STYLE

Assessment of the efficacy and tolerability of the fixed-dose combination of bisoprolol/perindopril in patients with arterial hypertension and stable CAD in daily clinical practice

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Multicenter observational open program.

Assessment of the efficacy and tolerability of the fixed-dose combination of bisoprolol/perindopril in patients with arterial hypertension and stable CAD in daily clinical practice (STYLE)

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Introduction

Patients with coronary artery disease (CAD) have a very high risk of cardiovascular events. Unfortunately, many of them remain suboptimally treated because of inadequate therapy and/or poor adherence. Therefore, the actual unmet needs in CAD patients are the reduction in the risk of cardiovascular events, achievement of the 24-hour blood pressure control, and increase of the adherence to therapy(1)

The sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) play pivotal role in the pathogenesis and progression of arterial hypertension (HT) and CAD. Therefore, patients with concomitant CAD and HT require prescription of beta-blocker and angiotensin-converting enzyme (ACE) inhibitor in their pathogenetic therapy(2).

These classes of drugs became the basis of the contemporary cardiovascular pharmacotherapy in CAD patients disease. The key role of beta-blockers and ACE inhibitors, which are widely used in the world, is highlighted in the numerous guidelines on the treatment of CAD.

The accumulating evidence suggests that beta-blockers and ACE inhibitors have additional cardioprotective properties. The recent subanalysis of the EUROPE (3) trial in patients treated with combination of beta-blocker and perindopril demonstrated a greater reduction in the rate of cardiovascular events.

PRESTILOL is the first and only single-pill combination of the most frequently used beta-blocker bisoprolol and the widely known ACE inhibitor perindopril. Both components of this new

combination treatment have the documented prolonged effect, which provides 24-hour BP control and reduction in the risks of cardiovascular events.

Moreover, this new single-pill fixed-dose combination (FDC) has an important advantage in the increase of adherence to the therapy, which is especially important for patients with a high risk for cardiovascular events, including CAD and HT patients(4)

In conclusion, it should be noted that the benefit of the first and only single-pill combination of beta-blocker and ACE inhibitor consists in the combination of the proven efficacy and potentially higher adherence to treatment.

References:

1. World Health Organization. A global brief on hypertension. April 2013. WHO/DCO/WHD/2013.2
2. Gradman AH et al. J Clin Hypertens. 2011;13:146-154
3. Bertrand ME et al. Am Heart J. 2015; 170:1092-1098
4. Kotseva K et al. Eur J Prev Cardiol. 2016.23(6):636-648.

1. Study objectives and purposes

- to assess the efficacy, tolerability and adherence of bisoprolol/perindopril FDC in patients with HT and stable CAD in everyday practice

Primary endpoints:

-efficacy of bisoprolol/perindopril FDC in patients with HT and stable CAD in everyday practice regarding the BP

- efficacy of bisoprolol/perindopril FDC in patients with HT and stable CAD in everyday practice regarding the angina

Secondary endpoints:

-impact on the quality of life of bisoprolol/perindopril FDC in patients with HT and stable CAD in everyday practice

- adherence to bisoprolol/perindopril FDC therapy in patients with HT and stable CAD in everyday practice

2. Design and methodology

Type of the program: multicenter, observational, uncontrolled, open program.

The program will involve 480 general practitioners (GPs) and cardiologists from the primary care facilities.

It is planned to include into the program the patients with HT and concomitant stable CAD.

The patient is included in the program, if the doctor decides to prescribe FDC with beta-blocker bisoprolol and ACE inhibitor perindopril in accordance to the instruction for use.

Prescription of bisoprolol/peribdoprol FDC during the program is made on the decision of the doctor and in full compliance with the instruction for use.

Each doctor includes four patients. It is planned to include not less than 1920 patients in total.

Milestones of the program:

FSI – November, 2018
LSLV- January, 2019
Database Lock – February, 2019
Statistic Report- May, 2019
Clinical Study Report- January, 2020

3. Inclusion criteria

Inclusion criteria:

- Stable CAD, defined as stable angina pectoris of class 1-3 by CCS (Canadian Cardiovascular Society) classification;
- Previously or newly diagnosed essential hypertension
- Age 18 to 79 years old;
- Informed consent of the patient for participation in the program;
- Decision of the doctor to prescribe bisoprolol/perindopril FDC before the inclusion in the program in accordance to the instruction for use.

Non-inclusion criteria:

- Stable angina pectoris, class 4;
- History of myocardial infarction or cerebrovascular event within the past 3 months;
- Unstable angina within the past 6 months;
- Chronic heart failure classes 3-4 (NYHA);
- Type 1 diabetes mellitus or decompensated type 2 diabetes mellitus;

- Any serious decompensated concomitant diseases requiring the regular medical therapy;
- Inability to understand the essence of the program and follow the recommendations;
- Contraindications to beta-blockers or ACE inhibitors using;
- Participation of the patient in other trials in the present time or within 30 days before the start of observational program.

4. Variable.

- Average decrease of systolic and diastolic BP (in mm Hg) in the sitting position according to the office measurements;
- Percentage of the patients achieved the target levels of clinical BP among included patients (SBP < 140 mm Hg and DBP < 90 mm Hg);
- Average decrease of the number of angina attacks per week according to the data from CRFs based on diaries;
- Average decrease of the tablets/sprays of short-acting nitroglycerin taken per week, according to the data from CRFs based on diaries;
- Percentage of the patients with definite answer on question from questionnaire regarding adherence
- Changes of the score in the visual analog scale (VAS) to assess the wellbeing;

5. Methods and measurements

- 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 right arm of the patient after 5 minute 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 consequent measurements of SBP are ≥ 15 mm Hg, it is necessary to perform the repeated BP measurement. (V1-V2-V3)
- Assessment of the symptomatic status (including the collection of data on the number of angina attacks, number of taking of tablets/sprays of short-acting nitroglycerin, angina grades, limitation of physical activity to prevent attacks; presence of symptoms of CHF; grades of CHF by NYHA classification). (V1-V2-V3)
- Assessment of the adherence of patient to the treatment/ compliance to the treatment regimen. (V1-V2-V3)

- Assessment of the efficacy and tolerability of the treatment according to the number of angina attacks per week and number of taking of short-acting nitroglycerin according to the data from diaries (V1-V2-V3)
- Collection of the data on the adverse events/adverse drug reactions and special situations. (V1-V2-V3)
- Assessment of the quality of life by VAS (V1, V2, V3)

6. Materials of the program

1. Protocol.
2. Case report form (CRF) (includes the informed consent form).
3. Patient's self-control diary.

7. Timeline of the study

Overview	**V1 Inclusion visit**	**V2 Follow-up visit (1 month)**	**V3 Final visit (3 months)**
Inclusion of patients in accordance with the inclusion/exclusion criteria	V		
Obtaining the informed consent of the patient	V		
Medical history, risk factors, and life style	V		
Recording of the current therapy	V	V	V
BP and HR measurements	V	V	V
Therapy correction	V		
Assessment of symptomatic status	V	V	V
Assessment of compliance with treatment	V	V	V
Assessment of efficacy and tolerability of the treatment by doctor's and patient's opinion			V
Completion of the diaries with recording of the number of angina attacks and tablets/sprays of nitrates used by patient	V	V	V
Adverse events / reactions / special situations		V	V
Assessment of the quality of life using the VAS	V	V	V

8. Safety considerations

8.1 Definitions

8.1.1 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, occupational exposure (including professional one);
- lack of the treatment efficacy of drugs.

8.1.2. Adverse event (AE)

Adverse event (AE) is any untoward medical occurrence in a patient or clinical-trial participant 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 unfavorable 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 as related to the medicinal product.

8.1.3. 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.

8.1.4. 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 in case of more severe course.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered as serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardize 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 as a serious adverse reaction.

8.2 Responsibilities

8.2.1. Events to be reported

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

- All serious adverse drug reactions related to the use of bisoprolol/perindopril FDC
- All non-serious adverse drug reactions related to the use of bisoprolol/perindopril FDC
- All reports about special situations (see 8.1.1)
- All adverse events

8.2.2. Responsibilities of investigator

In prospective studies, at medical visits the investigator will ask a participating patient to indicate whether or not an adverse event (serious or not) has occurred.

Investigator has to assess causal relationship between an adverse event and the investigated drug intake, as well as the seriousness criteria and later on the outcome of the event.

In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the study (both serious and non-serious), the investigator must complete the “Adverse event / Adverse drug reaction / Special Situation Reporting Form” (Appendix 4) without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, it will be notified 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 connection with the adverse event should be attached to the form.

All other events should be reported by investigator within 2 working days.

The same rules apply for the transferring of additional information about the event.

The investigator must ensure the appropriate follow-up of the patient depending on the nature of event, until it resolves. The investigator will continue to notify follow up data according to timeframes defined above.

If investigator does not follow-up a patients anymore (i.e. in case of hospitalisation followed by the treatment by specialist or the participant's general practitioner,…), he/she will do every effort to contact the specialist or department in charge of follow-up of the patient, so as to have additional information and report it to Servier company in Russia.

8.2.3. Responsibilities of sponsor/marketing authorization holder (MAH)

Independently of the regulatory obligations of investigator, the sponsor/MAH must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations.

Cases are closed when an adverse event has recovered or patient’s condition was stabilized and the report is deemed sufficiently detailed for adequate medical analysis of the case.

9. Statistical parameters

All parameters (changes of BP, achieving of target BP, number of angina attacks per week; number of tablets/sprays of short-acting nitroglycerin taken per week, assessment of efficacy, tolerability and adherence using the questionnaire) will be analyzed using the methods of descriptive statistics. AE will be assessed in all patients, who started the treatment, with list indication of all AE, SAE, ADR, SADR and special situations.

10. Administrative considerations

1. The rights for documentation, data, and research results

The sponsor reserves the exclusive right to all materials, information, unpublished documentation, results and information obtained during the research. The Sponsor reserves the right to send research data to the health authorities (individual registration cards, analysis results, reports).

No unpublished documentation or information transmitted to researchers can be transferred to unauthorized persons without the prior written consent of Sponsor.

2. Publications and communication

The sponsor is responsible for communicating and publishing research data. No part of the results of this study or other data may be published, presented or distributed without the express written permission of Sponsor. Participants in the study fully transfer to the Sponsor the authority for the first presentation, communication and publication of the results on behalf of all employees. No other communication or publication is permitted before this first publication. Any subsequent communication or publication must first be reviewed and approved by the Sponsor and should refer to the research and the first publication.

Glossary and definitions

CAD: coronary artery disease

RAAS renin-angiotensin-aldosterone system

HT hypertension

ACE angiotensin-converting enzyme

FDC fixed doze combination

SBP systolic blood pressure

DBP diastolic blood pressure

CCS Canadian cardiovascular society

NYHA New York Heart Association

BP blood pressure

CHF chronic heart failure

CRF case report form

AE adverse event

SAE serious adverse event

ADR adverse drug reaction

SADR serious adverse drug reaction

MAH marketing authorization holder

Appendices

Appendix 1: Canadian Cardiovascular Society (CCS) classification of angina pectoris.

Appendix 2: New York Heart Association (NYHA) classification of chronic heart failure.

Appendix 3: Compliance evaluation form.

Appendix 4: Adverse event / Adverse drug reaction / Special Situation Reporting Form.

Appendix 5: Definition of hypertension

Appendix 1.

Canadian Cardiovascular Society (CCS) grading of angina pectoris

Class I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
Class II	Slightly limited ordinary physical activities. Angina occurs on: walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the same level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks (equivalent to 100-200m) on the same level and climbing one flight of stairs at a normal pace under normal conditions.
Class IV	Inability to carry on any physical activity without any discomfort. Angina occurs at rest.

Source: Campeau L. Letter: grading of angina pectoris. *Circulation* 1976; 54:522-.

Appendix 2.

New York Heart Association (NYHA) classification of chronic heart failure

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

Source: Hurst JW, Morris DC, Alexander RW. L'utilisation de la New York Heart Association de classification du des maladies cardiovasculaires dans le cadre du patient compléter la liste des problèmes. [Article in French] *Clin Cardiol*. 1999 Jun ;22 (6):385-90. (The use of the New York Heart Association's classification of cardiovascular disease as part of the patient's complete Problem List).

Appendix 3.

Compliance evaluation test

Question	Yes	No
1. Did you forget to take your medication this morning?		
2. Since the last visit to the doctor, have you run out of your medication?		
3. Have you ever taken your medication later than the usual time?		
4. Have you ever not taken your medication because, on some days, you forgot?		
5. Have you ever not take your medication because you had the impression that it was doing more harm than good?		
6. Do you think that you have too many tablets to take?		

Answer «No» to all questions: good compliance;

Answer «Yes» to 1-2 questions: minor compliance;

Answer «Yes» to 3 or more questions: noncompliance.

Source: Girerd X, Radauceanu A, Achard JM, Fourcade J, Tournier B, Brillet G, Silhol F, Hanon O. [Evaluation of patient compliance among hypertensive patients treated by specialists]. [Article in French] *Arch Mal Coeur Vaiss*. 2001 Aug;94 (8):839-42.

Appendix 4.

Adverse event / Adverse drug reaction / Special Situation Reporting Form* [Form0.32,3.0]

[№ IC4-05150-056-RUS]

Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass it 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>investigational</u> drug: ☐☐
☐ NO ☐ ☐ YES ☐ NOT APPLICABLE

***If «Yes»**, please indicate dates of the use of investigational 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 treatment failure…*

Appendix 6:

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥ 180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90