



**READY.
SET.
REACH
TARGET
MAP.
FAST.**

Rapidly stabilize MAP in a median of 5 minutes.

For septic or other distributive shock, act fast with GIAPREZA—the first and only vasopressor designed to regulate RAAS in your patients.¹

MAP=mean arterial pressure; RAAS=renin-angiotensin-aldosterone system.

SELECTED IMPORTANT SAFETY INFORMATION

Indication

GIAPREZA® (angiotensin II) increases blood pressure in adults with septic or other distributive shock.

Contraindications

None.

Warnings and Precautions

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.

Please see additional Important Safety Information throughout. Before administering, please see the Full Prescribing Information for GIAPREZA.

/// GIAPREZA®
(angiotensin II)
injection for intravenous infusion

DISTRIBUTIVE SHOCK CAN TURN INTO A *FIGHT FOR SURVIVAL*²

The longer hypotension persists, the higher the mortality risk²



Nearly **2/3** of ICU patients with distributive shock **have low MAP** (<65 mmHg) for **≥2 hours** despite **vasopressor support**²



If low MAP persists for **0–2 hours**, mortality risk ranges from **22% to 31%**²



If low MAP persists for **6–8 hours**, mortality risk ranges from **39% to 74%**²

ICU=intensive care unit.

Like mortality rates, hospital costs rise as severity increases, with septic shock costing \$31,704 to \$68,671 per patient.³

NOW IS THE TIME TO *REASSESS TREATMENT CHOICES*

Traditional vasopressors can be toxic at high doses and ineffective in some patients^{4,5}



Catecholamines and **vasopressin** can cause cardiac **toxicity** and **mortality** at higher doses^{4,6}



Mortality may reach **40%** at >0.2 mcg/kg/min of norepinephrine, and **may reach 90%** at >1 mcg/kg/min⁷



Vasopressin may reduce the need for high-dose catecholamines but less than **50% of patients** respond to it^{5,8}

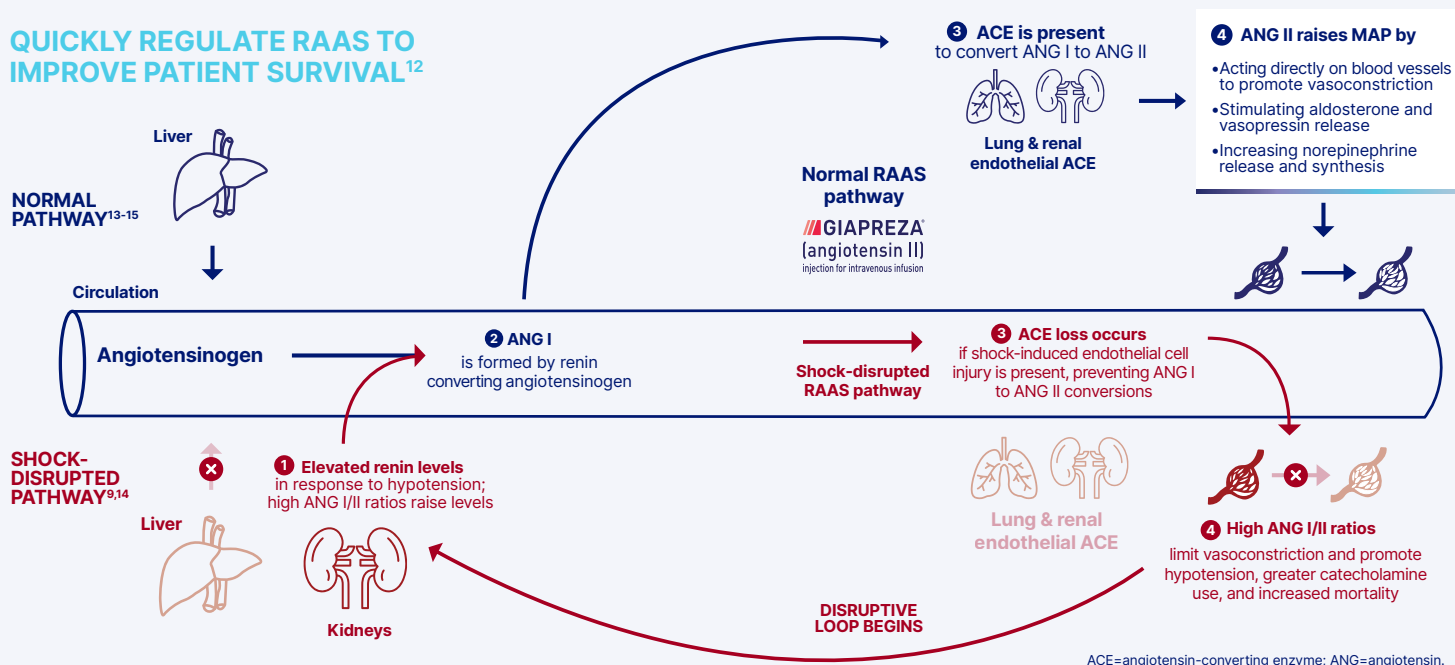
The right catecholamine-sparing agent may make the difference.

HARNESS THE POWER OF AN UNDERUTILIZED SYSTEM

GIAPREZA is the first and only synthetic ANG II treatment—the only vasopressor to regulate RAAS and stabilize MAP in adults with septic or other distributive shock¹

The renin-angiotensin-aldosterone system (RAAS) is crucial for producing angiotensin II (ANG II), **a naturally occurring peptide hormone** that triggers vasoconstriction and increases blood pressure.⁹

QUICKLY REGULATE RAAS TO IMPROVE PATIENT SURVIVAL¹²



Despite its significance, standard-of-care vasopressors neglect RAAS, leaving a gap in stabilizing MAP.⁹⁻¹¹

In addition, shock may disrupt RAAS by causing an ACE deficiency, leading to abnormally high ANG I/II ratios. This disruption can result in increased catecholamine use and can trap patients in a potentially fatal cycle.^{9,12}

SELECTED IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reactions reported in greater than 10% of GIAPREZA-treated patients were thromboembolic events. Adverse reactions occurring in $\geq 4\%$ of patients treated with GIAPREZA and $\geq 1.5\%$ 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.

BREAK THE DISRUPTIVE LOOP

GIAPREZA is a catecholamine-sparing agent that regulates RAAS to stabilize MAP in a median of 5 minutes.^{9,16}

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THE **LANDMARK TRIAL** BEHIND THE **FIRST AND ONLY** SYNTHETIC ANG II TREATMENT^{1,13}

GIAPREZA was studied in ATHOS-3, an international, randomized, double-blind, placebo-controlled study of 321 patients with distributive shock, who remained hypotensive despite fluid and vasopressor therapy.¹⁷

Treatment arms¹⁷

GIAPREZA (n=163) plus standard-of-care (SOC) vasopressors ^{††}	Placebo (n=158) plus standard-of-care (SOC) vasopressors ^{††}
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Primary endpoint¹⁷:

An increase in MAP at Hour 3 of at least 10 mmHg, or a MAP response of ≥ 75 mmHg, without an increase in baseline vasopressor dosing.

Select additional endpoint¹⁷:

All-cause mortality through Day 28.

Select baseline patient characteristics (N=321) ¹⁷	GIAPREZA + SOC (n=163)	Placebo + SOC (n=158)
Median MAP, mmHg (IQR)	66.3 (63.7–69.0)	66.3 (63.0–68.3)
Median APACHE II score (IQR)	27 (22–33)	29 (22–34)
Cause of shock, sepsis (%)	127 (77.9%)	132 (83.5%)
Median vasopressor dose (NED), mcg/kg/min (IQR)	0.33 (0.23–0.56)	0.34 (0.23–0.56)
Vasopressin use during 6 h before randomization (%)	113 (69.3%)	111 (70.3%)

SELECTED IMPORTANT SAFETY INFORMATION

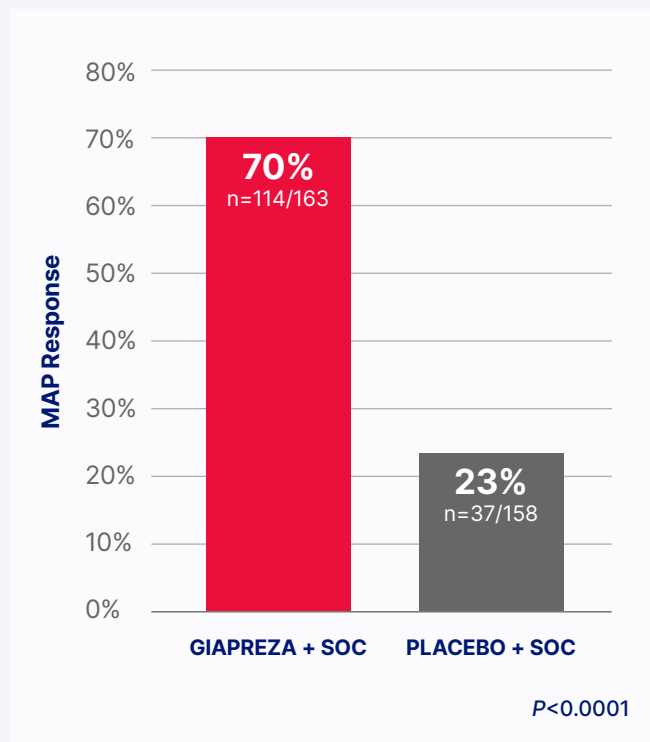
Drug Interactions

Angiotensin converting enzyme (ACE) inhibitors may increase response to GIAPREZA. Angiotensin II receptor blockers (ARBs) may reduce response to GIAPREZA.

Contraindications

None.

3X MORE PATIENTS ACHIEVED AND SUSTAINED TARGET MAP¹⁷



Median time to reach target MAP was 5 minutes

*Standard-of-care vasopressors included norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin.

†Doses of GIAPREZA or placebo were titrated to a target 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 was titrated to maintain a MAP between 65 and 70 mmHg while reducing doses of other vasopressors.

APACHE II=Acute Physiology and Chronic Health Evaluation II; ATHOS-3=Angiotensin II for the Treatment of High-Output Shock; IQR=interquartile range; NED=norepinephrine-equivalent dose: the sum of all vasopressor doses with each vasopressor dose converted to the clinically equivalent norepinephrine dose.

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RAPIDLY STABILIZE MAP AND REDUCE VASOPRESSOR NEEDS¹⁷



70% of patients who achieved **target MAP** reached it within the **first 30 minutes** of treatment at doses ≤ 5 ng/kg/min¹⁸



During the **first 48 hours**, patients on **GIAPREZA** required consistently **lower** mean doses of **background vasopressors**¹⁷



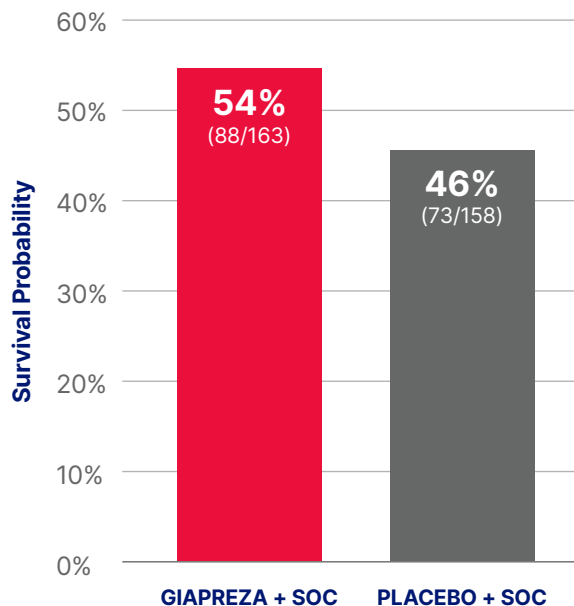
The **effect on MAP** was **sustained** for at least the first **3 hours** of treatment

SELECTED IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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INCREASED PATIENT SURVIVAL AT DAY 28^{12,17}



A meta-analysis found no difference in mortality rates between angiotensin II and norepinephrine (46.2% vs. 54.2%; RR, 0.85 [95% CI, 0.69–1.06])

- 2021 SSC Guidelines^{19,*}



Not statistically significant. Mortality through Day 28 was an exploratory endpoint in ATHOS-3. The study was not powered to detect a difference in mortality. There were secondary endpoints not reported in this brochure.¹⁷

*The SSC released updated global guidelines in October 2021 for clinicians caring for adult patients with sepsis or septic shock.¹⁹

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GREATER SURVIVAL BENEFIT WITH LOWER VASOPRESSOR DOSES²⁰

In an exploratory post hoc analysis of ATHOS-3, early use of GIAPREZA plus standard of care was associated with improved survival vs. placebo plus standard of care.²⁰



SELECTED IMPORTANT SAFETY INFORMATION

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.

POWERFUL RESULTS IN A BROAD RANGE OF PATIENTS

Characteristics	GIAPREZA [®] arm n/N(%)	Placebo arm n/N(%)	Odds ratio (95% CI)
Overall treatment group			
All (100%)	114/163 (69.9%)	37/158 (23.4%)	8.0 (4.8, 13.3)
Baseline MAP (mmHg)			
<65 (32%)	28/52 (53.8%)	10/50 (20.0%)	4.7 (1.9, 11.3)
≥65 (68%)	86/111 (77.5%)	27/108 (25.0%)	10.3 (5.5, 19.2)
Baseline APACHE II			
≤30 (62%)	76/105 (72.4%)	20/93 (21.5%)	9.6 (5.0, 18.4)
>30 (38%)	38/58 (65.5%)	17/65 (26.2%)	5.4 (2.5, 11.6)
Baseline dialysis			
No (64%)	83/109 (76.1%)	23/95 (24.2%)	10.0 (5.2, 19.0)
Yes (36%)	31/54 (57.4%)	14/63 (22.2%)	4.7 (2.1, 10.5)
Baseline creatinine clearance (mL/min)			
<60 (69%)	75/113 (66.4%)	28/107 (26.2%)	5.6 (3.1, 10.0)
≥60 (31%)	38/49 (77.6%)	9/51 (17.6%)	16.1 (6.0, 43.1)
Baseline albumin (g/dL)			
<2.5 (62%)	64/103 (62.1%)	15/89 (16.9%)	8.1 (4.1, 16.0)
≥2.5 (38%)	44/51 (86.3%)	21/67 (31.3%)	13.8 (5.3, 35.6)
Baseline NE equiv (mcg/kg/min)			
<0.5 (71%)	91/117 (77.8%)	29/110 (26.4%)	9.8 (5.3, 18.0)
≥0.5 (29%)	23/46 (50.0%)	8/48 (16.7%)	5.0 (1.9, 13.0)

Patients with a history of ACEi and ARB favored GIAPREZA over placebo but interpretation should consider the small sample sizes (9% and 7% respectively).

Note: The figure above presents effects in select 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.

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CI=confidence interval.

DON'T WAIT—start GIAPREZA sooner to help reduce mortality and lower doses of other vasopressors.²⁰

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GIAPREZA[®]
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A CATECHOLAMINE-SPARING AGENT TO HELP INCREASE SURVIVAL^{9,12,16}

An exploratory post hoc analysis of ATHOS-3 uncovered RAAS dysfunction in patients and a much higher risk of mortality⁹:

- 255 patients were studied
- 76% had elevated renin levels
- 3x the upper limit of normal*

High renin levels correlated with⁹:

↑ACE inhibitor use ↑NED needs ↑ANG I/II ratios

GIAPREZA effectively reduced renin and ANG I levels for better outcomes ⁹ :	GIAPREZA + SOC	Placebo + SOC
Reduction in serum renin levels, %	54.3	14.1
Reduction in serum ANG I levels, %	39.7	7
28-day mortality, % [median (IQR)] [†]	51 (39–65)	70 (59–80)
Ventilator liberation by Day 7 (alive and ventilator-free), % [median (IQR)] [†]	28 (18–43)	14 (8–25)
RRT liberation by Day 7 (alive and RRT free), % [median (IQR)] [†]	43 (25–66)	12 (5–27)
ICU discharge by Day 28, % [median (IQR)] [†]	44 (32–58)	22 (14–33)

*The upper limit of normal was defined as 58.78 pg/mL; the median renin level was 172.7 pg/mL.⁹
†Values represent outcomes in patients who had renin concentrations above the study population median.⁹
RRT=renal replacement therapy.

REGULATE RAAS NOW—GIAPREZA may help increase survival, reduce catecholamine use, and shorten days on ventilators, RRT, and in the ICU.^{9,17}

SELECTED IMPORTANT SAFETY INFORMATION

Drug Interactions

Angiotensin converting enzyme (ACE) inhibitors may increase response to GIAPREZA. Angiotensin II receptor blockers (ARBs) may reduce response to GIAPREZA.

Contraindications

None.

WELL-TOLERATED VS. STANDARD OF CARE (SOC) + PLACEBO IN ATHOS-3¹⁷

	GIAPREZA + SOC (n=163)	Placebo + SOC (n=158)
Adverse event of any grade, % (n)	87.1% (142)	91.8% (145)
Adverse event leading to discontinuation, % (n)	14.1% (23)	21.5% (34)
Any serious adverse event with frequency ≥1% in either study group, % (n)	60.7% (99)	67.1% (106)

Adverse reactions occurring in ≥4% of patients treated with GIAPREZA and ≥1.5% more often than in placebo-treated patients included thromboembolic events, including arterial and venous thrombosis events (12.9% vs. 5.1%), deep vein thrombosis (4.3% vs. 0.0%), thrombocytopenia (9.8% vs. 7.0%), tachycardia (8.6% vs. 5.7%), fungal infection (6.1% vs. 1.3%), delirium (5.5% vs. 0.6%), acidosis (5.5% vs. 0.6%), hyperglycemia (4.3% vs. 2.5%), and peripheral ischemia (4.3% vs. 2.5%).

Thromboembolic events

- In ATHOS-3, serious adverse events (SAEs) were reported. The Prescribing Information grouped SAEs and adverse events, including thromboembolic events, as presented under a single category¹⁷
- The incidence of patients with a Grade 3 or 4 (severe or life-threatening) thromboembolic event was 9 (5.5%) events in the GIAPREZA group vs. 5 (3.2%) in the placebo group²¹
- In the GIAPREZA group, 12/25 (48%) thromboembolic events occurred within 5 days of randomization in comparison to 7/8 (87.5%) events in the placebo arm²¹

Use concurrent venous thromboembolism (VTE) prophylaxis

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FLEXIBLE AND EASILY TITRATABLE FOR RAPID MAP CONTROL

1. INITIATE

- The recommended starting dose of GIAPREZA is 20 ng/kg/min (0.02 mcg/kg/min)

2. ASSESS

- The median time to reach target MAP was 5 minutes
- The median dose of GIAPREZA was 10 ng/kg/min at 30 minutes

3. OPTIMIZE

- Titrate GIAPREZA as frequently as every 5 minutes by increments of up to 15 ng/kg/min as needed to achieve or maintain target blood pressure
- The half-life of GIAPREZA is less than 1 minute
- Once the underlying shock has sufficiently improved, down-titrate every 5 to 15 minutes in increments of up to 15 ng/kg/min, based on blood pressure

- > **Doses as low as 1.25 ng/kg/min may be used**
- > **During the first 3 hours, the maximum dose should not exceed 80 ng/kg/min**
- > **Maintenance dose should not exceed 40 ng/kg/min**



Administer GIAPREZA via continuous intravenous infusion



Administration through a central venous line is recommended



Monitor blood pressure closely after GIAPREZA initiation

SELECTED IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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**GIAPREZA IS
AVAILABLE IN
0.5 MG AND 2.5 MG
VIAL OPTIONS**

References: 1. National Center for Biotechnology Information. PubChem Compound Summary for CID 172198, angiotensin II. <https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-II-human>. Accessed January 22, 2024. 2. Vincent JL, Nielsen ND, Shapiro NJ, et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. *Ann. Intensive Care*. 2018;8(1):107. doi: 10.1186/s13613-018-0448-9 3. Paoli CJ, Reynolds MA, Sinha M, et al. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med*. 2018;46(12):1889-1897. doi: 10.1097/CCM.0000000000003342 4. Schmittinger CA, Torgersen C, Luckner G, et al. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. *Intensive Care Med*. 2012;38(6):950-8. doi: 10.1007/s00134-012-2531-2 5. Sacha GL, Lam SW, Duggal A, et al. Predictors of response to fixed-dose vasopressin in adult patients with septic shock. *Ann. Intensive Care*. 2018;8(1):35. doi: 10.1186/s13613-018-0379-5 6. Dünser MW, Mayr AJ, Tür A, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med*. 2003;31(5):1394-8. doi: 10.1097/01.CCM.0000059722.94182.79 7. Martin C, Medam S, Antonini F, et al. Norepinephrine: not too much, too long. *Shock*. 2015;44(4):305-9. doi: 10.1097/SHK.0000000000000426 8. Reardon DP, DeGrado JR, Anger KE, et al. Early vasopressin reduces incidence of new onset arrhythmias. *J Crit Care*. 2014;29(4):482-5. doi: 10.1016/j.jccr.2014.03.005 9. Bellomo R, Forni LG, Busse LW, et al. Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock. A Clinical Trial. *Am J Respir Crit Care Med*. 2020;202(9):1253-1261. doi: 10.1164/rccm.201911-2172OC 10. Paravati S, Rosani A, Warrington SJ | Physiology, Catecholamines | StatPearls. Published 2022. <https://www.ncbi.nlm.nih.gov/books/NBK507716/>. Accessed January 22, 2024. 11. Demiselle J, Fage N, Radermacher P, et al. Vasopressin and its analogues in shock states: a review. *Ann. Intensive Care*. 2020;10(1):9. doi: 10.1186/s13613-020-0628-2 12. Supplementary appendix to: Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017;377(5):419-430. doi: 10.1056/NEJMoa1704154 13. Andrews L, Benken J, Benedetti E, et al. Effects of angiotensin II in the management of perioperative hypotension in kidney transplant recipients. *Clin Transplant*. 2022;36(9):e14754. doi: 10.1111/ctr.14754 14. Fountain JH, Kaur J, Lappin SL. Physiology, Renin Angiotensin System. StatPearls Publishing; 2023. <https://www.ncbi.nlm.nih.gov/books/NBK470410/>. Accessed January 22, 2024. 15. Wang Y, Seto SW, Golligorsky J. Angiotensin II, sympathetic nerve activity and chronic heart failure. *Heart Fail Rev*. 2014;19(2):187-98. doi: 10.1007/s10741-012-9368-1 16. Buckley MS, Barletta JF, Smithburger PL, et al. Catecholamine Vasopressor Support Sparing Strategies in Vasodilatory Shock. *Pharmacotherapy*. 2019;39(3):382-398. doi: 10.1002/phar.2199 17. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017;377(5):419-430. doi: 10.1056/NEJMoa1704154 18. Ham KR, Boldt DW, McCurdy MT, et al. Sensitivity to angiotensin II dose in patients with vasodilatory shock: a prespecified analysis of the ATHOS-3 trial. *Ann. Intensive Care*. 2019;9(1):63. doi: 10.1186/s13613-019-0536-5 19. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y 20. Wierszewska PM, Bellomo R, Busse LW, et al. Initiating angiotensin II at lower vasopressor doses in vasodilatory shock: an exploratory post-hoc analysis of the ATHOS-3 clinical trial. *Crit Care*. 2023;27(1):175. doi: 10.1186/s13054-023-04446-1 21. Data on File. Innoviva Specialty Therapeutics; 2023.

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WHEN MAP DROPS, **ACT FAST** **WITH GIAPREZA**



Regulate RAAS to help increase survival, reduce catecholamine use, and shorten days in the ICU^{9,17}



Rapidly achieve and sustain target MAP in a median of 5 minutes¹⁷



Initiate GIAPREZA early—survival benefit was greater with lower vasopressor doses^{20,*}

*Exploratory post hoc analysis.²⁰

**Click here to learn more about how
GIAPREZA may help save lives⁹**

SELECTED IMPORTANT SAFETY INFORMATION

Adverse Reactions

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You are encouraged to report negative side effects of prescription drugs to the FDA. To report SUSPECTED ADVERSE REACTIONS, please contact:

La Jolla Pharmaceutical Company
[1-800-651-3861](tel:1-800-651-3861) medicalinformation@ljpc.com

U.S. Food and Drug Administration
[1-800-FDA-1088](tel:1-800-FDA-1088) www.fda.gov/medwatch

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