



Public Assessment Report

National Procedure

Metronidazole 200 mg Film-coated Tablets
Metronidazole 400 mg Film-coated Tablets

(metronidazole)

PL 43461/0067-0068

Flamingo Pharma UK Ltd.

LAY SUMMARY

Metronidazole 200 mg Film-coated Tablets Metronidazole 400 mg Film-coated Tablets (metronidazole)

This is a summary of the Public Assessment Report (PAR) for Metronidazole 200 and 400 mg Film-coated Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Metronidazole Tablets in this lay summary for ease of reading.

For practical information about using Metronidazole Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Metronidazole Tablets and what are they used for?

These applications are for generic medicines. This means that these medicine are the same as, and considered interchangeable with, reference medicines already authorised in the United Kingdom (UK) called Flagyl 200 mg and 400 mg Tablets.

Metronidazole Tablets can be used to:

- Treat infections of the blood, brain, lung, bones, genital tract, pelvic area, stomach and intestines
- Treat gum ulcers and other dental infections
- Treat infected leg ulcers and pressure sores
- Prevent infections after surgery

How do Metronidazole Tablets work?

Metronidazole Tablets contain an active ingredient called metronidazole. This belongs to a group of medicines called antibiotics. It works by killing bacteria and parasites that cause infections in the body.

How are Metronidazole Tablets used?

The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (via the mouth).

The patient should always take Metronidazole Tablets exactly as their doctor has told them. It is important to finish a full course of treatment. The length of a course will depend on the patient's needs and the illness being treated.

The patient should check with their doctor or pharmacist if they are not sure.

- Swallow the tablets whole with a drink of water
- Do not crush or chew the tablets
- Take these tablets during or just after a meal
- The dose of Metronidazole Tablet will depend on the patient's needs and the illness being treated
- The length of treatment will depend on the type of illness the patient has and how bad it is

The usual dose for adults and children is given below:

To treat bacterial infection**Adults**

- The initial dose is 800mg
- After 8 hours take another dose of 400 mg and repeat this dose every 8 hours

Children

- The patient's doctor will work out how much the child should take depending on their weight
- Repeat the dose every 8 hours
- If the child is a baby under 8 weeks of age, their doctor will give them one daily dose or two separate doses 12 hourly

To prevent infections from happening after surgery**Adults**

- Start taking Metronidazole Tablets 24 hours before the operation
- Take 400 mg of Metronidazole Tablets every 8 hours
- After the operation the patient may be given Metronidazole Tablets either through a drip into a vein or rectally as a suppository until they are able to take tablets again

Children

- Give the child Metronidazole Tablets 1-2 hours before their operation
- The patient's doctor will work out how much the child should take depending on their weight
- After the operation the child may be given Metronidazole Tablets either through a drip into a vein or rectally as a suppository until they are able to take tablets again

Other types of infections

For treatment of other infections caused by parasites and some bacteria the patient's doctor will decide how much Metronidazole Tablets they need to take and how often. This will depend on their illness and how bad it is. The pharmacist's label on the packaging will tell the patient how many tablets to take and how often to take them.

People having kidney dialysis

Kidney dialysis removes Metronidazole Tablets from the blood. If the patient is having kidney dialysis they must take this medicine after their dialysis treatment.

People with liver problems

The patient's doctor may tell them to use a lower dose or to use the medicine less often.

For further information on how Metronidazole Tablets are used, refer to the PIL and Summaries of Product Characteristics available (SmPCs) on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Metronidazole Tablets have been shown in studies?

Metronidazole Tablets are generic medicines that fulfil criteria meaning that no additional studies are required. Metronidazole Tablets have been considered generic medicines of the reference medicines based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Metronidazole Tablets?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Metronidazole Tablets are generic medicines, their benefits and possible side effects are considered to be the same as for the reference medicines.

Why were Metronidazole Tablets approved?

It was concluded that, Metronidazole Tablets have been shown to be comparable to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Metronidazole Tablets?

A Risk Management Plan (RMP) has been developed to ensure that Metronidazole Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Metronidazole Tablets

Marketing Authorisations for Metronidazole Tablets were granted in the United Kingdom (UK) on 31 March 2021

The full PAR for Metronidazole Tablets follows this summary.

This summary was last updated in May 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Metronidazole 200 and 400 mg Film-coated Tablets (PL 43461/0067-0068) could be approved.

Metronidazole 200 and 400 mg Film-coated Tablets are indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Metronidazole 200 and 400 mg Film-coated Tablets are active against a wide range of pathogenic micro-organisms notably species of *Bacteroides*, *Fusobacteria*, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

They also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*.

Metronidazole 200 and 400 mg Film-coated Tablets are 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 v aginosis 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

These applications were submitted under Regulation 51 of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicines of suitable originator medicinal products, Flagyl 200 mg and 400 mg Tablets that have been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

A biowaiver was submitted with these applications, which was accepted. No bioequivalence study was required and no new clinical studies were provided with these applications.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 31 March 2021.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 200 mg or 400 mg metronidazole.

In addition to metronidazole, these products also contain microcrystalline cellulose, crospovidone, hydroxypropylcellulose, colloidal anhydrous silica and stearic acid. The 200 mg strength also contains opadry white (consisting of HPMC 2910 (E464), titanium dioxide (E171), and macrogol (E1521)) and the 400 mg strength also contains opadry yellow (consisting of HPMC 2910 (E464), titanium dioxide (E171), macrogol (E1521) and iron oxide yellow (E172)).

Metronidazole 200 and 400 mg Film-coated Tablets are available in cartons containing blister packs of aluminium-PVC/PVDC foil of 7's, 10's, 14's, 21's, 28's, 30's, 84's and 100's along with a leaflet inside and HDPE bottles of 100's and 250's in a carton along with a leaflet inside.

Not all pack sizes may be marketed

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

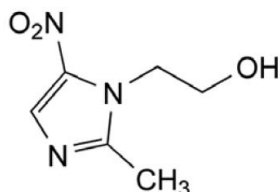
II.2 ACTIVE SUBSTANCE

rINN: Metronidazole

Chemical Name: 2-(2-Methyl-5-nitro-1 H-imidazol-1-yl) ethanol

Molecular Formula: $C_6H_9N_3O_3$

Chemical Structure:



Molecular Weight: 171.2

Appearance: White or yellowish, crystalline powder.

Solubility: Slightly soluble in water, in acetone, in alcohol and in methylene chloride.

Metronidazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of metronidazole are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of metronidazole are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics

No new pharmacokinetic data have been submitted for these applications and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Flagyl 200 mg and 400mg tablets.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with the requirements of Regulation 267 of The Human Medicines Regulations 2012, as amended (previously article 61(1) of Council Directive 2001/83/EC).

The PIL has been evaluated via a user consultation with target patient groups in accordance with the requirements of Regulation 260(3) of The Human Medicines Regulations 2012, as amended (previously Article 59(3) of Council Directive 2001/83/EC) on the basis of a

bridging report making reference to Flagyl 200 mg and 400mg tablets (PL 04425/0745-0746; Sanofi, UK) for PIL content and Metronidazole 200 mg, 400 mg and 500 mg Tablets (PL 36722/071-073; Rx Farma) for PIL layout. The bridging report submitted by the applicant is acceptable.

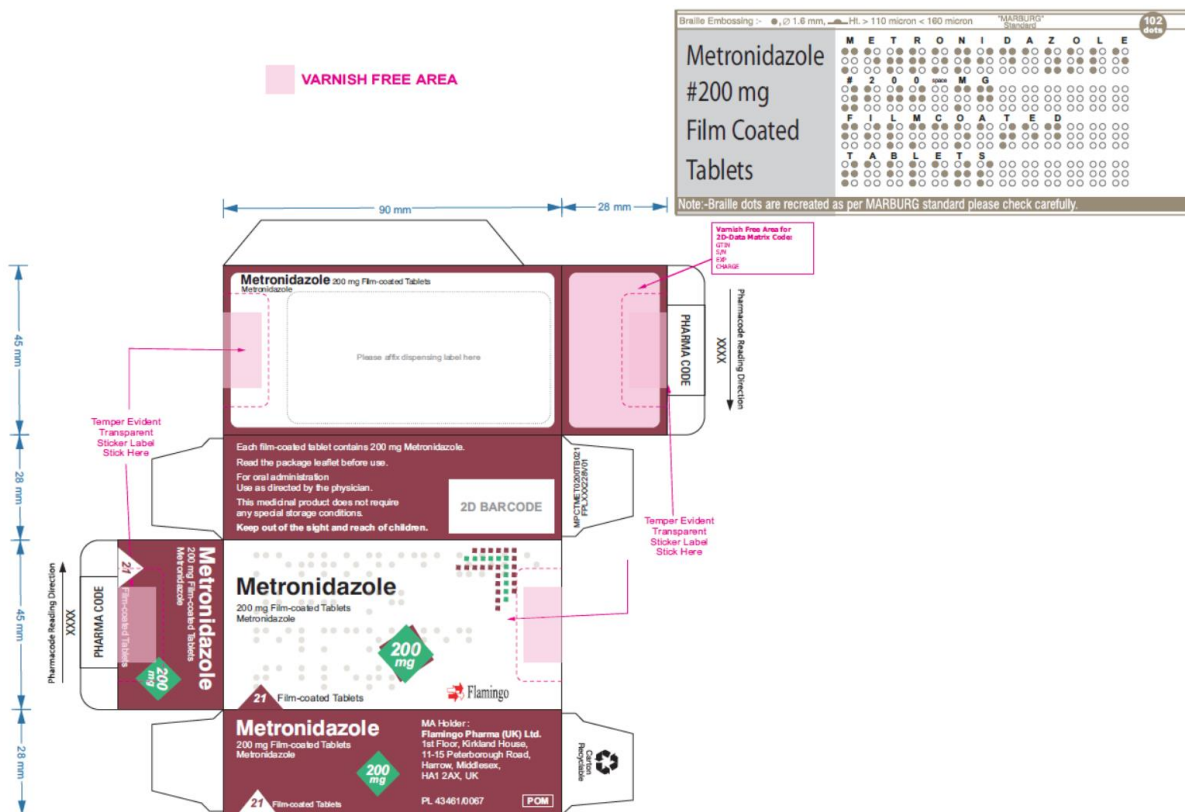
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

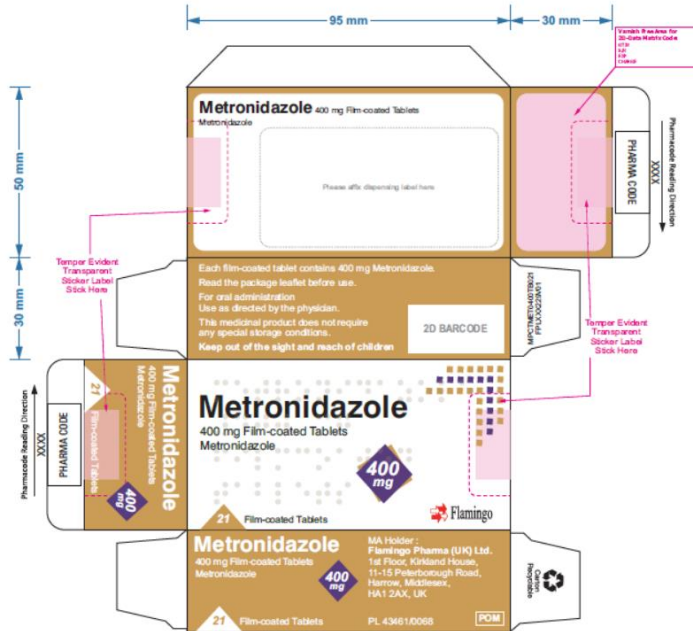
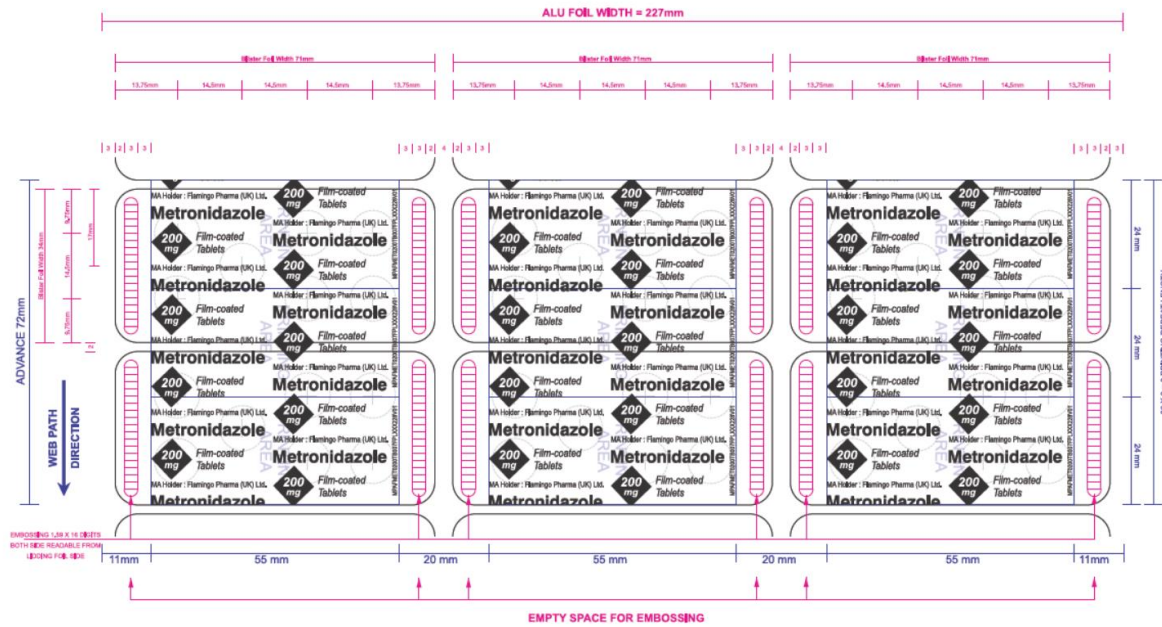
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with metronidazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Regulation 203(2) of The Human Medicines Regulation 2012, as amended, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.





Braille Embossing - @ 1.8 mm, > 110 micron < 180 micron

Metronidazole
#400 mg
Film Coated
Tablets

103

M E T R O N I D A Z O L E
4 0 0 m g
F I L M C O A T E D
T A B L E T S

Note:-Braille dots are recreated as per MARBURG standard please check carefully.



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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N