Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for GIAPREZA (angiotensin II)

This is a summary of the risk management plan (RMP) for GIAPREZA. The RMP details important risks of GIAPREZA, how these risks can be minimised, and how more information will be obtained about GIAPREZA's risks and uncertainties (missing information).

GIAPREZA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how GIAPREZA should be used.

This summary of the RMP for GIAPREZA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of GIAPREZA's RMP.

I. The medicine and what it is used for

GIAPREZA is authorised for treatment of adults with low blood pressure due to shock (see SmPC for the full indication). It contains angiotensin II acetate as the active substance and it is given by intravenous infusion.

Further information about the evaluation of GIAPREZA's benefits can be found in GIAPREZA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/giapreza.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of GIAPREZA, together with measures to minimise such risks and the proposed studies for learning more about GIAPREZA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of GIAPREZA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of an association with the use of GIAPREZA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Thromboembolic events Transient hypertension
Important potential risks	Peripheral ischaemia
Missing information	None

II.B Summary of Important Risks

Important Identified Risk – Thromboembolic Events	
Evidence for linking the risk to the medicine	In Study LJ501-CRH01, there was a higher incidence of arterial and venous thromboembolic events (formation of blood clots in intact blood vessels) in subjects who received GIAPREZA (12.9%) than in controls (5.1%). Deep vein thrombosis (clotting in large veins, usually in the legs) was the most frequently reported type of thrombosis, occurring in 7 subjects (4.3%) treated with GIAPREZA and in no subjects in the control group. Most of the thromboembolic events were not severe. The proportion of subjects with more severe (Grade 3 or Grade 4) thromboembolic events was 5.5% for GIAPREZA, compared with 3.2% for placebo. In the subset of patients with deep vein thrombosis, only 1 event was Grade 3 and none of these events led to pulmonary embolisms. The percentage of patients in the angiotensin II and placebo arms with a history of embolic or thrombotic events at baseline was similar (52% versus 49%). In Study LJ501-CRH01, the incidence of patients receiving a prior or concomitant antithrombotic medication was 84.7% in the LJPC-501 arm compared to 70.9% in the placebo arm. This difference was present at baseline with 69.3% of patients from the LJPC-501 arm receiving an antithrombotic at study drug initiation compared to 56.3% of patients in the placebo arm. There is a trend towards fewer thromboembolic adverse events in the patients who received preventive antithrombotic medication compared to those who did not receive preventative medication. In the LJPC-501 arm, the incidence of patients with a thromboembolic adverse event was 16.0% for patients not receiving an antithrombotic at baseline compared to 11.5% for patients receiving an antithrombotic at baseline. The same trend was observed for patients in the placebo arm; the incidence of patients with a thromboembolic adverse event was 5.8% for patients not receiving an antithrombotic at baseline compared to 4.5% for patients receiving an antithrombotic at baseline. A similar trend was observed when analyses were restricted to Grade 3/4 thromboembolic adverse events. The evidence linking this type of event to treatment with GIAPREZA is derived from a randomised, controlled study. Evidence derived from randomised, controlled studies is conventionally considered to be reliable.

Important Identified Risk – Thromboembolic Events	
Risk factors and risk groups	No risk factors for thromboembolic events in subjects given GIAPREZA for the treatment of shock have been identified, other than the indication for treatment itself. There is a trend towards fewer thromboembolic adverse events in subjects that received preventive antithrombotic medication.
Risk minimisation measures	Routine risk communication: *SmPC sections 4.4 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Intended to be used in hospital only under specialist supervision* *Instructions for venous thromboembolism prophylaxis is included in SmPC sections 4.4 and 4.8.* *Concurrent venous thromboembolism prophylaxis should be used unless contraindicated during treatment with GIAPREZA. Non-pharmacologic VTE prophylaxis may be considered where pharmacologic prophylaxis is contraindicated.* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Identified Risk – Transient Hypertension	
Evidence for linking the risk to the medicine	Within the LJPC-501 arm, 37 patients had an increase in reported MAP above 100 mmHg (range: 101.3 to 142 mmHg) within 15 minutes of initiating study drug. Study drug dose was then down-titrated in all 37 patients and the median time to MAP reported below 85 mmHg was 25 minutes (range: 7 to 65 minutes). In the placebo arm, 3 patients showed an increase in MAP above 100 mmHg (range: 101.5 to 104.3 mmHg) within 15 minutes. The evidence linking this type of event to treatment with GIAPREZA is derived from a randomised, controlled study. Evidence derived from randomised, controlled studies is conventionally considered to be reliable.
Risk factors and risk groups	No risk factors for transient hypertension in subjects given GIAPREZA for the treatment of shock have been identified.

Important Identified Risk – Transient Hypertension	
Risk minimisation measures	Routine risk communication: *SmPC section 4.8* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for continuous intravenous infusion under close and continuous monitoring of hemodynamic parameters are included in SmPC section 4.2.* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Potential Risk – Peripheral Ischaemia	
Evidence for linking the risk to the medicine	In Study LJ501-CRH01, there was a higher incidence of peripheral ischaemia (insufficient delivery of oxygen to the tissues due to inadequate blood flow) in subjects who received GIAPREZA (4.3%) than in controls (2.5%). The evidence linking this type of event to treatment with GIAPREZA is derived from a randomised, controlled study. Evidence derived from randomised, controlled studies is conventionally considered to be reliable.
Risk factors and risk groups	Vasoconstriction (narrowing of blood vessels) is an intrinsic property of angiotensin II and the main mechanism by which GIAPREZA increases blood pressure. Vasoconstriction is dose-dependent; the more GIAPREZA that is administered, the greater the narrowing of blood vessels. Subjects receiving higher infusion rates of GIAPREZA will be more likely to experience low blood flows due to vessel narrowing, and will, therefore, be at higher risk of peripheral ischaemia (insufficient delivery of oxygen to the tissues due to inadequate blood flow).

Important Potential Risk – Peripheral Ischaemia	
Risk minimisation measures	Routine risk communication: *SmPC sections 4.4 and 4.8* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for continuous intravenous infusion under close and continuous monitoring of organ-specific parameters are included in SmPC section 4.2* *Recommendations for managing peripheral ischaemia by administering the lowest dose compatible to achieve or maintain adequate arterial blood pressure and tissue perfusion are included in SmPC section 4.4* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Not applicable.

II.C.2 Other Studies in Post-Authorisation Development Plan

The efficacy study, LJ501-CRH06, is planned for post-authorisation development.

Study Name: A Phase 4, Randomized, Double-blind, Placebo-controlled, Multicenter Study of LJPC-501 in Adult Patients with Vasodilatory Shock and Associated Severe Acute Kidney Injury Requiring Renal Replacement Therapy

Purpose of the Study:

To compare the efficacy of LJPC-501 to placebo on reduction in doses of standard-of-care (SOC) vasopressors required for hemodynamic stability from baseline to Hour 2 in patients with vasodilatory shock and associated severe acute kidney injury