PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for FIRAZYR (icatibant acetate)

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

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

This summary of the RMP for FIRAZYR 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 FIRAZYR 's RMP.

I. The medicine and what it is used for

FIRAZYR is authorised for symptomatic treatment of acute attacks of HAE in adults, adolescents, and children aged 2 years and older with C1-INH deficiency. It contains icatibant acetate as the active substance and it is given by subcutaneous injection.

For centrally authorised medicinal product only:

Further information about the evaluation of FIRAZYR’s benefits can be found in FIRAZYR’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage link to the EPAR summary landing page. https://www.ema.europa.eu/en/medicines/human/EPAR/firazyr link to product’s EPAR summary landing page on the EMA webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of FIRAZYR, together with measures to minimise such risks and the proposed studies for learning more about FIRAZYR '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 (e.g. 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.

If important information that may affect the safe use of FIRAZYR is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of FIRAZYR 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 a link with the use of FIRAZYR. 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 (e.g. on the long-term use of the medicine).

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 1. List of Important Risks and Missing Information	
Important identified risks	Injection site reactions
Important potential risks	Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism Partial bradykinin agonism (excluding injection site reactions) Antigenicity manifesting as drug hypersensitivity and lack of efficacy Lack of efficacy Medication errors Effect on reproductive hormone levels in pubertal/ post-pubertal children
Missing information	Use in pregnant and lactating women Use in children below 2 years of age

II.B Summary of important risks

Table 2. Important Identified Risk: Injection Site Reactions	
Evidence for linking the risk to the medicine	In vitro studies and clinical trials.
Risk factors and risk groups	None identified.
Risk minimisation measures	Injection site reactions are described in the SmPC Section 4.8 Undesirable effects.
Additional pharmacovigilance activities	None

Table 3. Important Potential Risk: Deterioration of Cardiac Function under Ischaemic Conditions	
Evidence for linking the risk to the medicine	Preclinical findings and theoretical risk
Risk factors and risk groups	None identified
Risk minimisation measures	Ischaemic heart disease addressed in Section 4.4 of the SmPC.
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS).

Table 4. Important Potential Risk: Partial Bradykinin Agonism (Excluding Injection Site Reactions)	
Evidence for linking the risk to the medicine	Preclinical findings
Risk factors and risk groups	Overdose (for iv formulation), not known for sc formulation.
Risk minimisation measures	None proposed. At the currently labelled dose and administration form in patients with HAE attacks (30 mg per injection given by sc administration, and no more than 3 injections of icatibant should be administered in a 24-hour period), no systemic bradykinin agonistic reactions are expected. Various in vitro and in vivo studies have demonstrated partial bradykinin agonism only at high icatibant concentrations.
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 5. Important Potential Risk: Antigenicity manifesting as drug hypersensitivity and lack of efficacy.	
Evidence for linking the risk to the medicine	Preclinical findings
Risk factors and risk groups	Repeated attacks with multiple subsequent treatments.
Risk minimisation measures	**Sections 4.4** in the EU SmPC
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 6. Important Potential Risk: Lack of Efficacy	
Evidence for linking the risk to the medicine	Theoretical risk.
Risk factors and risk groups	All HAE patients.
Risk minimisation measures	Sections 4.2, 4.4 in the EU SmPC
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 7. Important Potential Risk: Medication Error	
Evidence for linking the risk to the medicine	Post marketing reports - Clinical Studies
Risk factors and risk groups	Paediatric patients when weight adjustments are required.
Risk minimisation measures	Sections 4.1, 4.2 in the EU SmPC
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 8. Important Potential Risk: Effect on reproductive hormone levels in pubertal/ post-pubertal children	
Evidence for linking the risk to the medicine	Post-marketing reports, IOS registry, Study HGT-FIR-086, Study HGT-FIR-062.
Risk factors and risk groups	Pubertal and post pubertal children.
Risk minimisation measures	Sections 4.6 in the EU SmPC
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 9. Use of Firazyr in Pregnant/Lactating Women	
Risk minimisation measures	Text in the SmPC: Section 4.6 Fertility, pregnancy and lactation
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS)

Table 10. Use of Firazyr in Children less than 2 years of Age	
Risk minimisation measures	Text in the SmPC: Indication in Section 4.1. Section 4.2 (Posology and method of administration)
Additional pharmacovigilance activities	Icatibant Outcome Survey (IOS) None