Part VI: Summary of the risk management plan

Summary of risk management plan for <Metronidazole> 5mg/ml solution for infusion

This is a summary of the risk management plan (RMP) for <Metronidazole> 5mg/ml solution for infusion (hereinafter referred to as METRONIDAZOLE). The RMP details important risks of METRONIDAZOLE, how these risks can be minimised, and how more information will be obtained about METRONIDAZOLE's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

METRONIDAZOLE is authorised in adults and children for the prophylaxis and treatment of infections in which susceptible anaerobic microorganisms have been identified or are suspected to be the cause (see SmPC for the full indication). It contains metronidazole as the active substance and it is given by slow intravenous infusion.

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

Important risks of METRONIDAZOLE, together with measures to minimise such risks and the proposed studies for learning more about METRONIDAZOLE'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, 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 METRONIDAZOLE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of METRONIDAZOLE 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 METRONIDAZOLE. 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).

List of important risks and missing information	
Important identified risks	• Hypersensitivity (e.g. anaphylaxis, angioedema, severe skin reactions) • Disulfiram-like effect • Pseudomembranous colitis • Bone marrow depression and haematopoiesis • Convulsive seizures, myoclonus and peripheral neuropathy • Use in patients with active or chronic severe peripheral and central nervous system diseases • Hepatic impairment • QT interval prolongation/torsade de pointes in coadministration with amiodarone
Important potential risks	• Overgrowth of non-susceptible organisms • Mutagenic and tumorigenic activity in long term therapy • Increased rate of malformations during use in 1st trimester pregnancy • Secretion into breast milk
Missing information	• Use in patients with renal insufficiency • Use in elderly

II.B Summary of important risks

The SmPC proposed by the applicant was initially based on the English translation of the currently approved SmPC of the reference medicinal product, FLAGYL 0,5 POUR CENT, solution injectable pour perfusion en poche, registered in France, by Sanofi Aventis France. However, as commented by the Authorities, SmPCs nationally approved for metronidazole throughout EU Member States have not been part of any European harmonisation procedure and consequently differ in many respects. It was thus felt that the wording of some sections should be brought in line with the existing guidelines. As a

result, the Authorities concluded that the SmPC and PL should be amended according to the recently approved SmPC of Metronidazole Hikma 5 mg/ml solution for infusion (PT/H/1400/001/DC with CMSs: AT/DE/IT/NL/UK, EoP 21-04-2017).

The reference medicinal product does not have additional risk minimization activities and no additional pharmacovigilance activities are requested.

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 METRONIDAZOLE.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for METRONIDAZOLE.