ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Giapreza 2.5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains angiotensin II acetate equivalent to 2.5 mg angiotensin II.

One vial of 1 ml concentrate for solution for infusion contains 2.5 mg of angiotensin II.

One vial of 2 ml concentrate for solution for infusion contains 5 mg of angiotensin II.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear and colourless solution.
pH: 5.0 to 6.0
Osmolality: 130 to 170 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Giapreza is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies (see section 5.1).

4.2 Posology and method of administration

Giapreza should be prescribed by a physician experienced in the treatment of shock and is intended for use in an acute and hospital setting.

Posology

The recommended starting dose of Giapreza is 20 nanograms (ng)/kg per minute via continuous intravenous infusion.

When initiating, it is important to closely monitor blood pressure response and adjust dose accordingly. Concurrent venous thromboembolism (VTE) prophylaxis should be used unless contraindicated during treatment with Giapreza (see section 4.4).

Once an infusion has been established, the dose may be titrated as frequently as every 5 minutes in steps of up to 15 ng/kg per minute, as needed, depending on the patient's condition and target mean arterial pressure. Approximately one in every four patients experienced transient hypertension with the angiotensin II 20 ng/kg per minute starting dose in clinical trials (see section 4.8), thus needing dose down-titration. For critically ill patients, the usual target mean arterial pressure is 65 – 75 mmHg. Do

not exceed 80 ng/kg per minute during the first 3 hours of treatment. Maintenance doses should not exceed 40 ng/kg per minute. Doses as low as 1.25 ng/kg per minute may be used.

It is important to administer Giapreza at the lowest compatible dose to achieve or maintain adequate arterial blood pressure and tissue perfusion (see section 4.4). The median duration of treatment in clinical trials was 48 hours (range: 3.5 to 168 hours).

In order to minimise the risk of adverse events derived from prolonged vasoconstriction, treatment with Giapreza should be withdrawn once underlying shock is sufficiently improved. Down-titrate by gradual decrements of up to 15 ng/kg per minute, as needed, based on blood pressure, in order to avoid hypotension due to abrupt withdrawal (see section 4.4).

Special populations

Elderly
There are limited efficacy and safety data of Giapreza in patients > 75 years. No special dose adjustment is required in patients over 75 years. As for other age groups, it is important to closely monitor blood pressure response and adjust dose accordingly.

Renal or hepatic impairment
No special dose adjustment is required in patients with renal insufficiency or those with hepatic impairment (see section 5.2). As for other patient populations, it is important to closely monitor blood pressure response and adjust dose accordingly.

Paediatric population
The safety and efficacy of Giapreza in children less than 18 years old has not yet been established. No data are available.

Method of administration

Giapreza should only be administered by continuous intravenous infusion under close monitoring of haemodynamics and end-organ perfusion.

For intravenous use only after dilution. Giapreza is recommended to be administered via a central venous line.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The clinical experience with Giapreza is limited to septic or other distributive shock. The use of Giapreza is not recommended in other types of shock (e.g. cardiogenic shock, etc) as patients with non-distributive shocks were excluded from clinical trials (see section 5.1).

Thromboembolic events

Thromboembolic events have been reported with the use of angiotensin II in clinical trials. The major imbalance compared to placebo was in venous thromboembolism (6.1% vs 0%) (see section 4.8). Concurrent venous thromboembolism (VTE) prophylaxis should be used unless contraindicated during treatment with Giapreza. Non-pharmacologic VTE prophylaxis may be considered where pharmacologic prophylaxis is contraindicated.

Peripheral ischaemia

Peripheral ischaemia has been reported with the use of angiotensin II (see section 4.8). It is important to administer Giapreza at the lowest compatible dose to achieve or maintain adequate mean arterial pressure and tissue perfusion.

Withdrawal of therapy

Giapreza should be gradually decreased since patients may experience hypotension or worsening of the underlying diagnosis of shock on abrupt withdrawal or premature discontinuation (see section 4.2).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 2.5 mg/ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No *in vitro* metabolism studies have been performed with Giapreza.

Patients who have recently received angiotensin converting enzyme (ACE) inhibitors may be more sensitive to Giapreza's action with an increased response. Patients who have recently received angiotensin II receptor blockers (ARBs) may be less sensitive to Giapreza's actions with a reduced response.

Concomitant administration of Giapreza and other vasopressors may have an additive effect on mean arterial pressure (MAP). The addition of Giapreza may require a reduction in doses of other vasopressors (e.g. adrenergic or dopaminergic agents).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of angiotensin II in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Use during pregnancy should be avoided if possible and the potential benefit to the patient weighed against any possible risk to the foetus.

Breast-feeding

It is unknown whether angiotensin II or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Giapreza.

Fertility

There are no data available on the potential effects on fertility in humans.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions described in this section were identified in the pivotal clinical trial (N = 163 treated with Giapreza). The most frequent adverse reactions reported in the Giapreza versus placebo arm are thromboembolic events (12.9% vs 5.1%) and transient hypertension (22.7% vs 1.9%) respectively.

Tabulated list of adverse reactions

Table 1 lists the adverse reactions recorded in clinical trials in the total safety population treated with Giapreza by MedDRA system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), and very rare (< 1/10 000).

Table 1: Frequency of adverse reactions

MedDRA System organ class	Very common	Common
Cardiac disorders		Tachycardia
Vascular disorders	Thromboembolic events[a] Transient hypertension[b]	Peripheral ischaemia

[a] Grouped term to include arterial and venous thrombotic events
[b] Defined as an increase in mean arterial pressure > 100 mmHg

Description of selected adverse reactions

Transient hypertension
A total of 37 patients (23%) experienced transient hypertension with the angiotensin II 20 ng/kg/min starting dose. Transient hypertension may be promptly mitigated by dose down-titration (see section 4.2).

Thromboembolic events
More patients experienced venous and arterial thromboembolic events in the Giapreza arm compared to placebo arm in the Phase 3 (ATHOS-3) study (21 [12.9%] vs 8 [5.1%]). The major imbalance corresponded to venous thromboembolism (10 [6.1%] vs 0 [0%] respectively). Of these, 7 cases corresponded to deep vein thrombosis. Two (1.2%) patients in the Giapreza arm experienced a fatal thromboembolic event compared with no patients in the placebo arm. Concurrent venous thromboembolism prophylaxis should be used unless contraindicated during treatment with Giapreza (see section 4.4).

Peripheral ischaemia
More patients experienced peripheral ischaemia in the Giapreza arm compared to the placebo arm (7 [4.3%] vs 4 [2.5%]). Of them, 5 cases (3.1%) in the Giapreza arm and 3 (1.9%) cases in the placebo arm were considered serious. One patient in each arm discontinued treatment as a result. Peripheral ischaemia may be a consequence of the mechanism of action of Giapreza. It is important to administer Giapreza at the lowest compatible dose to achieve or maintain adequate mean arterial pressure and tissue perfusion. In order to minimise adverse events derived from prolonged vasoconstriction, treatment should be withdrawn as soon as the underlying shock is sufficiently improved (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose may result in severe hypertension. Down-titration of therapy, careful observation, and initiation of appropriate supportive measures are the indicated treatment of overdose of angiotensin II. Hypertensive effects are expected to be brief because the half-life of angiotensin II is less than one minute.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac stimulants, ATC code: C01CX09

Mechanism of action and pharmacodynamic effects

Angiotensin II raises blood pressure by vasoconstriction; increased aldosterone release via direct action of angiotensin II on the vessel wall is mediated by binding to the G-protein-coupled angiotensin II receptor type 1 on vascular smooth muscle cells which stimulates Ca^{2+}/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction.

Giapreza is titrated to effect for each individual patient. In the ATHOS-3 trial, the median time to increase blood pressure was approximately 5 minutes. The effect on blood pressure is sustained for at least the first three hours of continuous intravenous infusion. Due to the short half-life of angiotensin II (less than one minute), an abrupt withdrawal of angiotensin II may lead to rebound hypotension (see section 4.4). Therefore, once underlying shock is sufficiently improved, a slow down-titration is recommended by gradual decrements of up to 15 ng/kg per minute, as needed, based on blood pressure (see sections 4.2 and 4.4).

Clinical efficacy and safety

The angiotensin II for the Treatment of High-Output Shock (ATHOS-3) was a Phase 3 randomised, placebo-controlled, double-blind, international, multi-centre safety and efficacy trial in which 321 adults with septic or other distributive shock who remained hypotensive despite fluid and vasopressor therapy were randomised 1:1 to Giapreza or placebo. Doses of Giapreza or placebo were titrated to a target mean arterial pressure (MAP) of ≥ 75 mmHg during the first 3 hours of treatment while doses of other vasopressors were maintained. From Hour 3 to Hour 48, Giapreza or placebo were titrated to maintain MAP between 65 and 70 mmHg while reducing doses of other vasopressors.

For their inclusion in the trial, patients had to have clinical features of high-output shock defined as a cardiac index > 2.3 l/min/m^2 or the sum of central venous oxygen saturation > 70% with central venous pressure (CVP) > 8 mmHg. Patients also had to have catecholamine refractory hypotension (CRH) defined as requiring a total sum vasopressor dose of > 0.2 mcg/kg/min for 6 to 48 hours, to maintain a mean arterial pressure (MAP) between 55-70 mmHg and receiving at least 25 ml/kg of crystalloid or colloid equivalent over the previous 24-hour period and be adequately volume resuscitated in the opinion of the treating investigator.

Of the 321 patients treated in the Phase 3 trial, 195 patients were male (60.7%), 257 (80%) patients were White, 33 (10%) were Black, and 31 (10%) were Other. Median age was 64 years (range: 22-89 years). Patients requiring high doses of steroids, patients with a history of asthma or bronchospasm who were not mechanically ventilated, and patients with Raynaud's syndrome were excluded. Patients with active bleeding, mesenteric ischaemia, liver failure and MELD score of ≥ 30, CV SOFA score ≤ 3 and patients with extensive burns were also excluded. 91% of subjects had septic shock; the remaining subjects had other forms of distributive shock such as neurogenic shock. Patients with cardiogenic shock were excluded (see section 4.4).

At the time of study drug administration, 97% of subjects were receiving norepinephrine, 67% vasopressin, 15% phenylephrine, 13% epinephrine, and 2% dopamine. 83% of subjects had received two or more vasopressors and 47% three or more vasopressors prior to study drug administration. Patients were not necessarily on maximum doses of other vasopressors at the time of randomisation. Of the 321 patients, 227 (71%) were receiving a baseline norepinephrine equivalent dose (NED) < 0.5 mcg/kg/min, 73 patients (23%) were receiving baseline NED ≥ 0.5 to < 1 mcg/kg/min and 21 (6%) patients were receiving high doses of vasopressors (NED ≥ 1.0 mcg/kg/min). The effect of Giapreza when added to maximum doses of other vasopressors is unknown.

The primary endpoint was the percentage of subjects who achieved either a MAP ≥ 75 mmHg or a ≥ 10 mmHg increase in MAP without an increase in baseline vasopressor therapy at 3 hours.

The primary endpoint was achieved by 70% of patients randomised to Giapreza compared to 23% of placebo subjects; p < 0.0001 (a treatment effect of 47%). The treatment effect was consistent in high-risk subsets of patients with low baseline MAP or high APACHE II score, which were stratification variables (Table 2).

Table 2: Primary efficacy endpoints: MAP response at hour 3 (mITT population and subgroups)

Subgroup	Placebo response rate	Giapreza response rate
All patients	37/158 patients 23%	114/163 patients 70%
Baseline MAP < 65 mmHg	10/50 patients 20%	28/52 patients 54%
Baseline APACHE II > 30	17/65 patients 26%	38/58 patients 66%

mITT=modified intent-to-treat population

In the Giapreza-treated group, the median time to reach the target MAP endpoint was 5 minutes. The effect on MAP was sustained for at least the first three hours of treatment. The median dose of Giapreza was 10 ng/kg/min at 30 minutes. Of the 114 responders at Hour 3, only 2 (1.8%) received more than 80 ng/kg/min.

Mortality through day 28 was 46% on Giapreza and 54% on placebo (hazard ratio 0.78; 95% confidence interval 0.57-1.07).

The effect of Giapreza on morbidity and mortality has not been determined in appropriate studies.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Giapreza in one or more subsets of the paediatric population for the treatment of hypotension in children who remain hypotensive despite fluid and vasopressor therapy.

5.2 Pharmacokinetic properties

Giapreza is titrated to effect for each individual patient. Plasma levels of angiotensin II were evaluated at baseline and hour 3 of infusion in the phase 3 pivotal trial.

Distribution

No specific studies have been conducted to investigate the distribution of Giapreza.

Biotransformation and elimination

No specific studies have been conducted to investigate the metabolism and excretion of Giapreza. The plasma half-life of angiotensin II administered intravenously is less than one minute. It is metabolised by end terminal cleavage (at both the amino and carboxy termini) in a variety of tissues including erythrocytes, plasma and many of the major organs (i.e., intestine, kidney, liver and lung).

Renal impairment

No trials have been conducted to investigate the pharmacokinetics of angiotensin II in renally impaired patients since the kidneys are not a major organ for angiotensin II metabolism or excretion.

Hepatic impairment

No trials have been conducted to investigate the pharmacokinetics of angiotensin II in patients with hepatic impairment since the liver is not a major organ for angiotensin II metabolism or excretion.

5.3 Preclinical safety data

In a cardiovascular safety pharmacology study in normotensive dogs, Giapreza elicited increased heart rate, systemic vascular resistance, left ventricular systolic pressure and left ventricular diastolic pressure, and PR interval prolongation.

In a 48-hour continuous intravenous administration of angiotensin II in neonatal lambs, the nominal dose rates of 4, 12 and 40 ng/kg/min were well tolerated. No treatment related adverse effects were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 2°C – 8 °C diluted in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C or 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml vial

1 ml solution in a Type I glass vial with an aluminium over-seal, stopper (elastomeric), and plastic cap. Pack size of 1 or 10 vials per carton.

2 ml vial

2 ml solution in a Type I glass vial with an aluminium over-seal, stopper (elastomeric), and plastic cap. Pack size of 1 vial per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single dose only.

Instructions for preparation of the medicinal product before administration

1. Inspect each vial for particulate matter prior to dilution.
2. Dilute 1 or 2 ml of Giapreza in sodium chloride 9 mg/ml (0.9%) solution for injection to achieve a final concentration of 5 000 ng/ml or 10 000 ng/ml.
3. Diluted solution should be clear and colourless.
4. Discard the vial and any unused portion of the medicinal product after use.

Table 3: Preparation of diluted solution

Fluid restricted?	Vial strength	Withdraw amount (ml)	Infusion bag size (ml)	Final concentration (ng/ml)
No	2.5 mg/ml	1	500	5 000
Yes	2.5 mg/ml	1	250	10 000
	5 mg/2 ml	2	500	10 000

Diluted solution may be stored at room temperature or under refrigeration. Discard prepared solution after 24 hours at room temperature or under refrigeration.

Giapreza may be co-administered with norepinephrine, epinephrine, vasopressin, terlipressin, dopamine, and/or phenylephrine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1384/001
EU/1/19/1384/002
EU/1/19/1384/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2019
Date of lastest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

PAION Netherlands B.V.
Vogt 21
6422 RK Heerlen
Netherlands

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for batch release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy and safety of Giapreza in the treatment of refractory hypotension in adults with septic or other distributive shock, the MAH should conduct and submit the results of a randomized, double-blind placebo-controlled multicentre study in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy to provide: (1) data on the effect of the product on morbidity events and organ perfusion with and adequate representation of European patients, (2) reassurance that there is no detrimental effect on mortality at day 28, (3) additional safety data about ischemic and thromboembolic events associated with the use of the product and to record clinical global impression of the response to treatment.	Submission of study results: 30 June 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Giapreza 2.5 mg/ml concentrate for solution for infusion
angiotensin II

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2.5 mg of angiotensin II (as acetate).

3. LIST OF EXCIPIENTS

Excipients: mannitol, water for injections, sodium hydroxide, hydrochloric acid.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial
2.5 mg/1 ml
5.0 mg/2 ml

10 vials
2.5 mg/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-dose
Read the package leaflet before use.
Intravenous use only after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After dilution, use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C - 8 °C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1384/001
EU/1/19/1384/002
EU/1/19/1384/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Giapreza 2.5 mg/mL sterile concentrate
angiotensin II

2. METHOD OF ADMINISTRATION

IV use only after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mg/1 ml
5.0 mg/2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Giapreza 2.5 mg/ml concentrate for solution for infusion
angiotensin II

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Giapreza is and what it is used for

Giapreza contains the active substance angiotensin II, a compound normally produced by the body. It makes the blood vessels tighten and become narrower, thus increasing blood pressure.

Giapreza is used in an emergency setting to increase blood pressure to normal levels in adult patients with seriously low blood pressure who do not respond to fluids or other medicines that raise blood pressure.

2. What you need to know before you are given Giapreza

You must not be given Giapreza:
- if you are allergic to angiotensin II or any of the other ingredients of this medicine (listed in section 6).

Your doctor or nurse should be told if any of the above applies to you before this medicine is used.

Warnings and precautions
Giapreza has only been tested in people with septic and distributive shock. It has not been tested in other types of shock.

This medicine has been associated with the formation of blood clots. As a part of your treatment, you will be given medicine to prevent the formation of blood clots unless your doctor considers it inappropriate.

When you are first given Giapreza, it is expected that your blood pressure will increase. You will be monitored closely to make sure that your blood pressure is at the right level.

Tell your doctor or nurse immediately if you experience a change of colour (redness or paleness), pain, numbness in any of your limbs, or if any of your limbs are cold to the touch, as these could be signs that a blood clot has blocked blood flow to a part of the body.

Children and adolescents
Giapreza should not be used in children or adolescents under 18 years of age as it has not been studied in these age groups.

Other medicines and Giapreza
Your doctor should be told if you are using, have recently used, or might use any other medicines.

A number of medicines may affect the way Giapreza works, such as:
- Angiotensin converting enzyme (ACE) inhibitors like enalapril (medicines used to lower blood pressure). ACE inhibitors may increase to the effect of Giapreza.
- Angiotensin II receptor blockers like candesartan (medicines used to lower blood pressure) may lessen the effect of Giapreza.

Your doctor may already be giving you other medicines used to increase your blood pressure. Adding Giapreza to these medicines may require that the doses of the other medicines be lowered.

Pregnancy, breast-feeding and fertility
Your doctor should be told if you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby before this medicine is given.

There is limited information about the effects of Giapreza during pregnancy. Use of this medicine during pregnancy should be avoided if possible. Your doctor will give you this medicine only if the possible benefit is greater than the possible risks.

It is not known whether Giapreza can pass into breast milk. Your doctor should be told if you are breast-feeding before this medicine is given.

Breastfeeding should be discontinued during treatment.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 2.5 mg/1 ml, that is to say essentially ‘sodium-free’.

3. How Giapreza is used

Giapreza will be given to you in a hospital by a doctor or a nurse. It is first diluted and then given as a drip (infusion) into a vein, supplying a specified dose each minute.

The dose depends on your body weight. The recommended starting rate of Giapreza is 20 nanograms (ng) per kilogram of your body weight per minute. After the initial dose, your doctor will adjust the rate as often as every 5 minutes until you achieve your target blood pressure. Your doctor will continue to assess your response and will adjust the dose accordingly up to a maximum of 80 ng per kilogram each minute during the first 3 hours of treatment. The maximum dose after the first 3 hours will be 40 ng per kilogram each minute.

Giapreza will be given to you at the lowest dose that helps you to achieve or maintain your blood pressure. In order to minimise the risk of side effects to this medicine, Giapreza will be withdrawn as soon as your condition improves.

Elderly
Giapreza was tested in a small number of patients more than 75 years of age. There are no dose adjustments needed for patients more than 75 years of age. Your doctor will monitor your blood pressure and adjust your dose as needed.

Impairment of liver or kidneys
There are no dose adjustments needed for patients with impairment of the function of the liver or kidneys. Your doctor will monitor your blood pressure and adjust your dose as needed.

If you are given more Giapreza than you should
Giapreza will be given to you by a doctor or a nurse, so it is unlikely you will be given the wrong dose. However, if you have side effects or think you have been given too much Giapreza, tell your doctor or nurse straight away. If you have too much Giapreza, you may experience high blood pressure. If this occurs, hospital staff will monitor your vital signs and you will be provided with supportive care.

Stopping Giapreza treatment
Your doctor will gradually decrease the amount of Giapreza you are given over time once your blood pressure has increased to appropriate levels. If Giapreza is stopped suddenly or stopped too early, you may experience a decrease in your blood pressure or your condition may worsen.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience:
- Pain, redness or pale colour, swelling or coolness to the touch of the skin or limbs, as these may be symptoms of a blood clot in one of your veins. These clots may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms, seek medical advice immediately. These types of symptoms occur in greater than 1 out of every 10 patients. While not all of these symptoms lead to life-threatening complications, your doctor should be told about them immediately.

Other side effects are:
Very common side effects (may affect more than 1 in 10 people) are:
- Too high blood pressure

Common side effects (may affect up to 1 in 10 people) are:
- Rapid heartbeat
- Poor circulation to your hands, feet, or other bodily areas which can be severe and cause tissue damage.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Giapreza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).

The diluted solution should be used immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 2 °C - 8 °C.

Do not use if you notice any signs of visible damage or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Giapreza contains

- The active substance is angiotensin II acetate. Each ml contains angiotensin II acetate equivalent to 2.5 mg angiotensin II.
  - One vial of 1 ml concentrate for solution for infusion contains 2.5 mg of angiotensin II
  - One vial of 2 ml concentrate for solution for infusion contains 5 mg of angiotensin II
- The other ingredients are mannitol and water for injections, pH adjusted with sodium hydroxide and/or hydrochloric acid (see section 2 under ‘Sodium’).

What Giapreza looks like and contents of the pack
Giapreza 2.5 mg/ml is presented as a concentrate for solution for infusion (sterile concentrate). The solution is a clear, colourless solution free of any visible particles.

Giapreza is supplied in a carton containing either 1 × 1 ml, 10 x 1 ml or 1 x 2 ml single use vial. Not all pack sizes may be marketed.

Marketing Authorisation Holder
PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

Manufacturer
PAION Netherlands B.V.
Vogt 21
6422 RK Heerlen
Netherlands

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien Viatris Tél/Tel: + 32 (0)2 658 61 00	**Lietuva** PAION Deutschland GmbH Tel: + 49 800 4453 4453
България PAION Deutschland GmbH Тел.: + 49 800 4453 4453	**Luxembourg/Luxemburg** PAION Deutschland GmbH Tél/Tel: + 49 800 4453 4453
Česká republika PAION Deutschland GmbH Tel: + 49 800 4453 4453	**Magyarország** PAION Deutschland GmbH Tel.: + 49 800 4453 4453
Danmark PAION Deutschland GmbH Tlf: + 49 800 4453 4453	**Malta** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Deutschland PAION Deutschland GmbH Tel: + 49 800 4453 4453	**Nederland** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Eesti PAION Deutschland GmbH Tel: + 49 800 4453 4453	**Norge** PAION Deutschland GmbH Tlf: + 49 800 4453 4453
Ελλάδα Viatris Hellas Ltd Τηλ: +30 210 0100002	**Österreich** PAION Deutschland GmbH Tel: + 49 800 4453 4453
España Viatris Pharmaceuticals, S.L. Tel: + 34 900 102 712	**Polska** Viatris Healthcare Sp. z o.o. Tel.: + 48 22 546 64 00
France Viatris Santé Tél: +33 4 37 25 75 00	**Portugal** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Hrvatska PAION Deutschland GmbH Tel: + 49 800 4453 4453	**România** BGP Products SRL Tel: +40 372 579 000
Ireland PAION Deutschland GmbH Tel: + 49 800 4453 4453	**Slovenija** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Ísland PAION Deutschland GmbH Sími: + 49 800 4453 4453	**Slovenská republika** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Italia Viatris Italia S.r.l. Tel: + 39 02 612 46921	**Suomi/Finland** PAION Deutschland GmbH Puh/Tel: + 49 800 4453 4453
Κύπρος PAION Deutschland GmbH Τηλ: + 49 800 4453 4453	**Sverige** PAION Deutschland GmbH Tel: + 49 800 4453 4453
Latvija PAION Deutschland GmbH Tel: + 49 800 4453 4453	**United Kingdom (Northern Ireland)** PAION Deutschland GmbH Tel: + 49 800 4453 4453

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Posology and method of administration

For intravenous use only after dilution. Giapreza is recommended to be administered via a central venous line.

Giapreza should only be administered by continuous intravenous infusion under close monitoring of haemodynamics and end-organ perfusion.

Instructions for dilution

1. Inspect each vial for particulate matter prior to dilution.
2. Dilute 1 or 2 ml of Giapreza in sodium chloride 9 mg/ml (0.9%) solution for injection to achieve a final concentration of 5 000 ng/ml or 10 000 ng/ml.
3. Diluted solution should be clear and colourless.
4. Discard the vial and any unused portion of the medicinal product after use.

Table 1: Preparation of diluted solution

Fluid restricted?	**Vial strength**	**Withdraw amount (ml)**	**Infusion bag size (ml)**	**Final concentration (ng/ml)**
No	2.5 mg/ml	1	500	5 000
Yes	2.5 mg/ml	1	250	10 000
	5 mg/2 ml	2	500	10 000

Administration

When initiating Giapreza, it is important to closely monitor blood pressure response and adjust dose accordingly.

Once an infusion has been established, the dose may be titrated as frequently as every 5 minutes in steps of up to 15 ng/kg per minute, as needed, depending on the patient's condition and target mean arterial pressure. Approximately one in every four patients experienced transient hypertension with the angiotensin II 20 ng/kg/min starting dose in clinical trials , thus needing dose down-titration. For critically ill patients, the usual target mean arterial pressure is 65 – 75 mmHg. Do not exceed 80 ng/kg per minute during the first 3 hours of treatment. Maintenance doses should not exceed 40 ng/kg per minute. Doses as low as 1.25 ng/kg per minute may be used.

It is important to administer Giapreza at the lowest compatible dose to achieve or maintain adequate arterial blood pressure and tissue perfusion. The median duration of treatment in clinical trials was 48 hours (range: 3.5 to 168 hours).

In order to minimise the risk of adverse events derived from prolonged vasoconstriction, treatment with Giapreza should be withdrawn once underlying shock is sufficiently improved. Down-titrate by gradual decrements of up to 15 ng/kg per minute, as needed, based on blood pressure in order to avoid hypotension due to abrupt withdrawal.

Storage conditions

Store in a refrigerator (2 °C - 8 °C). Dilute before use. Administer as a diluted solution.

Diluted solution may be stored at room temperature or under refrigeration. Discard prepared solution after 24 hours at room temperature or under refrigeration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.