New technology add-on payment (NTAP)
Effective date of October 1, 2018

Information Guide

GIAPREZA™ (angiotensin II) injection for intravenous infusion
GIAPREZA rapidly increased MAP, with a median response time of approximately 5 minutes for GIAPREZA responders, while some patients took longer.

Only GIAPREZA activates the renin-angiotensin-aldosterone system to increase MAP.

70% of patients treated with GIAPREZA achieved target MAP at Hour 3 versus 23% of patients treated with placebo.

GIAPREZA is the first and only FDA-approved synthetic human angiotensin II that increases blood pressure in adults with septic or other distributive shock.

In the ATHOS-3 trial, GIAPREZA effectively increased mean arterial pressure (MAP) in patients with distributive shock.

More patients treated with GIAPREZA experienced thromboembolic events compared with patients treated with placebo (12.9% versus 5.1%). Use concurrent venous thromboembolism prophylaxis.
Calculating the NTAP for GIAPREZA

The NTAP reimbursement for Medicare inpatient stays shall be limited to the lesser of:

50% of the average cost of GIAPREZA as calculated by CMS or 50% of the hospital’s cost in excess of the applicable MS-DRG payment for the specific patient case.

CMS imposes a payment cap for each qualified patient case. For FY2019, CMS has assigned a maximum payment of $1500 for GIAPREZA.

If the costs of a given case do not exceed the hospital’s MS-DRG payment, additional payment for GIAPREZA will not be provided.

SAFETY INFORMATION

Drug interactions
Angiotensin converting enzyme inhibitors may increase response to GIAPREZA. Angiotensin II receptor blockers may reduce response to GIAPREZA.

Contraindications
No

Warnings and precautions
The safety of GIAPREZA was evaluated in 321 adults with septic or other distributive shock in the randomized, double-blind, placebo-controlled ATHOS-3 study. There was a higher incidence of arterial and venous thrombotic and thromboembolic events in patients who received GIAPREZA compared to placebo-treated patients in the ATHOS-3 study (3% (21/163 patients) vs. 5% (8/150 patients)). The major imbalance was in deep venous thrombosis. Use concurrent venous thromboembolism prophylaxis.

Adverse reactions
The most common adverse reactions reported in greater than 10% of GIAPREZA-treated patients were thromboembolic events. Adverse reactions occurring in ≥4% of patients treated with GIAPREZA and ≤1.5% more often than placebo-treated patients in the ATHOS-3 study were thromboembolic events (including deep vein thrombosis), thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia.

References
Medicare will provide an add-on payment for GIAPREZA of up to $1500 per qualifying case to Inpatient Prospective Payment System-participating acute care hospitals. The additional payment for GIAPREZA will be determined on a case-by-case basis.

The New Technology Add-on Payment (NTAP) program was implemented to ensure Medicare beneficiaries have access to new clinically beneficial technologies while the Inpatient Prospective Payment system is recalibrated to reflect the cost of the new technology.

The Centers for Medicare & Medicaid Services (CMS) approved an NTAP for GIAPREZA because it determined that:

1. GIAPREZA provides a substantial clinical improvement over existing therapies
2. GIAPREZA is not substantially similar to another technology and is new
3. The existing Medicare Severity-Diagnosis Related Group (MS-DRG) payment for the services involving GIAPREZA are likely inadequate

Medicare will provide an add-on payment for GIAPREZA of up to $1500 per qualifying case to Inpatient Prospective Payment System-participating acute care hospitals.

The additional payment for GIAPREZA will be determined on a case-by-case basis.

Common adverse reactions

The most common adverse reactions reported in greater than 10% of GIAPREZA-treated patients were thromboembolic events. Adverse reactions occurring in ≥ 4% of patients treated with GIAPREZA and ≥ 1.5% more often than placebo-treated patients in the ATHOS 3 study were thromboembolic events (including deep vein thrombosis), thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia.

"...[W]e believe that GIAPREZA has a unique mechanism of action to achieve a therapeutic outcome because it leverages the RAAS system to increase blood pressure."3

The Centers for Medicare & Medicaid Services, August 2018
NTAP Qualifying Hospitals and Patients
The add-on payment is applicable only to Medicare-qualified hospitals that are paid through the Inpatient Prospective Payment System treating a Medicare fee-for-service patient. This excludes critical access hospitals, long-term care hospitals, Maryland rural hospitals, prospective payment exempt hospitals, inpatient psychiatric hospitals, inpatient rehabilitation facilities, and religious, nonmedical healthcare institutions.

Timing for NTAP
The payment takes effect beginning with hospital discharges on October 1, 2018, and can last up to two years.
SAFETY INFORMATION

Drug interactions
Angiotensin converting enzyme inhibitors may increase response to GIAPREZA.
Angiotensin II receptor blockers may reduce response to GIAPREZA.

Contraindications
None.

Warnings and precautions
The safety of GIAPREZA was evaluated in 321 adults with septic or other distributive shock in the randomized, double-blind, placebo-controlled ATHOS-3 study. There was a higher incidence of arterial and venous thrombotic and thromboembolic events in patients who received GIAPREZA compared to placebo-treated patients in the ATHOS-3 study (7% vs. 5% [16/163 patients] vs. 8/158 patients). The major imbalance was in deep venous thrombosis. Use concurrent venous thromboembolism prophylaxis.

Adverse reactions
The most common adverse reactions reported in greater than 10% of GIAPREZA-treated patients were thromboembolic events. Adverse reactions occurring in ≥4% of patients treated with GIAPREZA and ≥1.5% more often than placebo-treated patients in the ATHOS-3 study were thromboembolic events (including deep vein thrombosis), thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia.

References:
1. GIAPREZA® (angiotensin II) [prescribing information]. San Diego, CA: La Jolla Pharmaceutical Company; 2017.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GIAPREZA™ safely and effectively. See full prescribing information for GIAPREZA.

GIAPREZA (angiotensin II) Injection for Intravenous Infusion
Initial U.S. Approval: 2017

INDICATIONS AND USAGE
GIAPREZA is a vasoconstrictor to increase blood pressure in adults with septic or other distributive shock. (1)

DOSAGE AND ADMINISTRATION
Dilute GIAPREZA in 0.9% sodium chloride prior to use. See Full Prescribing Information for instructions on preparation and administration of injection. Diluted solution may be stored at room temperature or under refrigeration and should be discarded after 24 hours. GIAPREZA must be administered as an intravenous infusion. (2.1)

- Start GIAPREZA intravenously at 20 nanograms (ng)/kg/min. Titrate as frequently as every 5 minutes by increments of up to 15 ng/kg/min as needed. During the first 3 hours, the maximum dose should not exceed 80 ng/kg/min. Maintenance dose should not exceed 40 ng/kg/min. (2.2)

DOSAGE FORMS AND STRENGTHS
Injection: 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL) in a vial.

CONTRAINDICATIONS
None (4.1)

WARNINGS AND PRECAUTIONS
- There is a potential for venous and arterial thrombotic and thromboembolic events in patients who receive GIAPREZA. Use concurrent venous thromboembolism (VTE) prophylaxis. (5.1, 6.1)

ADVERSE REACTIONS
The most common adverse reactions reported in greater than 10% in GIAPREZA treated patients were thromboembolic events. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact La Jolla Pharmaceutical Company at 1-800-651-3861 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Angiotensin converting enzyme (ACE) inhibitors ACE inhibitors may increase response to GIAPREZA. (7.1)
- Angiotensin II Receptor Blockers (ARB) ARBs may reduce response to GIAPREZA. (7.2)

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE
GIAPREZA increases blood pressure in adults with septic or other distributive shock.

2. DOSAGE AND ADMINISTRATION

2.1. Preparation
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

GIAPREZA must be administered as an intravenous infusion. GIAPREZA must be diluted in 0.9% sodium chloride prior to use. Dilute the contents of one vial of GIAPREZA in 0.9% saline to achieve a final concentration of 5,000 ng/mL or 10,000 ng/mL.

Discard vial and any unused portion of the drug product after use.

Table 1: Preparation of Diluted Solution

<table>
<thead>
<tr>
<th>Fluid Restricted?</th>
<th>Vial Strength</th>
<th>Withdraw Amount (mL)</th>
<th>Infusion Bag Size (mL)</th>
<th>Final Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2.5 mg/mL</td>
<td>1</td>
<td>500</td>
<td>5,000</td>
</tr>
<tr>
<td>Yes</td>
<td>2.5 mg/mL</td>
<td>1</td>
<td>250</td>
<td>10,000</td>
</tr>
<tr>
<td></td>
<td>5 mg/2 mL</td>
<td>2</td>
<td>500</td>
<td>10,000</td>
</tr>
</tbody>
</table>

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

2.2. Administration
The recommended starting dosage of GIAPREZA is 20 nanograms (ng)/kg/min via continuous intravenous infusion. Administration through a central venous line is recommended.

Monitor blood pressure response and titrate GIAPREZA every 5 minutes by increments of up to 15 ng/kg/min as needed to achieve or maintain target blood pressure. Do not exceed 80 ng/kg/min during the first 3 hours of treatment. Maintenance doses should not exceed 40 ng/kg/min. Doses as low as 1.25 ng/kg/min may be used.

Once the underlying shock has sufficiently improved, down-titrate every 5 to 15 minutes by increments of up to 15 ng/kg/min based on blood pressure.

3. DOSAGE FORMS AND STRENGTHS
Injection: 2.5 mg/mL angiotensin II and 5 mg/2 mL angiotensin II (2.5 mg/mL) in a vial.
GIAPREZA is a clear, aqueous solution.

4. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS

5.1 Risk for Thrombosis

The safety of GIAPREZA was evaluated in 321 adults with septic or other distributive shock in a randomized, double-blind, placebo-controlled study, ATHOS-3. There was a higher incidence of arterial and venous thrombotic and thromboembolic events in patients who received GIAPREZA compared to placebo-treated patients in the ATHOS-3 study (13% vs. 5%). The major imbalance was in deep venous thromboses. Use concurrent venous thromboembolism (VTE) prophylaxis.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ATHOS-3

The safety of GIAPREZA was evaluated in ATHOS-3 [see Warnings and Precautions(5.1)]. Patients in ATHOS-3 were receiving other vasopressors in addition to GIAPREZA or placebo, which were titrated to effect on mean arterial pressure (MAP).

Table 2 summarizes adverse reactions with an incidence of at least 4% among patients treated with GIAPREZA and with a rate of at least 1.5% higher with GIAPREZA than with placebo.
Table 2: Adverse Reactions Occurring in ≥ 4% of Patients Treated with GIAPREZA and ≥ 1.5% More Often than in Placebo-treated Patients in ATHOS-3

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GIAPREZA N=163</th>
<th>Placebo N=158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic eventsa</td>
<td>21 (12.9%)</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>7 (4.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (9.8%)</td>
<td>11 (7.0%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>14 (8.6%)</td>
<td>9 (5.7%)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10 (6.1%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Delirium</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>

*a Including arterial and venous thrombotic events

7. **DRUG INTERACTIONS**

7.1. **Angiotensin Converting Enzyme (ACE) Inhibitors**

Concomitant use of angiotensin converting enzyme (ACE) inhibitors may increase the response to GIAPREZA.

7.2. **Angiotensin II Receptor Blockers (ARB)**

Concomitant use of angiotensin II blockers (ARBs) may decrease the response to GIAPREZA.

8. **USE IN SPECIFIC POPULATIONS**

8.1. **Pregnancy**

**Risk Summary**

The published data on angiotensin II use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. Animal reproduction studies have not been conducted with GIAPREZA.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Clinical Considerations**

*Disease-associated maternal and/or embryo/fetal risk*
Septic or other distributive shock is a medical emergency that can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with septic or other distributive shock is likely to increase the risk of maternal and fetal morbidity and mortality.

8.2. Lactation

Risk Summary
It is not known whether GIAPREZA is present in human milk. No data are available on the effects of angiotensin II on the breastfed child or the effects on milk production.

8.4. Pediatric Use
The safety and efficacy of GIAPREZA in pediatric patients have not been established.

8.5. Geriatric Use
In ATHOS-3, 48% of the total patient population was aged 65 years and older. There was no significant difference in safety or efficacy between patients less than 65 and those 65 years or older when treated with GIAPREZA.

10. OVERDOSAGE
Overdose of GIAPREZA would be expected to result in hypertension, necessitating close monitoring and supportive care. Effects are expected to be brief because the half-life of angiotensin II is less than one minute.

11. DESCRIPTION
Angiotensin II is a naturally occurring peptide hormone of the renin-angiotensin-aldosterone system (RAAS) that causes vasoconstriction and an increase in blood pressure. GIAPREZA is a sterile, aqueous solution of synthetic human angiotensin II for intravenous administration by infusion. Each 1 mL of GIAPREZA contains 2.5 mg angiotensin II equivalent to an average of 2.9 mg angiotensin II acetate, 25 mg mannitol, and Water for Injection adjusted with sodium hydroxide and/or hydrochloric acid to pH of 5.5.

The chemical name of the synthetic angiotensin II acetate is L-Aspartyl-L-arginyLL-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine, acetate salt. The counter ion acetate is present in a non-stoichiometric ratio. It is a white to off-white powder, soluble in water.

The structure of angiotensin II acetate is shown below.
Molecular formula: C$_{50}$H$_{71}$N$_{13}$O$_{12}$$\cdot$(C$_{2}$H$_{4}$O$_{2}$)$_{n}$; ($n$ = number of acetate molecules; theoretical $n = 3$)

Average molecular weight: 1046.2 (as free base).

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Angiotensin II raises blood pressure by vasoconstriction and increased aldosterone release. 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.

12.2. Pharmacodynamics

For the 114 (70%) patients in the GIAPREZA arm who reached the target MAP at Hour 3, the median time to reach the target MAP endpoint was approximately 5 minutes. GIAPREZA is titrated to effect for each individual patient.

12.3. Pharmacokinetics

Following intravenous infusion of angiotensin II in adults with septic or other distributive shock, serum levels of angiotensin II are similar at Baseline and Hour 3 after intravenous infusion. After 3 hours of treatment, however, the serum level of angiotensin I (the angiotensin II precursor peptide) is reduced by approximately 40%.

Distribution:

No specific studies were conducted that examined the distribution of GIAPREZA.

Metabolism and Excretion:

No specific studies were conducted that examined the metabolism and excretion of GIAPREZA. The plasma half-life of IV administered angiotensin II is less than one minute. It is metabolized by aminopeptidase A and angiotensin converting enzyme 2 to angiotensin-(2-8) [angiotensin III] and angiotensin-(1-7), respectively in plasma, erythrocytes and many of the major organs (i.e.,
intestine, kidney, liver and lung). Angiotensin II type 1 receptor (AT1) mediated activity of angiotensin III is approximately 40% of angiotensin II; however, aldosterone synthesis activity is similar to angiotensin II. Angiotensin-(1-7) exerts the opposite effects of angiotensin II on AT1 receptors and causes vasodilation.

**Specific Populations**
No formal pharmacokinetic studies were conducted with GIAPREZA in the following specific populations.

*Renal Impairment*
The clearance of angiotensin II is not dependent on renal function. Therefore, the pharmacokinetics of GIAPREZA are not expected to be influenced by renal impairment.

*Hepatic Impairment*
The clearance of angiotensin II is not dependent on hepatic function. Therefore, the pharmacokinetics of GIAPREZA are not expected to be influenced by hepatic impairment.

*Age*
The effect of age was analyzed in the 163 patients receiving GIAPREZA in ATHOS-3. There were no significant differences in pharmacokinetics between age groups (< 65 years / ≥ 65 years).

*Male and Female Patients*
The effect of sex was analyzed in the 163 patients receiving GIAPREZA in ATHOS-3. There were no significant differences in pharmacokinetics between male and female patients.

13. **NONCLINICAL TOXICOLOGY**

13.1. *Carcinogenesis, Mutagenesis, Impairment of Fertility*
No genetic toxicity studies have been conducted with GIAPREZA. No carcinogenicity or fertility studies with GIAPREZA have been conducted in animals.

13.2. *Animal Toxicology and/or Pharmacology*
No animal toxicology studies were conducted with GIAPREZA.

13.3. *Safety Pharmacology*
In a cardiovascular safety pharmacology study in normotensive dogs, GIAPREZA doses of 150, 450, and 1800 ng/kg (5, 15 and 60 ng/kg/min) were infused intravenously for 30 minutes each. At ≥ 450 ng/kg, GIAPREZA caused significantly elevated MAP and systemic vascular resistance, as expected. The 1800 ng/kg dose also caused increased heart rate, increased systemic vascular resistance, increased left ventricular systolic and end-diastolic pressures, and PR interval prolongation. GIAPREZA did not significantly alter respiratory rate or cause electrocardiographic changes in QRS duration or QTc.
14. CLINICAL STUDIES

14.1. ATHOS-3

The Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial was a double-blind study in which 321 adults with septic or other distributive shock who remained hypotensive despite fluid and vasopressor therapy were randomized 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. 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.

91% of subjects had septic shock; the remaining subjects had other forms of distributive shock such as neurogenic shock. 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. 61% of subjects were male, 80% were White, 10% were Black, and 10% were other races. The median age of subjects was 64 years (range: 22-89 years). Patients requiring high doses of steroids, patients with a history of asthma or bronchospasm, and patients with Raynaud’s syndrome were not included.

The primary endpoint was achieved by 70% of patients randomized to GIAPREZA compared to 23% of placebo subjects; p < 0.0001 (a treatment effect of 47%). Figure 1 shows the results in all patients and in selected subgroups.
Figure 1: ATHOS-3: Primary Endpoint – Overall Result and Results in Selected Subgroups

NE Equiv = norepinephrine equivalent dose: the sum of all vasopressors doses with each vasopressor dose converted to the clinically equivalent norepinephrine dose

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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.

Patients were not necessarily on maximum doses of other vasopressors at the time of randomization. The effect of GIAPREZA when added to maximum doses of other vasopressors is unknown.
Mortality through Day 28 was 46% on GIAPREZA and 54% on placebo (hazard ratio 0.78; 95% confidence interval 0.57 – 1.07).

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied
GIAPREZA (angiotensin II) Injection is a clear, aqueous solution for administration by intravenous infusion supplied as a single dose vial in two strengths:

- 2.5 mg/mL vial: NDC 68547-501-02: A carton of one 1 mL single dose vial containing 2.5 mg angiotensin II (as a sterile liquid).
- 5 mg/2 mL vial: NDC 68547-002-05: A carton of one 2 mL single dose vial containing 5 mg (2.5 mg/mL) angiotensin II (as a sterile liquid).

16.2. Storage and Handling

- GIAPREZA vials should be stored in the refrigerator (36-46°F, 2-8°C).
- Discard prepared diluted solution after 24 hours at room temperature or under refrigeration.

Manufactured for:
La Jolla Pharmaceutical Company
San Diego, CA 92121