# 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

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]<br>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 Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 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 mm Hg | 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

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

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Heussstraße 25
52078 Aachen
Germany

## 8 MARKETING AUTHORISATION NUMBER(S)

PLGB 59768/0003

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/06/2024

## 10 DATE OF REVISION OF THE TEXT

30/09/2024