Metronidazole

EU Risk Management Plan

Version 1.0

Nov 2019

Active substance(s) (INN or common name):	Metronidazole
Pharmaco-therapeutic group (ATC Code):	Pharmaco-therapeutic group: Antibacterials for systemic use J01XD01
Name of Marketing Authorisation Holder or Applicant:	Flamingo Pharma (UK) Ltd.
Number of medicinal products to which this RMP refers:	Two (2)
Product(s) concerned (brand name(s)):	Metronidazole 200mg Film-coated Tablets Metronidazole 400mg Film-coated Tablets

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ABBREVIATIONS:

ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse event(s)
ATC	Anatomical-Therapeutic-Chemical Classification
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency; "the Agency"
EU	European Union
EURD	European Union Reference Date
MAH(S)	Marketing Authorisation Holder(s)
N/A	Not applicable
PIL	Patient Information Leaflet
PSUR(s)	Periodic Safety Update Report(s)
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC or SPC	Summary of Product Characteristics

EU Risk Management Plan for Metronidazole 200mg and 400mg Tablets

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 21-Nov-2019

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1. Part I: Product(s) Overview:

Invented name(s) in the European Economic Area (EEA)	Metronidazole 200mg and 400mg Film-coated Tablets
Pharmacotherapeutic group(s) (ATC Code)	ATC code: J01XD01
Marketing Authorisation Holder	Flamingo Pharma (UK) Ltd.
Medicinal products to which this RMP refers	Two (2)
Authorisation procedure	National procedure
Brief description of product chemical class, summary mode of action, important information about its composition).	Pharmaco-therapeutic group: Antibacterials for systemic use. Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardia lamblia* and against anaerobic bacteria. Metronidazole 200mg and 400mg Film coated Tablets contains Cellulose Microcrystalline, Hydroxypropylcellulose, Silica Colloidal anhydrous, Crospovidone, Stearic acid. Metronidazole 200mg Film coated Tablets : Opadry White. Metronidazole 400mg Film coated Tablets : Opadry Yellow.
Hyperlink to the Product Information	SmPC200mg SmPC400mg PIL
Indication(s) in the EEA	Metronidazole 200mg and 400mg Tablets is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause. Metronidazole 200mg and 400mg Tablets are active against a wide range of pathogenic micro-organisms notably species of *Bacteroides*, *Fusobacteria*, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

	It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*. Metronidazole 200mg and 400mg Tablets is indicated in adults and children for the following indications: 1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci. 2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated. 3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male. 4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis). 5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers). 6. Giardiasis. 7. Acute ulcerative gingivitis. 8. Anaerobically-infected leg ulcers and pressure sores. 9. Acute dental infections (e.g. acute pericoronitis and acute apical infections). Considerations should be given to official guidance on the appropriate use of antibacterial agents.
Posology and route of administration in the EEA	Metronidazole 200mg and 400mg Tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal. *Prophylaxis against anaerobic infection:* Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery. **Adults** 400 mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

Children

Children < 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery. Newborns with a gestation age < 40 weeks: 10mg/kg body weight as a single dose before operation

Anaerobic infections: The duration of a course of Metronidazole 200mg and 400mg Tablets treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.

Treatment of established anaerobic infection:

Adults

800 mg followed by 400 mg 8 hourly.

Children

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours. In newborns with a gestation age < 40 weeks, accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Protozoal and other infections:

Dosage is given in terms of metronidazole or metronidazole equivalent					
	Duration of dosage in days	Adults and children over 10 years	Children		
			7 to 10 years	3 to 7 years	1 to 3 years

	Urogenital trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently	7 or 5-7	2000mg as a single dose or 200 mg three times daily or 400mg twice daily	40mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2-3 doses; not to exceed 2000mg/dose		
	Bacterial vaginosis	5-7 or	400 mg twice daily			
		1	2000mg as a single dose			
	Amoebiasis (a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three times daily	200 mg four times daily	200 mg three times daily
	(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5-10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
	(c) Amoebic liver abscess	5	400 mg three	200 mg three	100 mg	100 mg

also other forms of extra-intestinal amoebiasis		times daily	times daily	four times daily	three times daily
(d) Symptomless cyst passers	5-10	400-800 mg three times daily	200-400 mg three times daily	100-200 mg four times daily	100-200 mg three times daily
	Alternatively, doses may be expressed by body weight 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day				
Giardiasis	3	2000mg once daily or	1000mg once daily	600-800 mg once daily	500 mg once daily
	5	400mg three times daily Or			
	7-10	500mg twice daily			
	Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.				
Acute ulcerative gingivitis	3	200 mg three times	100 mg three times	100 mg twice	50 mg three times

			daily	daily	daily	daily
	Acute dental infections	3-7	200 mg three times daily			
	Leg ulcers and pressure sores	7	400 mg three times daily			
	Children and infants weighing less than 10 kg should receive proportionally smaller dosages. Elderly: Metronidazole 200mg and 400mg Tablets is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.					
	Eradication of Helicobacter pylori in paediatric patients: As a part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy. **Route of administration:** oral					
Pharmaceutical form(s) and strengths	Metronidazole 200mg Film-coated Tablets : White to off white, circular, biconvex, film coated tablets with '200' debossed on one side and plain on other side. Metronidazole 400mg Film-coated Tablets : Yellow, circular, biconvex, film coated tablet with '400' debossed on one side and plain on other side.					
Is/will the product be subject to additional monitoring in the EU?	No					

2. Part II: Safety specification:

Part II of this EU Risk Management Plan provides a synopsis of the safety profile of the medicinal products. It consists of eight RMP modules of which RMP modules SI to SIV and SVI to SVII will be omitted since the application refers to a generic medicinal product. Module SV will be omitted since this EU RMP version is not an update.

2.1 Module SI: Epidemiology of the indication(s) and target population(s)

Not applicable

2.2 Module SII: Non-clinical part of the safety specification

Not applicable

2.3 Module SIII: Clinical trial exposure

Not applicable

2.4 Module SIV: Populations not studied in clinical trials

Not applicable

2.5 Module SV: Post-authorisation experience

Not applicable

2.6 Module SVI: Additional EU requirements for the safety specification

Not applicable

2.7 Module SVII: Identified and potential risks

Not applicable

2.8 Module SVIII: Summary of the safety concerns

- important identified risk;
- important potential risk;
- Missing information.

Table 1. Summary of safety concerns:

The safety concerns proposed for Metronidazole 200mg and 400mg Film-coated Tablets are summarized in the following table:

Summary of safety concerns	
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*

3. Part III: Pharmacovigilance Plan:

The objective of pharmacovigilance strategy is to systematically collect ADRs from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals. Early detection of safety signals enables MA holder to develop and implement appropriate risk management strategy. The objective of the routine surveillance program conducted by the MA holder is to systematically review safety data from multiple sources. The purpose of surveillance is to detect and evaluate changes in reporting frequency of AEs and changes in overall adverse event pattern suggestive of potentially new safety concerns.

The routine pharmacovigilance practices comply with the pharmacovigilance practices covered in regulations 2010/84; 1235/2010 and the associated "Guidelines on good pharmacovigilance practices (GVP)".

III.1 Routine Pharmacovigilance activities*:*

Routine Pharmacovigilance activities such as ADR collection and reporting and signal detection are mentioned in pharmacovigilance system master file (i.e., PSMF) which is sufficient for this RMP.

III.2 Additional Pharmacovigilance activities:

No additional Pharmacovigilance activities are required. Pharmacovigilance activities described in Part III.1 (i.e., Routine Pharmacovigilance activities) are considered sufficient to monitor the benefit-risk profile of Metronidazole Tablets and detect any safety concerns.

III.3 Summary table of additional Pharmacovigilance activities:

Not applicable.

4. Part IV: Plans for post-authorisation efficacy studies:

Not applicable.

This new application refers to a generic medicinal product and the reference product has no additional pharmacovigilance activities.

5. Part V: Risk minimisation measures:

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

V.1. Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

Not Applicable

V.3 Summary of risk minimisation measures

Not Applicable

6. Part VI: Summary of risk management plan for Metronidazole 200mg and 400mg Tablets:

This is a summary of the risk management plan (RMP) for Metronidazole 200mg and 400mg Tablets. The RMP details important risks of Metronidazole 200mg and 400mg Tablets, how risks of 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, overgrowth of non-susceptible organisms, mutagenic and tumorigenic activity in long term therapy, increased rate of malformations during use in 1st trimester pregnancy and secretion into breast milk 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 200mg and 400mg Tablets is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.
Metronidazole 200mg and 400mg Tablets is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides, Fusobacteria*, *Clostridia, Eubacteria*, *anaerobic cocci* and *Gardnerella vaginalis*. It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*.

Metronidazole 200mg and 400mg Tablets is indicated in adults and children for the following indications:

1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.
2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.
3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).

5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
6. Giardiasis.
7. Acute ulcerative gingivitis.
8. Anaerobically-infected leg ulcers and pressure sores.
9. Acute dental infections (e.g. acute pericoronitis and acute apical infections).

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Metronidazole 200mg and 400mg Tablets are given orally.

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

Important risks of Metronidazole 200mg and 400mg Tablets, 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 the case of Metronidazole, 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 Metronidazole 200mg and 400mg Tablets is not yet available, it is listed under 'missing information' below.

Summary of safety concerns	
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. A List of important risks and missing information

Important risks of Metrnidazole 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 Metrnidazole. 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);

Summary of safety concern	
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*

Summary of safety concern	
Missing information	• *Use in patients with renal insufficiency* • *Use in elderly*

II.B Summary of important risks

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

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 Metrnidazole.

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

There are no studies required for Metronidazole.

7. Part VII: Annexes:

Annex 1 – Eudravigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 - Summary of changes to the risk management plan over time

Annex 1 – Eudravigilance Interface

Not applicable

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Not applicable.

Annex 8 - Summary of changes to the risk management plan over time

Not applicable.