Summary of risk management plan for Noxafil (posaconazole)

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

Noxafil's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Noxafil should be used. Along with the introduction of the Noxafil gastro-resistant powder and solvent for oral suspension (PFS), the product labeling and package carton will clearly state that Noxafil oral suspension (OS) and Noxafil PFS are not to be used interchangeably. Unlike Noxafil OS, which is a ready-to-use suspension, Noxafil PFS is provided as a powder that must be mixed with the suspending vehicle (also provided in the same product kit) before use. Notch-tip oral dosing syringes, a bottle of suspending vehicle, bottle adapter, mixing cups and a step-by-step Instruction for Use (IFU) are provided to guide the preparation and administration of weight-based dosing of the PFS. Additional syringes will be supplied with Noxafil PFS.

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

I. The Medicine and What It Is Used For

Noxafil (IV and tablet) is indicated for use in the treatment of invasive aspergillosis in adults.

Noxafil is authorised for treatment of the following fungal infections in adults (tablet, IV and oral suspension formulations) and in paediatric patients aged 2 years and above (tablet for patients who weigh greater than 40 kg, IV and PFS formulations):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;

- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor. (approved only in adults for Oral Suspension formulation)

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil is also indicated for prophylaxis of invasive fungal infections in adults (tablet, IV and oral suspension formulations) and paediatric patients aged 2 years and above (tablet for patients who weigh greater than 40 kg, IV and PFS formulations):

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;

- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

See the SmPC for the full indication.

Noxafil contains posaconazole as the active substance and it is given orally or by intravenous injection.

Further information about the evaluation of Noxafil's benefits can be found in Noxafil's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/noxafil

II. Risks Associated With the Medicine and Activities To Minimise or Further Characterise the Risks

Important risks of Noxafil, together with measures to minimise such risks and the proposed studies for learning more about Noxafil'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 the case of Noxafil, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Noxafil is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Noxafil are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Noxafil. 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);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None*
Important potential risks	Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)*
Missing information	Safety in children below 2 years of age*

* The important identified or potential risks included in prior versions of the RMP have been removed based on the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product.

II.B Summary of Important Risks

Table II.B.1: Important Potential Risk: Injury, Poisoning, and Procedural Complications - Medication error – related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)

Evidence for linking the risk to the medicine	There is a risk for medication errors since the 2 oral suspension formulations have different dosage recommendations.
Risk factors and risk groups	None identified
Risk minimisation measures	Communication via healthcare provider and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration) Package leaflet- Section 3 (How to take Noxafil) Outer carton A one-time Direct Healthcare Professional Communication will be distributed to healthcare providers to alert them of the new formulation and that the formulations are not interchangeable. Design of product and packaging

Table II.B.2: Missing Information: Safety in children below 2 years of age

Risk minimisation measures	Communication via healthcare professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) Package leaflet –Section 2, What you need to know before you use Noxafil
Additional pharmacovigilance	There are no additional pharmacovigilance activities for this safety concern. The safety of posaconazole in children will be further characterized in an ongoing clinical trial.

II.C Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Noxafil.

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

There are no studies required for Noxafil.