)		×	×	×
Bisoprolol/perindopril SPC dose adjustment and reasons Bisoprolol/perindopril SPC dose adjustment		×	×	×
Adverse events/drug reactions/special situations		×	×	×

COLLECTION DATA:

2.7.4.1. Data evaluation during the screening period:

HCPs participating in the study will conduct a retrospective analysis of patient's records for the purpose of evaluating patient's eligibility to be enrolled in the study. Patients with HTN and a

history of MI, who had been initiated with bisoprolol/perindopril SPC within first three months before the Index Date (see a definition in Study Design and definitions of Section 2) and who meet other inclusion / non inclusion criteria will be included in the study if they sign a consest form at the inclusion visit.

2.7.4.1. Data collection at the inclusion visit (V0):

- Obtaining patient informed consent;
- Checking for inclusion/non-inclusion criteria;
- Physical examination and vital signs;
- Current status of taking bisoprolol/perindopril SPC and a dose regimen;
- Number of weekly angina attacks;
- Current symptoms and the use of short-acting nitrates;
- Current use of antianginal agents;
- Current use of other cardiovascular drugs with doses for calcium channel blockers, diuretics, nitrates and statins;
- Baseline assessment of adherence to bisoprolol/perindopril SPC done by patient-reported 8 item Morisky Medication Adherence Scale;
- Adverse events/drug reactions/special situations.

2.7.4.2. Data collection at the follow-up visit (V1):

- Physical examination and vital signs;
- Current status of taking bisoprolol/perindopril SPC and a dose regimen;
- Number of weekly angina attacks;
- Current symptoms and the use of short-acting nitrates;
- Current use of antianginal agents;
- Adherence to bisoprolol/perindopril SPC assessed by patient-reported 8 items Morisky Medication Adherence Scale;
- Current use of other cardiovascular drugs with doses for calcium channel blockers, diuretics, nitrates and statins;
- Adverse events/drug reactions/special situations;

2.7.4.3. Data collection at the final visit (V2):

- Physical examination and vital signs;
- Current status of taking bisoprolol+perindopril SPC and a dose regimen;
- Number of weekly angina attacks ;
- Current symptoms and the use of short-acting nitrates;
- Current use of antianginal agents;
- Current use of other cardiovascular drugs with doses for calcium channel blockers, diuretics, nitrates and statins;

- Adherence to bisoprolol/perindopril SPC assessed by patient-reported 8 items Morisky Medication Adherence Scale;
- Adverse events/drug reactions/special situations;

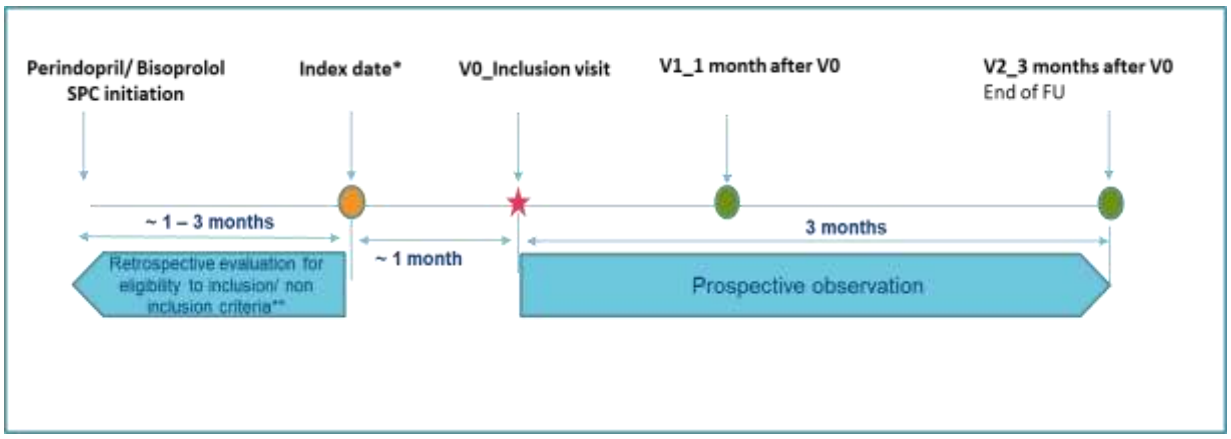

Figure 1. The scheme of the PRIDE study.

2.7.5 Implementation of non-intervention study

The treating physician will receive a documentation folder and instructions from the field staff of Servier. The patient should be informed of his/her participation in this study and the transfer of his/ her clinical data from the site to the responsible professional subcontractor for statistical analyses. Written informed consent must be obtained from the patient at the inclusion visit. The patient will receive a patient information sheet and a signed informed consent form. The second informed consent form must be archived by the doctor. Forms of documents should be filled in a readable form with a ballpoint pen in blue or black. In case of correction of erroneous data, they must be crossed out and replaced with the correct data. Corrections should be verified by the initials and date. No data should be deleted or erased. To ensure a high number of cases suitable for analysis, document forms should always be completed carefully and completely. In case of occurrence of adverse events (AEs), adverse drug reactions (ARDs), or special situations, it is necessary to follow the requirements listed in the section **Ошибка! Источник ссылки не найден.** «*Responsibilities of the investigator*». Please hand over the folder with the complete documentation to your Servier local executive.

Patients will undergo clinical assessment and receive the standard medical care as usual determined by the treating doctor based on their clinical judgement and national guidelines. Patients will not receive experimental treatment as a consequence of their participation in the observational study.

3 Pharmacovigilance

Definitions

3.1.1 Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;
- overdose, abuse, misuse, off-label uses, medication error, or occupational exposure (including professional one);
- lack of treatment effectiveness of a medicinal product;
- any suspected transmission via medicinal product of an infection agent;
- unintended therapeutic benefit.

3.1.2 Adverse Event (AE)

Adverse event is any untoward medical occurrence in a patient or a clinical-trial subject who received the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

3.1.3 Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

“Response” in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

3.1.4 Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

“Life threatening” in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Responsibilities

3.2.1. Events to be reported

All available information about the following reported events occurring during the study will be recorded:

- All serious adverse drug reactions related to the use of bisoprolol+perindopril SPC;
- All non-serious adverse drug reactions related to the use of SPC bisoprolol+perindopril);
- All reports about special situations (see **Ошибка! Источник ссылки не найден.**);
- All adverse events

3.2.2. Responsibilities of the investigator

At the visits during the study, the doctor clarifies in a patient participating in the study whether he/she had noticed any adverse events (serious or not serious according to the criteria of severity). The investigator should determine the presence/absence of a causal relationship between the use of the study drug and the adverse event, the presence/absence of criteria for severity, and then monitor the outcome of the event. In case of detection of any adverse event/adverse drug reaction or occurrence of a special situation during the study (serious or not serious according to the criteria of severity), the investigator must fill out the «*Adverse event/adverse drug reaction/special situation reporting form»* (Appendix) without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, the form should be sent immediately (same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.rus@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in relation to the adverse event should be attached to the form.

3.2.3 Responsibilities of the Sponsor/Marketing Authorisation Holder

Independently of the regulatory obligations of investigator, the sponsor/marketing authorisation holder (MAH) must report the pharmacovigilance data to the appropriate authorities in accordance with the Good PharmacoVigilance Practice and local regulations.

Cases of adverse event are considered to be closed when the patient has recovered or his/her condition was stabilised, providing that the available data are sufficiently detailed for adequate medical analysis of the case.

4 Data management, quality management, statistics and reporting

Data management

Data collection in this study is carried out using documentation forms. Centralized data entry will be carried out by a responsible professional subcontractor for statistical analyses after receiving documentation forms. Statistical analysis of the data and the creation of the final statistical report on the study will also be carried out by the responsible professional subcontractor for statistical analyses. The consistency of reported AE data will be ensured by reconciling the project database with the Servier drug safety database. Discrepancies will be resolved by mutual agreement between both parties (Servier and professional subcontractor for statistical analyses).

Statistical analysis

Due to the non-interventional nature of this study, statistical analysis will be carried out in descriptive and exploratory forms. All parameters will be analysed using descriptive statistics. For each parameter, the following will be specified: number of patients, mean value, standard error, minimum and maximum values, or proportion of each category. All composite endpoints will be listed and presented in visual form as graphs and in tables of parameters and their frequencies. For categorical variables, absolute values and rates in per cents be calculated. The calculations of relative rates will include only patients in whom values of the corresponding variables will be available.

All reports of adverse drug reactions (ARDs), adverse events (AEs), serious ADR/AE, and special situations will be encoded, and the results will be listed and classified according to the System-Organ-Classes (SOCs).

Accepted level of significance

In all tests, a significance level of 0.05 will be used, and 2-sided statistical tests will be carried out.

Report preparation

The preparation of the final report on the study will begin after the completion of the statistical analysis. The publication of the main results is planned within 12 months after the end of the study.

5 Ethical considerations

The study will be carried out in accordance with the principles of the Helsinki Declaration, according to the version revised in Brazil in 2013. The protocol must be reviewed and approved by an independent ethics committee after it is submitted by the coordinator or sponsor in accordance with local regulatory requirements, especially on the matters relating to data protection. Patients will be informed about the conditions for participation in the study, and they will have to provide written consent to participate in the study. The doctor must confirm in the Case report form (CRF) that the informed consent has been obtained, and he/she must keep one original of the signed informed consent form in the patient's file. "Informed consent" also means an individual discussion of procedures, that will be conducted as a part of the study, with the patient.

5.1Patient data privacy

Investigators should maintain confidentiality of information about patients included in this study. Confidential data should contain enough information to contact the patient in case of emergency, or if further monitoring is required. Patient's right to privacy is of utmost importance. To protect the data confidentiality and preserve patient anonymity, patient's identity will be encoded in the study documentation. Patients can be identified using a unique number, age and gender, which will be recorded in the CRF. To reveal the patient's identity, all investigators will keep a confidential list for patient identification containing the names and addresses of the patients, as well as their assigned numbers. Thus, only investigator will be able to decode the identity of a patient.

6 Appendices

Appendix 1. Cardiovascular risk assessment. Classification of angina severity according to the Canadian Cardiovascular Society (15).

Functional class	Signs
I	«Latent» angina. Angina with only strenuous exertion.
II	Angina with ordinary activity: brisk walking or climbing hill or more than one flight of ordinary stairs, after meals, or under emotional stresses.
III	Angina markedly limits physical activity. Angina with low efforts: walking at a normal pace for less than 500 m, climbing 1-2 flights of stairs. Angina sometimes occurs at rest.
IV	Inability to carry on any, even minimal physical activity without angina. Anginal attacks occur at rest. A history of myocardial infarction or heart failure is common.

Appendix 2. Classification of blood pressure, and definitions of hypertension grade (2).

BP categories	SBP, mm Hg		DBP, mm Hg
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1	140–159	and/or	90–99
Grade 2	160–179	and/or	100–109
Grade 3	≥180	and/or	≥110
Isolated systolic hypertension[1]	≥140	and	<90

[1] Isolated systolic hypertension (ISH) should be classified into grades 1, 2, and 3 according to the SBP level.

Appendix 3. The New York Heart Association (NYHA) functional classification of heart failure (15).

Functional class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 4. The (Modified) eight-item Morisky Medication Adherence Scale.

Patient Name:

Morisky Medication Adherence Scale (MMAS)

Please answer each question based on your personal experience with your medications. Note that there is not right or wrong answer. (Please circle your answer below)

1. Do you sometimes forget to take your medications?	NO	YES
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medications?	NO	YES
3. Have you ever cut back or stopped taking your medications without telling your doctor, because you felt worse when you took it?	NO	YES
4. When you travel or leave home, do you sometimes forget to bring along your medications?	NO	YES
5. Did you take your medications yesterday?	NO	YES
6. When you feel like your health condition is under control, do you sometimes stop taking you medications?	NO	YES
7. Taking medications every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	NO	YES
8. How often do you have difficulty remembering to take all your medications?	Never/rarely	4
	Once in a while	3
	Sometimes	2
	Usually	1
	All the time	0

Each "Never" response is rated as 1, except for item 5, in which "Yes" response is rated as 1, and other responses are rated as 0. Total scores range from 0 to 8, with scores of 8 reflecting high adherence, 7 or 6 reflecting medium adherence, and <6 reflecting low adherence.

Appendix 5. Adverse event / Adverse drug reaction / Special Situation Reporting Form

IC4-05150-065-RUS*Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass to the associate of the company.*

Year of birth or Age Gender **Height** **Weight** **Patient's ID:**

|__|__|__|__| or |__|__|__| M / F |__|__|__| |__|__|__| |_|_|_|_|_|_|_|_|_|_|

Description of adverse event/reaction/special situation:	**Date of event onset** |_|_| |_|_| |_|_|_|_|	**Date of event termination (in case of recovery)** |_|_| |_|_| |_|_|_|_|

Criteria of seriousness: □ NO □ YES (please, specify from stated below) □ Death □ Life threatening □ Hospitalization or prolongation of existing hospitalisation □ Persistent or significant disability or incapacity □ Congenital anomaly/birth defect □ Medically important event	**Outcome:** □ Recovered □ Recovered with consequences (persistent structural or functional impairment) □ Not yet recovered □ No recovery □ Death □ Unknown

General disease(s) / Concomitant disease(s) (please indicate year when first diagnosed).

Course adverse event/reaction/special situation (please enclose relevant findings, e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with intake of <u>studied</u> drug:□□
□ NO □ □ YES □ NOT APPLICABLE

***If «Yes»**, please indicate dates of the use of studied drug <u>in the first line</u> of the table below:*

***If «No» or «Not applicable»**, please specify whether the adverse event/special situation is related to the medication of Servier company (which is specified in the table below)*:
□ NO □ YES *Please indicate the name of the medication of Servier company: ……*

List of current medications	**Daily dose / route of administration**	**Dates of intake: from to**	**Indication**
		-	
		-	
		-	

Name (last, first, patronymic) of doctor: Speciality: Work address: Phone number: _____ (city code)	Date: Stamp Signature: (whenever possible)

**Special situations are cases when adverse event was not observed, but the information should be collected: the impact of the drug during pregnancy/breastfeeding, abuse, misuse, medication error, overdose, off-label use, occupational exposure, or lack of efficacy*, any suspected transmission via medicinal product of an infection agent, unintended therapeutic benefit…

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