Multicenter observational program VAP-PRO-C6

Protocol N° IC4-05682-066-RUS

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Effectiveness and tolerability of venoactive drugs in combination therapy and their effect on the overall treatment outcomes in patients with chronic venous diseases of CEAP classes C6 in real clinical practice.

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Rationale

Currently, about 40 million people in Russia, mostly of working-age population, suffer from various forms of chronic venous diseases (CVDs) [1].

Progressive trophic disorders of soft tissues in decompensated forms of CVD contribute to the development of long-term non-healing venous ulcers (VUs) and are the most common cause of this complication [2, 3].

The challenges in the treatment of patients with long-term non-healing VUs related to decompensated forms of chronic venous insufficiency (CVI) represent one of the urgent and socially significant problems in modern medicine.

The number of patients with VUs is growing steadily each year by 0.20 - 0.35% [4].

A high prevalence of trophic ulcers of venous ethiology and their tendency to recur sunstantiate the need for using optimal combination of the most effective modern methods of treatment.

The local wound care and the use of compression therapy constitute the basis of standard treatment of VUs [5]. According to published data, the rate of ulcer healing with this standard treatment varies widely and ranges from 45% [6] to 83% [7] after 24 weeks of treatment. However, the medical costs associated with the long-term treatment of such chronic wounds are substantial [5,8]. These problems in the treatment of VUs have generated interest in the use of pharmacotherapy to accelerate their healing.

To date, there is no consensus on this topic, and a comprehensive staged approach is underused in the treatment of patients with VUs in routine clinical practice. All of this became a rationale to carry out the present study.

References

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Design

The VAP-PRO-C6 is a Russian multicenter observational program to be implemented at the routine visits and assessments. The program will include patients with chronic venous disease of CEAP classes C6. This program is planned to be carried out in Russia in 2021-2022. It is expected that 90 phlebologists from 60 cities of Russia will take part in the program. The planned number of patients is 450.

Program milestones:

First Patient First Visit	Q1\2021
Last Patient Last Visit	Q4\2021
Completion of statistical analysis	Q1\2022
Preliminary report	Q2\2022
Final report	Q2\2022

Aim of the program

to describe effectiveness and tolerability of systemic pharmacotherapy as a part of combination therapy and its effect on the overall treatment outcomes in patients with venous ulcers (CEAP classes C6) treated in real clinical settings.

Primary goal:

1. Description of effectiveness of systemic pharmacotherapy as a part of combination therapy.
Variables:
- % of patients with complete healing of the reference* venous ulcer after 6 months;
- change in the mean Venous Clinical Severity Score (VCSS) (1);
- % of patients with reduction in the CVD clinical class by CEAP classification (2).

Secondary goals:

1. Description of additional parameters of the effectiveness of systemic pharmacotherapy as a part of combination therapy.
Variables:
- time to healing of the reference VU;
- % of patients with healed reference VU after 3 months of treatment;
- change in the area of reference VU in cm^2 (measured with LesionMeter application) (4)

2. Description of changes in the quality of life (QoL) measured by the CIVIQ-14 (3):
Variables:
- Global Index Score (GIS) of CIVIQ-14.

3. Description of the adherence to systemic pharmacotherapy as a part of the combination therapy in patients with VUs and CVD of CEAP class C6:
Variables:
- % of patients who continue to use the prescribed VAD at V1, V3 (interim), and V4 visits (if applicable)

* Reference venous ulcer is a primary active venous ulcer, selected by investigator for the follow-up and reporting in the Case Report Form (CRF) in case several ulcers are present in the patient.

The reference VU should meet the following criteria:

- area is no less than 5 cm^2 but no more than 30 cm^2
- phase 2 or 3 of the wound healing process;
- location on the medial aspect of lower third of leg.

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Methods

Each treating physiciann includes at least 5 patients in the program that meet the inclusion criteria. The inclusion period lasts for 6 months. The treatment will be consistent with routine clinical practice, local label for the medical use of drugs and the specific clinical situation. The following objective methods will be used to assess the changes in the skin condition:

- measurement of the area of reference ulcer (using LesionMeter[†]) before and after the treatment;
- changes in *status localis*.

Duplex ultrasound study (DUS):

- The presence and location of venous reflux and/or occlusion.

Important: Measurement data are recorded for the limb where the reference ulcer is located.

Please note, that DUS will be performed only at the inclusion visit to objectively confirm diagnosis of CVD. Once the diagnosis confirmed, further examination with DUS is not required without specific indications for reevaluation.

Patient management

The study does not implicate any intervention to routine management of patients with chronic venous disease (CVD). In particular, in this study the parameters that are usually evaluated during the examination of patients with classes C6 CVD (CEAP) will be recorded. Special attention will be paid to evaluating changes of the area of referent VU using objective methods (measuring ulcer area using LesionMeter, time to ulcer healing).

Treatment

The observational nature of the program implies that all examinations, procedures and changes in the treatment of patients, including changes in the dosing regimen, should be carried out only on the basis of judgment of the treating physician and in full compliance with the guidelines on the treatment of patients with CVD, local labels for medical use of drugs, and in the settings of daily routine practice.

[†] LesionMeter is a generally available tool for measuring the venous ulcer area.

Therapy is conducted in full accordance with existing guidelines. The patient's participation in the program, as well as his/her refusal to continue such participation, should not affect the current treatment, the availability of diagnostic procedures or the volume and quality of other necessary medical care.
The names and doses of drugs used for the CVD treatment, as well as changes in their doses will be recorded in the Case Report Form.

Inclusion criteria:

- CVD documented by venous DUS
- Age over 18 years
- Written informed consent is provided
- No treatment with venoactive drugs within 4 weeks prior to inclusion in the study
- Presence of a primary /active venous ulcer (class C6/ CEAP) that meets criteria for the referent ulcer
- No surgical intervention or procedure (including sclerotherapy) for CVD is planned

Non-inclusion criteria:

- Obliterating atherosclerosis
- Lymphatic edema of the lower extremities
- Angiodysplasia, neoplasia
- Peripheral artery disease (ankle-brachial index 0,8-1,3)
- Infectious process in the previous 6 weeks
- The presence of one or more comorbidities in the patient that can affect the results:
  - ✓ Connective tissue diseases (including rheumatoid arthritis, arthritis)
  - ✓ Chronic heart failure 3-4 function class (NYHA)
  - ✓ Chronic kidney disease
  - ✓ Diabetes mellitus experience of at least 10 years and more or Diabetes mellitus experience less than 10 years, but decompensated. Diabetic foot.
  - ✓ Skin diseases of non-venous origin
  - ✓ Intermittent claudication (peripheral artery disease)
  - ✓ Diseases of bones or joints of the lower limbs, that can affect the course of the ulcer according to the researcher
  - ✓ Malignant neoplasm
- Treatment with drugs that can cause edema of the lower extremities (calcium channel blockers, hormonal agents, NSAIDs, etc.)
- History of deep vein thrombosis (within 1 year prior to inclusion)
- History of superficial venous thrombophlebitis (within 3 months prior to inclusion)
- The patient underwent surgery for CVD in the previous 3 months
- Patient cannot walk (regardless of the cause)
- Poor predicted adherence to treatment
- Participation in an intervention study in the previous 3 months
- For women: pregnancy or breastfeeding, or willing to become pregnant within at least 2 months after the end of the study
- The necessity, according to the doctor-investigator, of treatment with any diosmin-containing drug outside of its approved indications (off-label) or in the presence of contraindications stated in the instruction for medical use of this drug relevant in the Russian Federation at the time of the study, within the scope of this protocol
- Use of a topical agent that is contraindicated in case of compromised skin integrity

Exclusion criteria:

- Withdrawal of the informed consent
- Pregnancy or willingness to become pregnant within at least 2 months after the end of the study
- Indications for surgery (including sclerotherapy)
- Serious violation or non adherence to the prescribed therapy/ regimen
- Use of prohibited drugs that can cause edema of lower extremities (calcium channel blockers, hormonal agents, NSAIDs, etc.)

Treatment effectiveness criteria

1. Venous Clinical Severity Score (VCSS)
2. Clinical class of CVD by CEAP classification (2020)
3. Changes in the parameters of skin condition:
   - area of the reference venous ulcer (measured by LesionMeter)
   - changes in *status localis*
   - changes in symptoms (pain) as assessed by visual analogue scale (VAS).
4. The quality of life (QoL) questionnaire CIVIQ-14 (**Appendix 2**).

Data collection during the study

At scheduled visits participating physycians will be assessing and collecting parameters of interest which they should input in eCRF.

At the inclusion visit (V0) following data will be collected: a signed consent form, demographic characteristics (age, sex, body weight, BMI and height), eligibility of a patient to the inclusion/ non inclusion criteria, history and risk factors of CVD, history and current status of taking drugs and non drug treatments for CVD; all parameters of VCCS including characteristics of symptoms for CVD such as pain, hyperaemia, characteristics of the ulcer(s) etc., characteristics of the reference ulcer; results of evaluation of the stage of the disease (CEAP classification); results of DUS characterizing venous reflux and its location, presence or absence of venous occlusion and its location; skin condition/ pain severity will be patient-reported evaluation with VAS, results of a self-assessed quality of life status performed by completing CIVIQ 14 questionnaire; assigned treatment for CVD including data on administered topicals, systematic pharmacotherapy, compression therapy.

At visits 1; 2; 3 (V1; V2;V3) following data will be collected: eligibility of a patient to exclusion criteria; characteristics of the ulcer(s) etc., characteristics of the reference ulcer; skin condition/ pain severity will be patient-reported evaluation with VAS; any changes in the administered treatment for CVD including usage of topicals, usage of systematic pharmacotherapy, usage of compression therapy; information regarding any adverse event/ adverse drug reaction or special situations (see chapter Safety Considerations).

At visit 4 (V4) following data will be collected: eligibility of a patient to exclusion criteria; all parameters of VCCS including characteristics of symptoms for CVD such as pain, hyperaemia, characteristics of the ulcer (s) etc., characteristics of the reference ulcer; results of evaluation of the stage of the disease (CEAP classification); skin condition/ pain severity will be patient-reported evaluation with VAS; results of a self-assessed quality of life status performed by

completing CIVIQ 14 questionnaire; any changes in the administered treatment for CVD including usage of topicals, usage of systematic pharmacotherapy, usage of compression therapy; information regarding any adverse event/ adverse drug reactions or special situations (see chapter Safety Considerations).

SCHEDULE OF THE STUDY

Actions	**V0 visit (inclusion)**	**V1 visit (1 month after V0 visit)**	**V2 visit (3 months after V0 visit)****	**V3 visit (interim), if applicable***	**V4 visit (6 months after V0 visit)**
Informed consent	+				
Inclusion/ Non inclusion criteria	+				
Exclusion criteria		+	+	+	+
Reporting of AEs		+	+	+	+
Completion of the CRF	+	+	+	+	+
VCSS	+				+
CEAP clinical class	+				+
Skin changes (by VAS)	+	+	+	+	+
Status localis	+	+	+	+	+
DUS (presence of reflux)	+				
QoL assessment (CIVIQ-14)	+				+
Data on the treatment and its change	+	+	+	+	+
Venoactive drug	+	+	+	+	+
Compression hosiery	+	+	+	+	+
Topical treatment	+	+	+	+	+

* The visit takes place if the venous ulcer is healed between V2 and V4 visits
**The visit can be replaced by telephone interview which remains at discretion of the doctor-investigator

Safety considerations.

1. Definitions

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);

- suspected transmission of an infectious agent via a medicinal product;

- unexpected beneficial action of the drug;

- lack of the treatment efficiency of drug.

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.

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.

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.

2. Responsibilities

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 any Servier drug and/or to other venoactive drugs
- All non-serious adverse drug reactions related to any Serveier drug and/or to other venoactive drugs
- All reports about special situations (see 1.1)
- All adverse events

2.2. Responsibilities of the treating physician

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

The treating physician has to assess the causal relationship between an adverse event and a 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 treating physician must complete the **"Adverse event / Adverse drug reaction / Special Situation Reporting Form" (Appendix 1)** without waiting for the clinical outcome or the results of additional investigations.

When assessing the quality of life using the EQ-5D, the treating physician should evaluate data (patient's answers), their clinical relevance, and fill out the " Adverse event / Adverse drug reaction / Special Situation Reporting Form" if he/she considers these data as AE, ADR or a special situation.

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.ru@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 a treating physician within 2 working days.

In case there is an ADR related to a non-Servier venoactive drug, the treating physician must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations

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

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

If a treating physician does not follow-up a patient 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.

2.3. Responsibilities of the Sponsor/Marketing Authorization Holder

Independently of the regulatory obligations of the treating physician, 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 stabilised and the report is deemed sufficiently detailed for adequate medical analysis of the case.

Statistical parameters

Statistical analysis:

The baseline characteristics will be analyzed in all included patients regardless of the patient's adherence to the protocol procedures (intention-to-treat analysis). The analysis of the study results will be carried out using the SPSS 12.0 software package (SPSS Inc., USA). Data entry errors will be corrected before the start of statistical processing. Quantitative parameters will be presented taking into account the distribution of raw data, in the form of arithmetic mean ± standard deviation for parametric, and in the form of a median (25; 75 percentile) for nonparametric variables. Accordingly, a comparison on quantitative parameters between the

groups with different adherence will be carried out using the Student's t-test for independent samples or using the Mann-Whitney U-test.

For multiple comparisons, a correction for continuity will be implemented. The changes in quantitative parameters during the follow-up period will be evaluated using the Student's t-test for paired samples or its nonparametric analogue, Wilcoxon test.

Changes in the quantitative parameters, both in the independent groups and during the follow-up period, will be evaluated as the difference between the mean values and the corresponding 95% confidence intervals.

Differences between the groups by the mean score of the VAS, VCSS, and CIVIC-14, and by an integrated index of skin changes (lesion area, ultrasound data) will be carried out using two-way analysis of variance with repeated measures, in order to compare scores before and after the treatment.

Safety will be assessed in all patients who received at least one dose of any venoactive drug during the study (studied drugs).

Adverse events will be recorded and analyzed in patients, and all adverse events, serious adverse events, adverse reactions, serious adverse reactions and special situations will be listed.

Ethical considerations:

The study will be conducted in accordance with the principles set out in the Declaration of Helsinki (version adopted in Fortaleza, Brazil, in 2013).

Participants will be fully informed about the program and provide their written consent to participate in it. Treating physician is obliged to indicate in the CRF that the informed consent has been obtained from the patient. The “informed consent” also means that individual discussion with a participant concerning nature of the program and necessity of examinations and evaluations used in the study took place.

The confidentiality of patient data will be guaranteed using identification code numbers (IDs). The relation between the ID and the patient identity will be known only to a treating physician, so that will ensure the anonymity of patient’s data.

Data collection:

Treating physician will inform patients about their participation in this program using the Patient Information form (attached to this file). All CRFs filled by a treating physician will be sent to Servier. Data anonymity is guaranteed.

Results:

The obtained data will be used to generate a study report under the supervision of independent scientific experts.

Publication of the results:

Any manuscript containing the results of this study must be submitted to Servier for review before submission to publication. Servier reserves the right to ask for modifications, if necessary.

Appendix 1.

Adverse event / Adverse drug reaction / Special Situation Form*

IC4-05682-066-RUS *Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.ru@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)	**Outcome:**
☐ Death ☐ Life threatening ☐ Hospitalization or prolongation of existing hospitalisation ☐ Persistent or significant disability or incapacity ☐ Congenital anomaly/birth defect ☐ Medically significant	☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Not recovered ☐ Fatal ☐ 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 the studied drug intake:**
☐ NO ☐ YES ☐ NOT APPLICABLE

If yes, please specify dates of treatment with the studied drug in the table below <u>on the first line</u>:

***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, treatment failure, suspected transmission of infectious agents via a medicinal product, or unexpected beneficial action of the drug.*

** *the studied drug is defined in the Safety Consideration section of the protocol.*

Appendix 2.

C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

Many people complain of leg pain. We would like to find out how often these leg problems occur and to what extent they affect the everyday lives of those who suffer from them.

Below you will find a list of symptoms, sensations or types of discomfort that you may be experiencing and which may make everyday life hard to bear to a greater or lesser extent. **For each symptom, sensation, or type of discomfort listed, we would like you to answer in the following way:**

Please indicate if you have experienced what is described in each sentence, and if the answer is 'yes', how **intense** it was. There are five possible answers, and we would like you to circle the one which best describes your situation.

Circle 1	if you feel the symtom, sensation of discomfort described does not apply to you
Circle 2, 3, 4 or 5	if you have felt it to a greater or lesser extent

C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

QUALITY OF LIFE WITH VENOUS INSUFFICIENCY

1) During the past four weeks, have you had any **pain** in your **ankles** or **legs**, and how severe has this pain been?
Circle the number that applies to you.

No pain	Slight pain	Moderate pain	Considerable pain	Severe pain
1	2	3	4	5

2) During the past four weeks, how much trouble have you experienced at **work** or during your **usual daily activities because of your leg problems**?
Circle the number that applies to you.

No trouble	Slight trouble	Moderate trouble	Considerable trouble	Severe trouble
1	2	3	4	5

3) During the past four weeks, have you **slept badly** because of your leg problems, and how often?
Circle the number that applies to you.

Never	Rarely	Fairly often	Very often	Every night
1	2	3	4	5

C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

	During the past four weeks, how much **trouble** have you experienced **carrying out the actions and activities** listed below **because of your leg problems**? *For each statement in the table below, indicate how much trouble you have experienced by circling the number chosen.*				
	No trouble	Slight trouble	Moderate trouble	Considerable trouble	Could not do it
4) Climbing several flights of stairs	1	2	3	4	5
5) Crouching, Kneeling down	1	2	3	4	5
6) Walking at a brisk pace	1	2	3	4	5
7) Going out for the evening, going to a wedding, a party, a cocktail party...	1	2	3	4	5
8) Playing a sport, exerting yourself physically	1	2	3	4	5

C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

	Leg problems can also affect your mood. How closely do the following statements correspond to what you have felt during the past four weeks? *For each statement in the table below, circle the number that applies to you.*				
	Not at all	A little	Moderately	A lot	Completely
9) I have felt nervous/tense	1	2	3	4	5
10) I have felt I am a burden	1	2	3	4	5
11) I have felt embarrassed about showing my legs	1	2	3	4	5
12) I have become irritated easily	1	2	3	4	5
13) I have felt as if I am handicapped	1	2	3	4	5
14) I have not felt like going out	1	2	3	4	5