Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Metronidazole 200 mg Tablets
Metronidazole 400 mg Tablets
Metronidazole 500 mg Tablets

(metronidazole)

PRODUCT LICENCE NUMBERS:
PL 30684/0307-0309

DAWA Limited.

LAY SUMMARY

Metronidazole 200, 400 & 500 mg Tablets (metronidazole)

This is a summary of the Public Assessment Report (PAR) for Metronidazole 200, 400 & 500 mg Tablets. It explains how this 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.

For practical information about using Metronidazole 200, 400 & 500 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Metronidazole 200, 400 & 500 mg Tablets and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Flagyl 200, 400 and 500mg Tablets.

Metronidazole 200 and 400 mg 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

Metronidazole 500 mg Tablets can be used to treat:
- Infections, caused by bacteria of the blood, brain, bone, lung, stomach lining and pelvic area, following childbirth or in a wound following an operation
- Urinary or genital infections caused by a parasite, Trichomonas
- Genital infection in women caused by bacteria
- The parasitic diseases amoebiasis
- The disease giardiasis
- Gum and teeth infections
- Infected leg ulcers or pressure sores
- Stomach ulcers caused by Helicobacter pylori.
- Or prevent infections occurring after operations

How do Metronidazole 200, 400 & 500 mg Tablets work?
Metronidazole 200, 400 & 500 mg Tablets contain the active substance metronidazole. Metronidazole belongs to a group of medicines called antibiotics. It works by killing bacteria and parasites that cause infections in the body.

How are Metronidazole 200, 400 & 500 mg 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 this medicine 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.

For Metronidazole 200 mg and 400 mg Tablets:
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 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 800 mg
- 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, the patient's doctor will give them one daily dose or two separate doses 12 hourly

To prevent infections from happening after surgery
Adults

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

Children

- The child should be given metronidazole 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 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 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 them how many tablets to take and how often to take them.

People having kidney dialysis
Kidney dialysis removes metronidazole 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 Metronidazole 500 mg Tablets:
Swallow the tablets whole, during or after meals, with a glass of water. Do not chew them.

The recommended dose is: For doses less than 500mg (one tablet) an alternative dosage form should be used.

To treat bacterial infection
Adults and children over 10 years: 800mg followed by 400mg at eight hourly intervals. Treatment is usually for 7 days but will depend upon the patient's condition.

To treat anaerobic infections
- Children 8 weeks-12 years: 20-30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours for 7 days. The daily dose may be increased to 40mg/kg, depending on the severity of the infection.
- Children under 8 weeks: 15mg/kg/day as a single dose or divided into 7.5mg/kg every 12 hours.
- Children under 10 years: A more suitable dosage form should be used for this age group.

To treat infection caused by Trichomonas
- Adults and adolescents: 2g as a single dose, or 200mg three times a day for 7 days, or 400mg twice a day for 5-7 days. The patient's partner should also be treated.
- Children under 10 years: 40mg/kg as a single dose or 15-30mg/kg/ day two to three times daily for 7 days. Doses should not exceed 2000mg/dose.
- Children under 10 years: A more suitable dosage form should be used for this age group

To treat non-specific genital infection in women
- Women: 400mg twice a day for 7 days, or 2g as a single dose for 1 day only.
- Adolescent girls: 400mg twice daily for 5 to 7 days or 2g as a single dose.

To treat amoebiasis
- Adults and children over 10 years: 400mg-800mg three times a day for 5 to 10 days.
- Children 7-10 years: 200mg-400mg three times a day for 5 to 10 days.
- Children 3-7 years: 100mg-200mg four times daily for 5 to 10 days.
- Children 1-3 years: 100mg-200mg three times daily for 5 to 10 days. Or 35-50mg/kg/day in 3 divided doses for 5 to 10 days.
- Children under 7 years: A more suitable dosage form should be used for this age group.

To treat giardiasis
- Adults and children over 10 years: 2g once a day for 3 days, or 400mg three times a day for 5 days or 500mg twice daily for 7 to 10 days.
- Children 7-10 years: 1 g once a day for 3 days.
- Children 3-7 years: 600mg-800mg once daily for 3 days.
- Children 1-3 years: 500mg once daily for 3 days. Or 15-40mg/kg/ day divided in two to three doses.
- Children under 7 years: A more suitable dosage form should be used for this age group.

To treat infections of the gums (for 3 days) or teeth (for 3-7days)

- Adults and children over 10 years: 200mg three times a day.

To treat infected leg ulcers or pressure sores (for 7 days)

- Adults and children over 10 years: 400mg three times a day.

To treat stomach ulcers caused by Helicobacter pylori

- To be taken as directed by the patient's doctor as part of a course with two other medicines.

To prevent infections after surgery

- Adults: 1g as a single dose 24 hours before surgery then, 400mg at 8 hourly intervals during the 24 hours before the operation.
- Children under 12 years: 20-30mg/kg as a single dose 1-2 hours before the operation.
- Newborns with a gestation age less than 40 weeks: 10 mg/kg body weight as a single dose before operation.
- Children under 10 years: A more suitable dosage form should be used for this age group.

If the patient is elderly or has liver disease, it is particularly important to take this medicine exactly as directed by the doctor.

For further information on how Metronidazole 200, 400 & 500 mg Tablets are used, refer to the package leaflets and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

What benefits of Metronidazole 200, 400 & 500 mg Tablets have been shown in studies?
Because Metronidazole 200, 400 & 500 mg Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Metronidazole 200, 400 & 500 mg Tablets?
Because Metronidazole 200, 400 & 500 mg Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflets or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Metronidazole 200, 400 & 500 mg Tablets approved?
It was concluded that, in accordance with EU requirements, Metronidazole 200, 400 & 500 mg Tablets have been shown to be comparable to and to be bioequivalent 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 200, 400 & 500 mg Tablets?

A Risk Management Plan (RMP) has been developed to ensure that Metronidazole 200, 400 & 500 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets, 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 200, 400 & 500 mg Tablets
Marketing Authorisations for Metronidazole 200, 400 & 500 mg Tablets were granted in the UK on 10 February 2020.

The full PAR for Metronidazole 200, 400 & 500 mg Tablets follows this summary.

This summary was last updated in March 2020.

TABLE OF CONTENTS

Contents

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, 400 & 500 mg Tablets (PL 30684/0307-309) could be approved.

The products are approved for the following indications:
Metronidazole 200 mg and 400 mg Tablets:
Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Metronidazole 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 is indicated in adults and children for the following indications:

- The prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroides* and anaerobic streptococci.
- 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.
- Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
- Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).
- All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
- Giardiasis.
- Acute ulcerative gingivitis.
- Anaerobically-infected leg ulcers and pressure sores.
- Acute dental infections (e.g. acute pericoronitis and acute apical infections).

Metronidazole 500 mg Tablets:
Metronidazole is active against a wide range of pathogenic micro-organisms, notably species of *Bacteroids, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci and Gardnerella vaginalis.*

It is also active against *Trichomonas vaginalis, Entamoeba histolytica, Gardia lamblia, Balantidium coli and Helicobacter pylori.*

Metronidazole is indicated in adults and children for the following indications:

- Prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroids* and anaerobic streptococci.
- 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.
- Urogenital trichomoniasis in the female (Trichomonas vaginalis), and in man.

- Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginalis).
- All forms of amoebiasis (intestinal and extra-intestinal disease and asymptomatic cyst passers).
- Giardiasis.
- Acute ulcerative gingivitis.
- Acute dental infections (eg acute pericoronitis and acute apical infections)
- Anaerobically-infected leg ulcers and pressure sores.
- Treatment of Helicobacter pylori infection associated with peptic ulcer as part of triple therapy.

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

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.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Flagyl 200, 400 and 500mg Tablets that have been licensed within the EU 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 based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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.

Marketing authorisations were granted for these products on 10 February 2020.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 200 mg. 400 mg or 500 mg of metronidazole.

In addition to metronidazole, these products also contain the excipients:

Tablet core:

Anhydrous calcium hydrogenphosphate, pregelatinized maize starch, povidone (PVP K30), maize starch, crospovidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Tablet coat:

Hypromellose and polyethylene glycol 400.

The finished products are packaged in aluminium and PVC foil blisters in pack sizes of 14, 21 & 100 tablets. 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 European regulations concerning materials in contact with food.

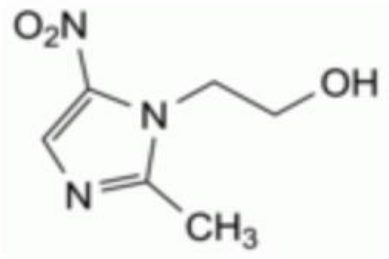
II.2 ACTIVE SUBSTANCE

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 PRODUCT

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.

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 formulae 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 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 36 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 is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

STUDY

This study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Metronidazole 500 mg Tablets versus the reference product Flagyl 500mg Tablets in subjects under fasted conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 500 mg tablet) of the test or reference product. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 6 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table: Summary of bioequivalence conclusion for metronidazole

Parameters	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% CI (%)	Intra Subject (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (ng/ml)	9.5537	9.5138	14096.064	13545.556	104.06	95.51 - 113.39	20.07	99.45
Ln (AUC_{0-t}) (hr *ng/ml)	11.9357	11.9342	152626.02	152383.89	100.16	97.57 - 102.81	6.07	100.0

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 500 mg product strength can be extrapolated to the other strengths.

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

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

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.

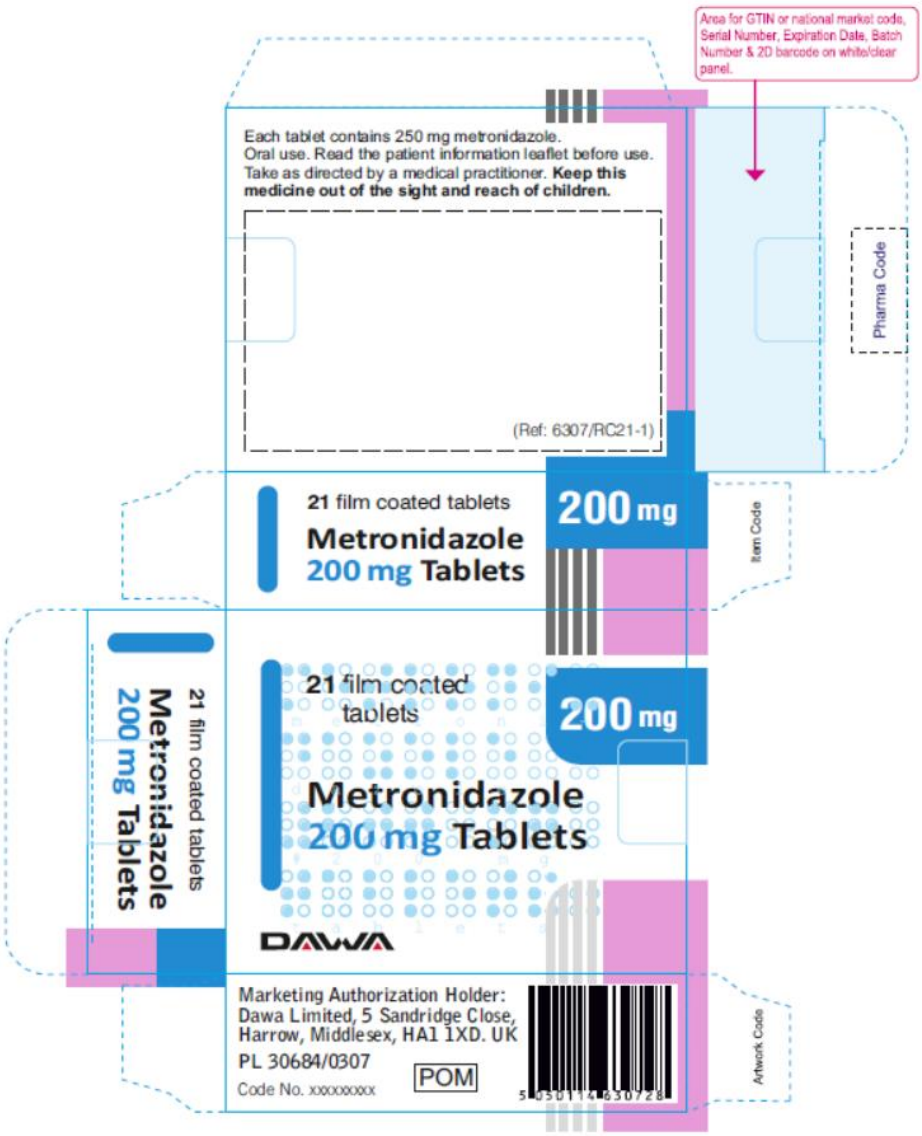
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product(s).

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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

Marburg Medium
Pharmabraille Fonts

Metroni-dazole #200 mg tablets

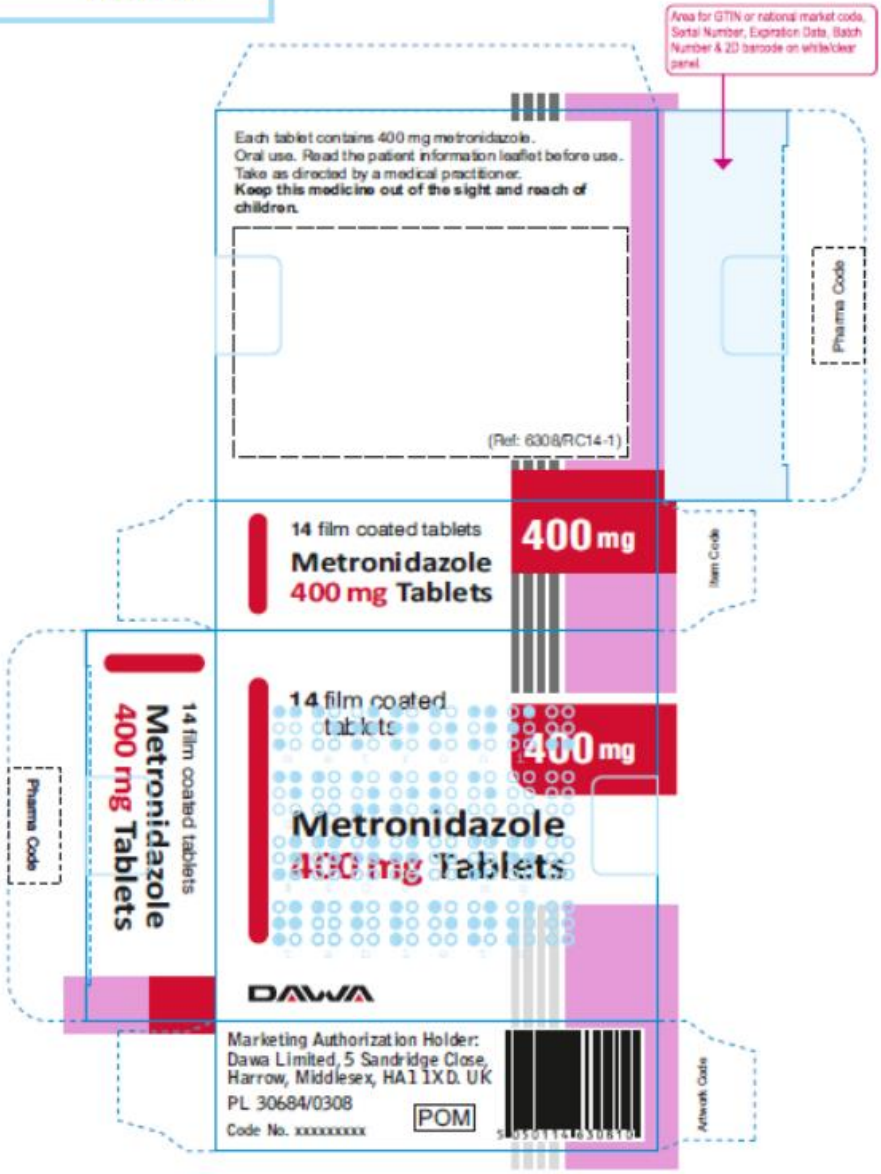


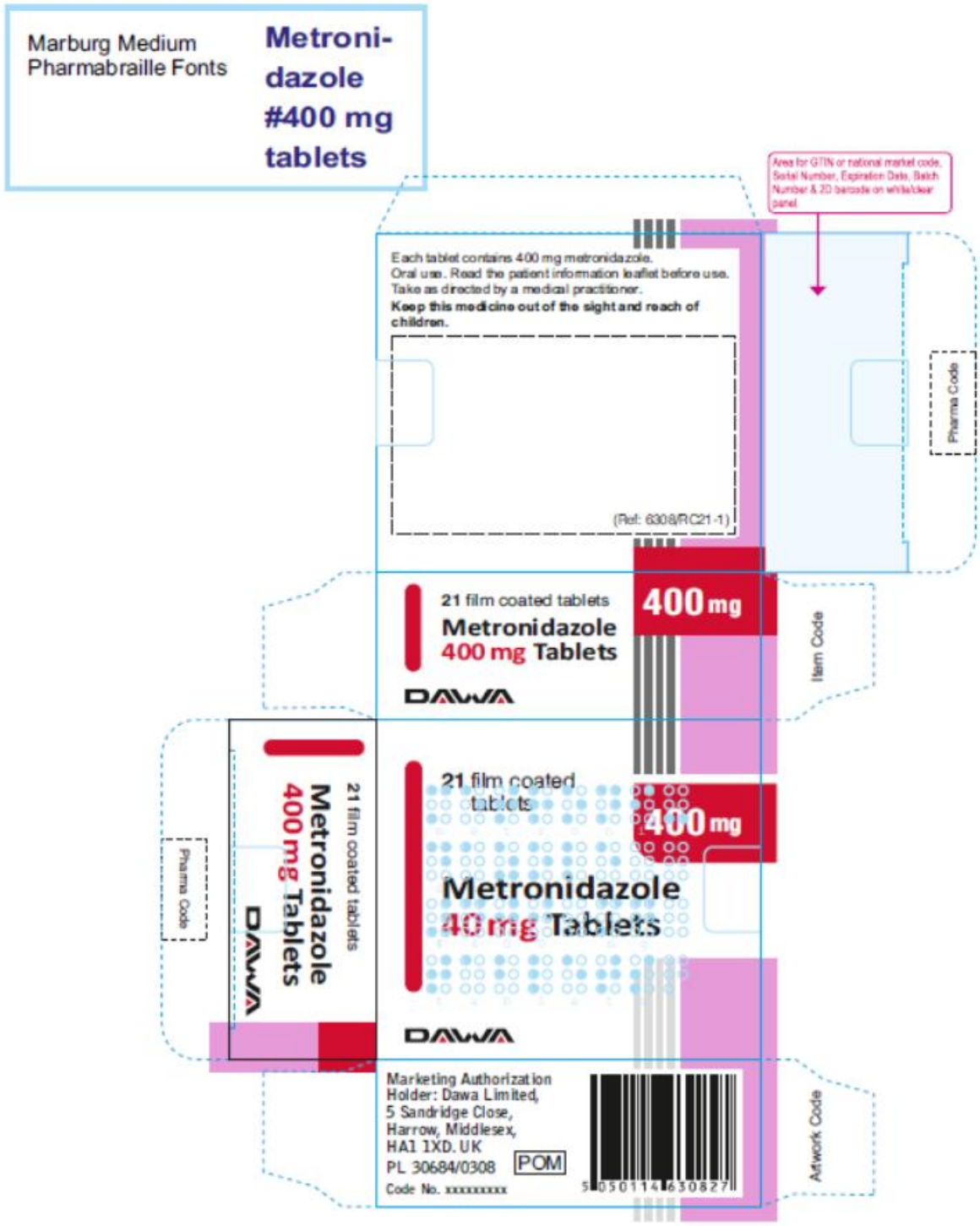

Metronidazole 200 mg
Tablets
Dawa Limited
EMPTY SPACE FOR EMBOSSING AREA
32mm


Metronidazole 200 mg
Tablets
Dawa Limited
32 mm
PRINT REPEAT

Marburg Medium
Pharmabraille Fonts

Metroni-dazole #400 mg tablets

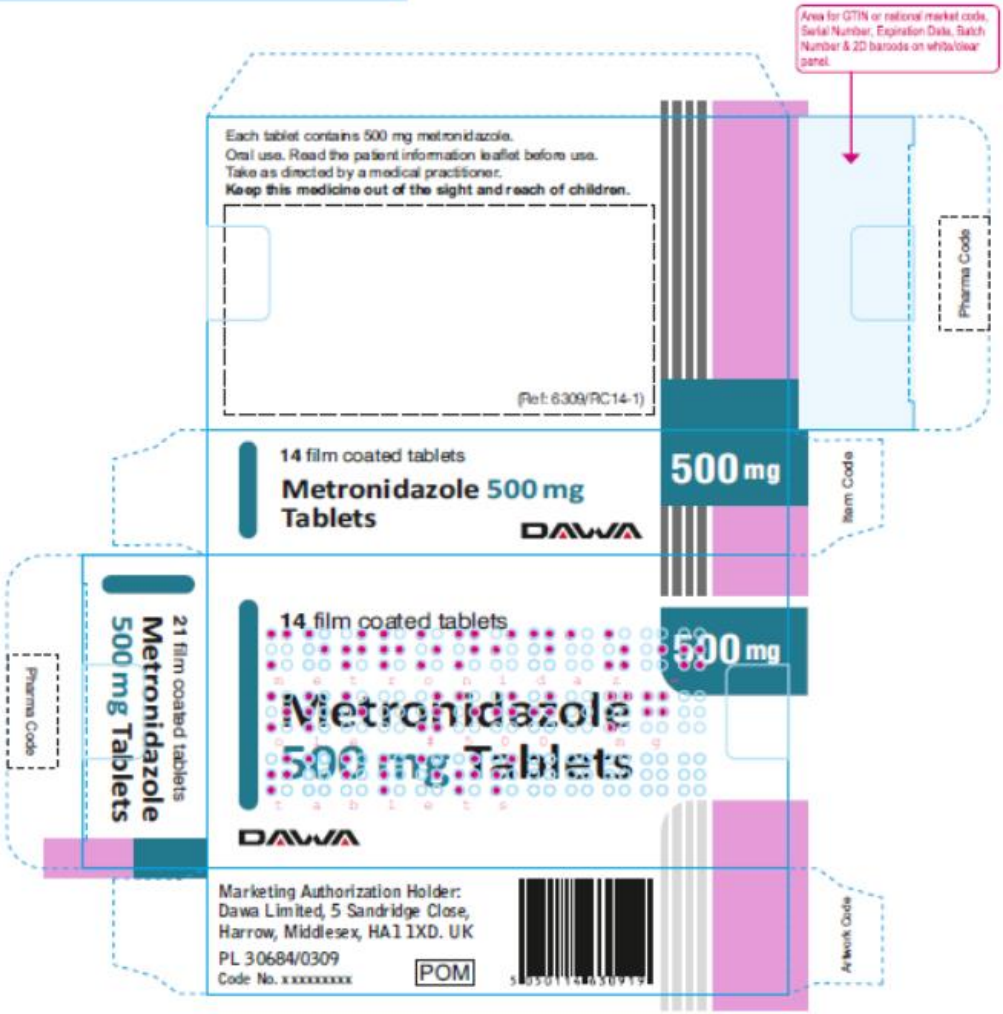


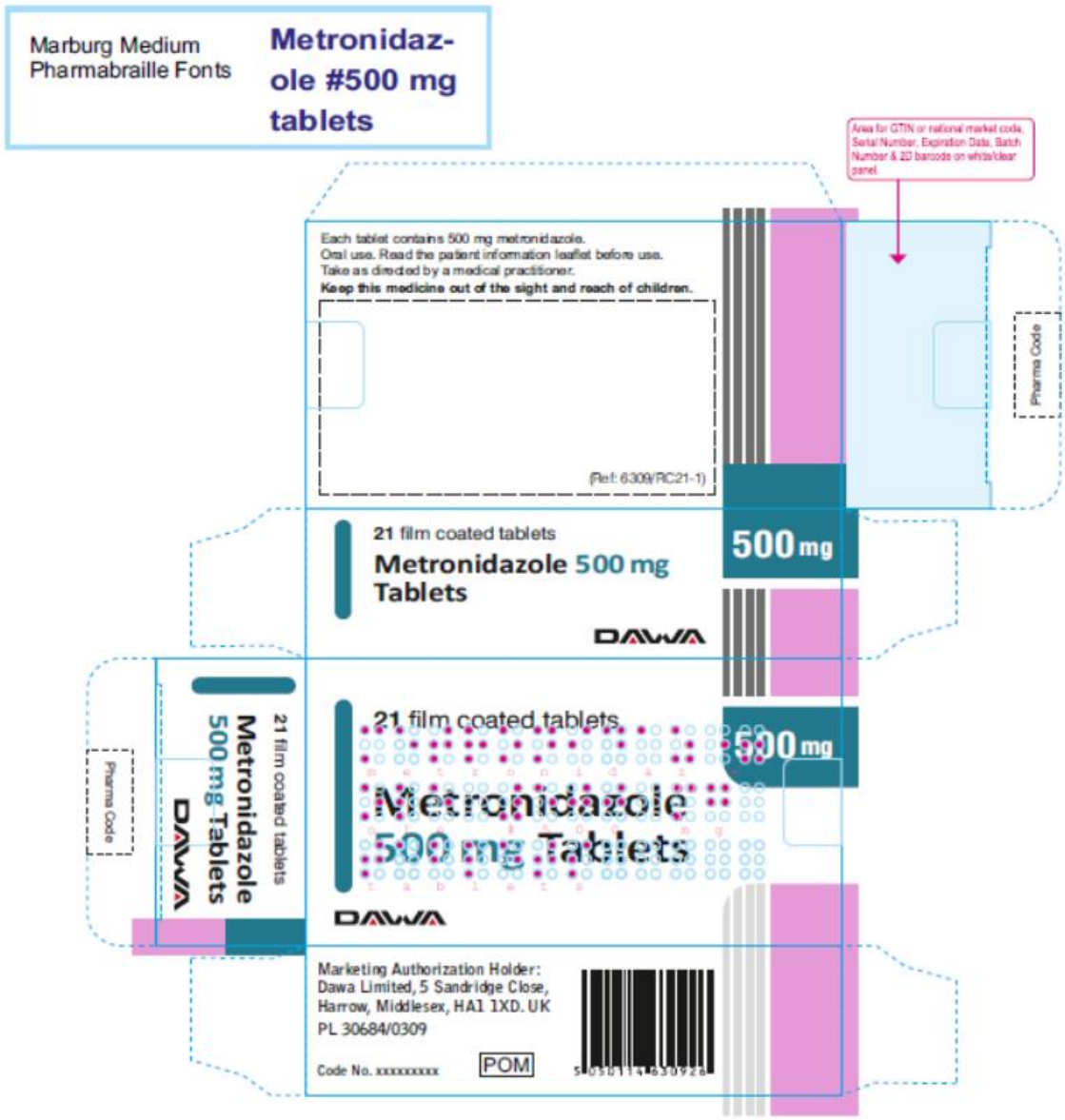

Marburg Medium
Pharmabraille Fonts
Metroni-
dazole
#400 mg
tablets
Area for GTIN or national market code, Serial Number, Expiration Date, Batch Number & 2D barcode on white/clear panel
Each tablet contains 400 mg metronidazole.
Oral use. Read the patient information leaflet before use.
Take as directed by a medical practitioner.
Keep this medicine out of the sight and reach of children.
Pharma Code
(Ref: 6308/RC21-1)
21 film coated tablets
Metronidazole
400 mg Tablets
400 mg
DAWA
Item Code
21 film coated tablets
Metronidazole
400 mg Tablets
DAWA
Pharma Code
21 film coated tablets
Metronidazole
400 mg Tablets
DAWA
Marketing Authorization Holder: Dawa Limited, 5 Sandridge Close, Harrow, Middlesex, HA1 1XD. UK
PL 30684/0308
POM
Code No. xxxxxxxx
Artwork Code

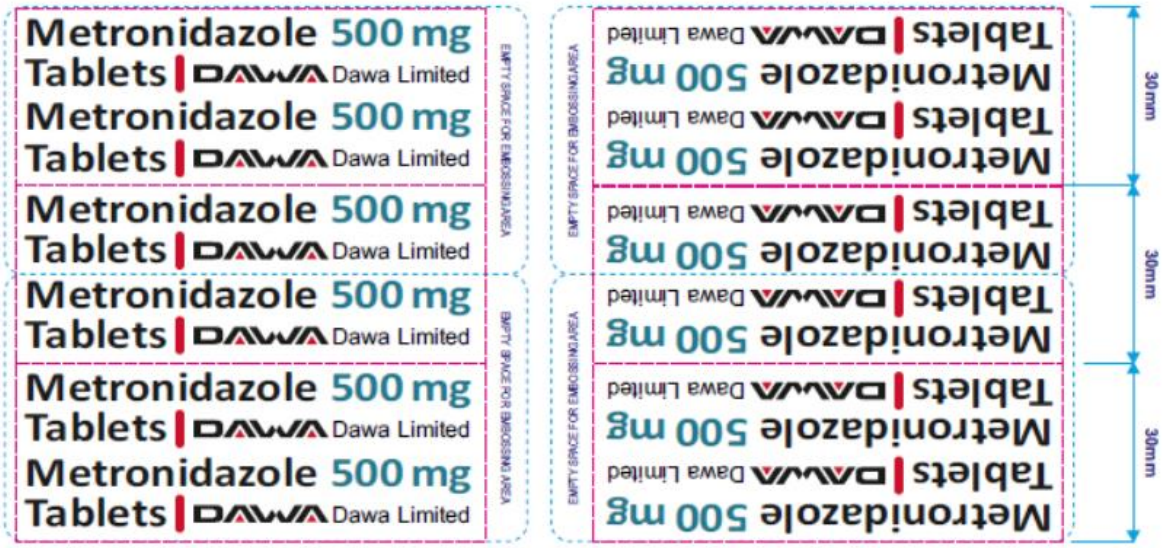

Metronidazole 400 mg
Tablets
Dawa Limited
EMPTY SPACE FOR EMBOSSING AREA
36mm
36 mm
PRINT REPEAT

Marburg Medium Pharmabraille Fonts

Metronidaz-ole #500 mg tablets




Marburg Medium
Pharmabraille Fonts
Metronidaz-
ole #500 mg
tablets
Area for GTIN or national market code, Serial Number, Expiration Date, Batch Number & 2D barcode on white/clear panel
Each tablet contains 500 mg metronidazole.
Oral use. Read the patient information leaflet before use.
Take as directed by a medical practitioner.
Keep this medicine out of the sight and reach of children.
Pharma Code
(Ref: 6309/RC21-1)
21 film coated tablets
Metronidazole 500 mg
Tablets
500 mg
DAWA
21 film coated tablets
Metronidazole
500 mg Tablets
DAWA
Pharma Code
21 film coated tablets
500 mg
Metronidazole
500 mg Tablets
DAWA
Marketing Authorization Holder:
Dawa Limited, 5 Sandridge Close,
Harrow, Middlesex, HA1 1XD. UK
PL 30684/0309
Code No. xxxxxxxx
POM



30 mm
PRINT REPEAT

TABLE OF CONTENT OF THE PAR UPDATE

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**