



## **Public Assessment Report**

**UKPAR**

**Metronidazole 500 mg Film-Coated Tablets**

**(metronidazole)**

**UK Licence Number: PL 31862/0015**

**Creo Pharma Limited.**

## LAY SUMMARY

**Metronidazole 500 mg Film-Coated Tablets**  
(metronidazole)

This is a summary of the Public Assessment Report (PAR) for Metronidazole 500 mg Film-Coated Tablets (PL 31862/0015). It explains how Metronidazole 500 mg Film-Coated Tablets were assessed and why authorisation was recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Metronidazole 500 mg Film-Coated Tablets.

The product will be referred to as Metronidazole 500 mg Film-Coated Tablets throughout the remainder of this PAR.

For practical information about using Metronidazole 500 mg Film-Coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Metronidazole 500 mg Film-Coated Tablets and what are they used for?**

Metronidazole 500 mg Film-Coated Tablets are a 'generic medicine'. This means that Metronidazole 500 mg Film-Coated Tablets are similar to a 'reference medicine' already authorised in the EU called Flagyl 500mg film-coated tablets (Sanofi Aventis, France).

This medicine is used to treat the following:

- Ulcers in the stomach caused by a type of bacteria called *Helicobacter pylori*
- Genital or urinary tract infections caused by a parasite called *Trichomonas*
- Infections of the gums and/or teeth
- Bacterial infection of the genitals in females
- Bacterial infections in:
  - the blood
  - the brain
  - the bones
  - the lungs
  - the stomach lining
  - the pelvic area, after childbirth
  - a wound after an operation
- A parasitic disease called *Giardiasis*
- A parasitic disease called *Amoebiasis*
- Infected leg ulcers or bedsores

Metronidazole can also be used to prevent infections following an operation.

**How do Metronidazole 500 mg Film-Coated Tablets work?**

This medicine contains the active ingredient metronidazole which belongs to a group of medicines called anti-infectives. It works by stopping the growth of certain bacteria and parasites and is effective against a wide variety of micro-organisms.

**How are Metronidazole 500 mg Film-Coated Tablets used?**

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are unsure.

Metronidazole should be taken during or after meals. Swallow the tablets whole, do not crush or chew them.

The recommended dose will vary depending on the condition being treated. Metronidazole should be taken exactly as directed by the patient's doctor.

For doses less than 500mg (one tablet) an alternative dosage form should be used.  
If the patient is elderly or has liver disease, this may affect the dosage their doctor prescribes.

**To treat anaerobic infections**

- Children aged 8 weeks to 12 years: 20-30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection.
- Children under 8 weeks: 15 mg/kg as a single daily dose or divided into 7.5 mg/kg every 12 hours.
- Children under 10 years: a more suitable dosage form should be used.

**To prevent infections after surgery**

- Adults: 1000 mg as a single dose 24 hours before surgery followed by 400 mg at 8 hourly intervals during the 24 hours after the operation.
- Children under 12 years: 20-30 mg/kg as a single dose given 1-2 hours before surgery.
- Newborns with gestation age less than 40 weeks: 10 mg/kg body weight as a single dose before the operation.
- Children under 10 years: a more suitable dosage form should be used.

**Treatment of established infections**

- Adults and children over 10 years: 800 mg followed by 400 mg every 8 hours.
- Children under 10 years: a more suitable dosage form should be used.

**To treat infection caused by Trichomonas**

- Adults and adolescents: 2000 mg as a single dose or 200 mg 3 times a day for 7 days, or 400 mg twice a day for 5-7 days. The patient's partner should also be treated.
- Children under 10 years: 40 mg/kg taken orally as a single dose or 15-30 mg/kg/day divided into 2-3 doses taken over 7 days. Doses should not exceed 2000 mg/dose.
- Children under 10 years: a more suitable dosage form should be used.

**Genital infections in women**

- Adults: 400 mg taken twice daily for 7 days, or 2000 mg as a single dose for 1 day only.
- Adolescents: 400 mg taken twice daily for 5-7 days, or 2000 mg as a single dose.

**To treat amoebiasis**

- Adults and children over 10 years: 400 to 800 mg 3 times a day for 5-10 days.
- Children 7 to 10 years: 200 to 400 mg 3 times a day for 5-10 days.
- Children 3 to 7 years: 100 to 200 mg 4 times a day for 5-10 days.
- Children 1 to 3 years: 100 to 200 mg 3 times a day for 5-10 days, or 35 to 50 mg/kg daily in 3 divided doses for 5-10 days, not exceeding 2400 mg/day.
- Children under 7 years: a more suitable dosage form should be used.

**To treat giardiasis**

- Adults and children over 10 years: 2000 mg once a day for 3 days, or 400 mg three times a day for 5 days, or 500 mg twice daily for 7-10 days.
- Children 7 to 10 years: 1000 mg once a day for 3 days.
- Children 3 to 7 years: 600 to 800 mg once a day for 3 days.
- Children 1 to 3 years: 500 mg once a day for 3 days, or 15-40 mg/kg/day divided into 2-3 doses.
- Children under 7 years: a more suitable dosage form should be used.

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

- Adults and children over 10 years: 200 mg 3 times a day.
- Children under 10 years: a more suitable dosage form should be used.

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

- Adults and children over 10 years: 400 mg 3 times a day.

**To treat stomach ulcers caused by *Helicobacter pylori***

- To be taken as part of a combination therapy as directed by the patient's doctor, 20 mg/kg/day, not exceeding 500 mg twice daily for 7-14 days.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Metronidazole 500 mg Film-Coated Tablets are used, refer to the package leaflet and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Metronidazole 500 mg Film-Coated Tablets can only be obtained with a prescription.

**What benefits of Metronidazole 500 mg Film-Coated Tablets have been shown in studies?**

No additional studies were needed as the company submitted data to support a BCS-based biowaiver in line with the regulatory requirements of 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*).'

**What are the possible side effects of Metronidazole 500 mg Film-Coated Tablets?**

Metronidazole 500 mg Film-Coated Tablets are a generic medicine and are bioequivalent to the reference medicine Flagyl 500mg film-coated tablets (Sanofi Aventis, France) so the benefits and possible side effects are taken as being the same as for the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Metronidazole 500 mg Film-Coated Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Metronidazole 500 mg Film-Coated Tablets approved?**

It was concluded that, in accordance with EU requirements, Metronidazole 500 mg Film-Coated Tablets have been shown to have comparable quality and to be bioequivalent to Flagyl 500mg film-coated tablets (Sanofi Aventis, France). Therefore, the MHRA decided that, as for Flagyl 500mg film-coated tablets (Sanofi Aventis, France), 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 500 mg Film-Coated Tablets?**

A risk management plan (RMP) has been developed to ensure that Metronidazole 500 mg Film-Coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for Metronidazole 500 mg Film-Coated Tablets 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/reviewed continuously.

**Other information about Metronidazole 500 mg Film-Coated Tablets**

A Marketing Authorisation was granted in the UK on 11 October 2018.

The full PAR for Metronidazole 500 mg Film-Coated Tablets follows this summary.

For more information about treatment with Metronidazole 500 mg Film-Coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

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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) granted Creo Pharma Limited, a marketing authorisation for the medicinal product Metronidazole 500 mg Film-Coated Tablets (PL 31862/0015) on 11 October 2018.

Metronidazole 500 mg Film-Coated Tablets are a prescription only medicine (POM) indicated in adults and children for:

- 1) Prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroids* 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 (*Trichomonas vaginalis*), and in man.
- 4) Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or *Gardnerella vaginalis*).
- 5) All forms of amoebiasis (intestinal and extra-intestinal disease and asymptomatic cyst passers).
- 6) Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.
- 7) Giardiasis
- 8) Acute ulcerative gingivitis
- 9) Anaerobically-infected leg ulcers and pressure sores
- 10) Acute dental infections (e.g. acute pericoronitis and acute apical infections).

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

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Flagyl 500mg film-coated tablets (MA no: 331155-1) which was first authorised to Sanofi Aventis, France on 30 September 1988.

Metronidazole has antiprotozoan and antibacterial effects. It is effects against *Trichomonas vaginalis*, *Gardnerella vaginalis* and other protzoa including *Entamoeba histolytica*, *Gardia lamblia* and anaerobic bacteria.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. As the product meets the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*) a Biopharmaceutical Classification System (BCS)-based biowaiver was accepted and bioequivalence studies were not required.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Metronidazole 500 mg Film-Coated Tablets outweigh the risks and a Marketing Authorisation was granted.

## II QUALITY ASPECTS

### II.1 Introduction

Each film-coated tablet contains 500 mg of metronidazole as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

#### Tablet core

Wheat starch, povidone (K30) and magnesium stearate.

#### Film coating

Hypromellose and macrogol (type 20000).

The finished product is packaged in aluminium (25 µm)/PVC (250 µm) blisters and is available in a pack size of 21 tablets.

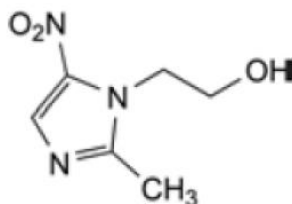
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

### II.2 Drug Substance

INN: Metronidazole

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

Structure:



Molecular formula: C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>

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, metronidazole, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

### II.3 Medicinal Product

#### Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 500 mg, metronidazole per tablet, that are generic versions of the reference product Flagyl 500mg film-coated tablets (Sanofi Aventis, France). A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

### **Manufacture of the products**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale batch size and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches and a satisfactory validation protocol has been provided.

### **Finished Product Specification**

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

### **Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 36 months for the unopened blisters with the storage conditions 'keep blister in the outer carton, protected from light.'

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**

There are no objections to the approval of this application from a pharmaceutical viewpoint.

## **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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### **III.2 Pharmacology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.3 Pharmacokinetics**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.4 Toxicology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.5 Ecotoxicity/environmental risk assessment (ERA)**

Since Metronidazole 500 mg Film-Coated Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.



### III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

## IV CLINICAL ASPECTS

### IV.1 Introduction

The clinical pharmacology of metronidazole is well-known. no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

According to the current guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*, a BCS-based biowaiver may be applicable for the proposed product as qualitatively;

- The drug substance has been proven to exhibit high solubility and complete absorption (BCS class I)
- Either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min ) *in vitro* dissolution characteristics of the test and reference product has been demonstrated
- Excipients that might affect bioavailability are qualitatively and quantitatively the same.

The data provided by the applicant are acceptable and sufficient in terms of the conditions laid down for a BCS-based biowaiver in the guideline on investigation of bioequivalence.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of metronidazole.

Based on the data provided, Metronidazole 500 mg Film-Coated Tablets can be considered bioequivalent to Flagyl 500mg film-coated tablets (Sanofi Aventis, France).

### IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none were required for applications of this type. A BCS-based biowaiver is accepted.

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none are required.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MHRA;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

-  
If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

#### **IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

#### **V User consultation**

The package leaflet 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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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 product 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 product is bioequivalent to the marketed reference product and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.

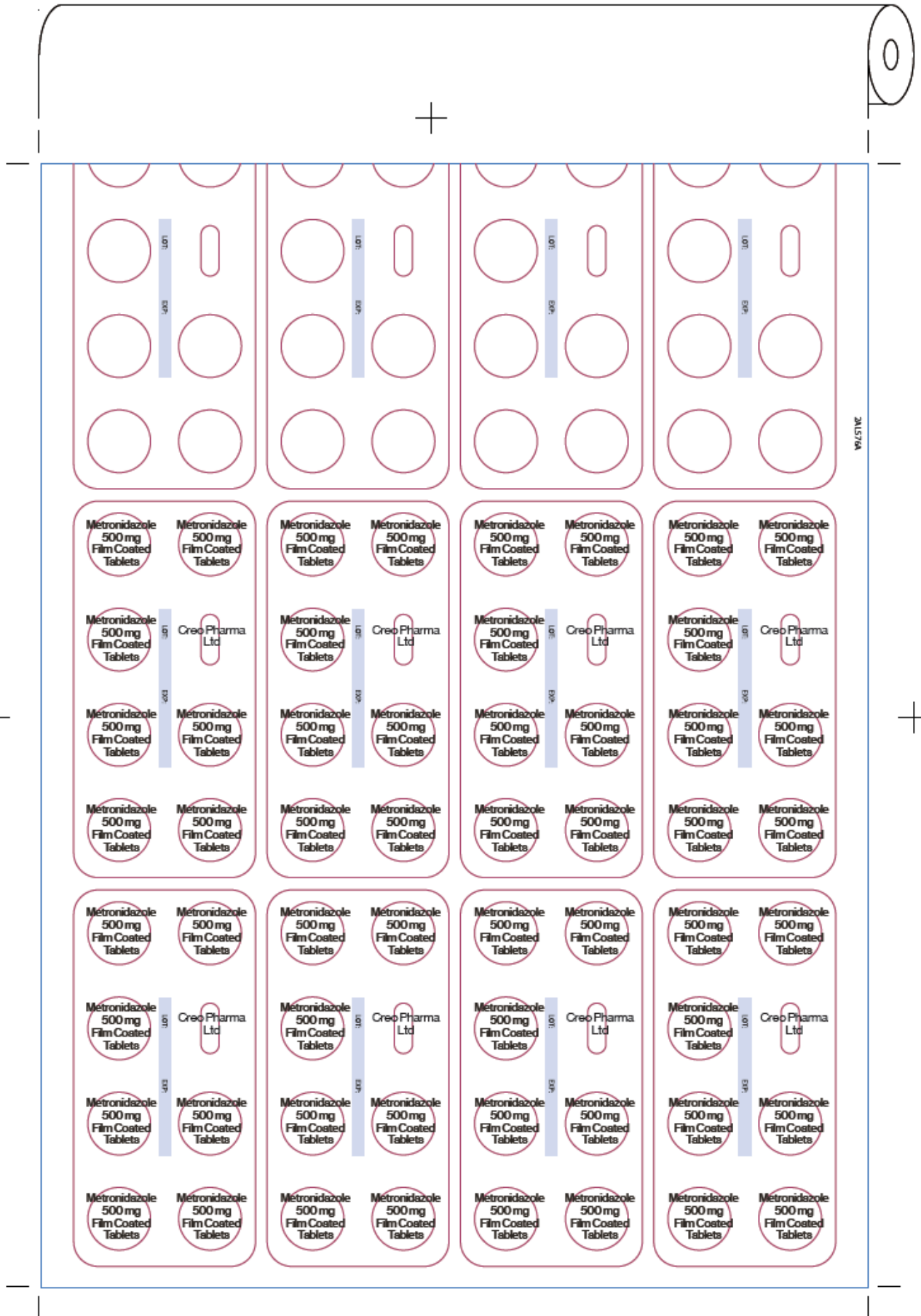
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:

Variable Data prompts will be overprinted at production





## Annex 1

### Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

| Date submitted | Application type | Scope | Outcome |
|----------------|------------------|-------|---------|
|                |                  |       |         |