SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metronidazol EQL Pharma 200 mg film-coated tablets
Metronidazol EQL Pharma 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg and 400 mg of metronidazole respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

200 mg film-coated tablets: White, circular, diameter approximately 9 mm.
400 mg film-coated tablets: White, capsule shaped, approximately 17 x 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> is indicated in adults and children for the following indications: Intra-abdominal, vaginosis and dental infections due to anaerobic bacteria. Pre-operative prophylaxis in abdominal surgery against infections due to anaerobic bacteria. Urogenital trichomonal vaginitis. Amoebiasis. Giardiasis. Acute Crohn's disease, preferably in the involvement of the colon and rectum.

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

4.2 Posology and method of administration

In case of combined infection (aerobic/anaerobic), metronidazole should be given in conjunction with an antibiotic active against the aerobic bacteria. Use of <Invented name> for longer treatment durations than those recommended below should be carefully considered, see sections 4.4 and 5.3.

Posology

Prophylaxis in abdominal surgery:
Oral treatment can be used provided the patient has normal ventricular and intestinal function. The prophylaxis should be given as a single dose about 1-2 hours before surgery.
Adults: 1000 mg.
Children <12 years of age: 20-30 mg/kg.
Newborn with a gestation age <40 weeks: 10 mg/kg.

Prophylaxis against and treatment of intra-abdominal infections:
Adults: 400 mg every 8 hours.
Children >8 weeks to 12 years of age: 20-30 mg/kg/day once daily or divided into 7,5 mg/kg every 8 hours. Depending on the severity of the infection, the daily dose may be increased to 40 mg/kg.
Children <8 weeks: 15 mg/kg as a single dose or divided into 7,5 mg/kg every 12 hours.

In newborns with a gestation age <40 weeks, accumulation of metronidazole can occur during the first week of life, the concentration of metronidazole in serum should preferably be monitored after a few days therapy.
Treatment period: 7-14 days.

Dental infections:
Adults: 400 mg every 8 hours for 5-7 days.
Children: 7,5 mg/kg every 8 hours for 5-7 days.

Urogenital trichomoniasis:
Adults and adolescents: 2000 mg (5 tablets of 400 mg) as a single dose. Alternatively 200 mg 3 times daily for 7 days or 400 mg twice daily for 5-7 days.

On occasions when the tablets cause gastrointestinal disorders, one pessary daily for 7-14 days can be given. In more severe cases of urogenital trichomonal vaginitis, combination therapy is recommended: Oral treatment according to one of the above alternatives and one pessary daily for 7-14 days. If possible, patients and partners should be treated at the same time.

Children <10 years: 40 mg/kg as a single oral dose or 15-30 mg/kg/day divided into 2-3 doses for 7 days. One single dose must not exceed 2000 mg.

Bacterial vaginosis
Adults: 400 mg orally every morning and evening for 5-7 days, alternatively 2000 mg (5 tablets of 400 mg) as a single dose for 2 days with one day treatment-free.

Adolescents: 400 mg orally every morning and evening for 5-7 days, alternatively 2000 mg (5 tablets of 400 mg) as a single dose.
In the case of trichomoniasis and Gardnerella vaginalis, the treatment for fertile women should be given postmenstrually, if possible.

Amoebiasis
Adults: 800 mg every 8 hours for 10 days.
Children: 35-50 mg/kg/day divided into 3 doses for 5-10 days. The dose must not exceed 2400 mg/day.

Giardiasis
Adults: 600 mg every morning and evening for 6 days.
Children: 25-40 mg/kg/day divided into 2-3 doses for 6 days.

Acute Crohn's disease:
Individual dosing.
Adults: Oral doses of 800-1200 mg/day divided into 2-3 doses. Duration of treatment 4-6 months. The minimum effective dose should be given and the daily dose should not exceed 15 mg/kg/day.

4.3 Contraindications

Blood dyscrasia and active central nervous system disease at the higher doses that is recommended for treatment of anaerobic infections, amoebiasis, giardiasis and Mb Crohn.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to imidazole derivatives.

4.4 Special warnings and precautions for use

In the case of severe hypersensitivity reactions (e.g. anaphylactic shock; see also section 4.8), treatment with metronidazole must be discontinued immediately and established emergency treatment must be initiated.

If treatment for more than 14 days is considered to be necessary, haematological values, especially leucocyte count, should be analysed regularly and the patient should be monitored for reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures) (see section 4.8).
<Invented name> should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.
<Invented name> should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological damage.
<Invented name> should be administered with caution to patients with hepatic encephalopathy.
<Invented name> may darken urine.
Metronidazole may, for some patients, have a disulfiram-like effect on the metabolism of alcohol, resulting in intolerance symptoms. Patients should be advised not to take alcohol during the treatment and for at least 24 hours after completed treatment with <Invented name>.

Hepatic impairment
Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Severe cutaneous adverse reactions (SCARs)
Cases of severe bullous skin reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of Stevens Johnson syndrome, toxic epidermal necrolysis or AGEP are present, <Invented name> treatment must be immediately discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Amiodarone: Prolongation of the QT-interval and Torsade de pointes has been reported during concomitant treatment with metronidazole and amiodarone. It is recommended to monitor the QT-interval on the ECG in patients receiving this combination therapy. Patients treated on an outpatient basis should be advised to contact immediately the doctor if symptoms of Torsade de pointes occur such as dizziness, palpitations, and syncope.

Disulfiram: Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently. The combination should be avoided.

Warfarin: Concomitant treatment with metronidazole may potentiate the anticoagulant effect and increase the risk of bleeding as a result of decreased hepatic degradation of warfarin. Dose adjustment of warfarin may be required.

Lithium: Concomitant treatment with metronidazole may increase the serum level of lithium. Plasma concentrations of lithium, creatinine and electrolytes should be monitored closely.

Ciclosporin: During concomitant treatment with metronidazole, there is a risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored.

Mycophenolate mofetil: Substances that alter the gastrointestinal flora (e.g., antibiotics) may reduce the oral bioavailability of mycophenolic acid products. Close clinical and laboratory monitoring for evidence of diminished immunosuppressive effect of mycophenolic acid is recommended during concomitant therapy with anti-infective agents.

Phenytoin or phenobarbital: Risk of increased elimination of metronidazole with reduced plasma levels as a result.

5-flourouracil (5-FU): When combined with 5-FU, the risk of side effects of 5-FU increases due to reduced clearance of the substance.

Busulfan: Plasma levels of busulfan may increase with concomitant treatment with metronidazole, which may lead to severe busulfan toxicity.

Tacrolimus: Increased blood concentrations of tacrolimus has been reported during concomitant treatment with metronidazole. Tacrolimus blood levels and renal function should be checked frequently and the dosage adjusted accordingly, particularly following initiation or discontinuation of metronidazole therapy in patients who are stabilized on their tacrolimus regimen.

Alcohol: Metronidazole may, for some patients, have a disulfiram-like effect on the metabolism of alcohol, resulting in intolerance symptoms. Patients should be advised not to take alcohol during the treatment and for at least 24 hours after completed treatment with <Invented name>.

4.6 Fertility, pregnancy and lactation

Pregnancy
Metronidazole crosses the placenta. There are limited amount of data from the use of metronidazole in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Metronidazole is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding
Metronidazole is excreted in breast milk. Breast-feeding should be discontinued during treatment with Metronidazol EQL Pharma. After the end of the treatment, nursing should not be resumed before another 3 days.

Fertility
There are no clinical fertility data.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Diffuse intestinal intolerance symptoms are most common (about 5-10%). High doses and long treatment time increases the risk of side effects. Frequency, type and severity of adverse reactions in children are the same as in adults.

The frequency of adverse events listed below is defined using the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data).

Infections and infestations	Uncommon: Superinfections with candida (e.g. genital infections)
Blood and lymphatic system disorders	Uncommon: Leucopenia. Rare: Agranulocytosis, neutropenia, thrombocytopenia,

	pancytopenia.
Immune system disorders	Rare: Angiodema. Anaphylaxis.
Psychiatric disorders	Rare: Hallucinations and confusion. Not known: Depressed mood.
Nervous system disorders	Rare: Peripheral sensory neuropathy, convulsions, paraesthesia, dizziness, headaches (see section 4.4). Very rare: Subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) and encephalopathy (e.g. confusion) has been reported. These effects may resolve on the discontinuation of the drug. Not known: Aseptic meningitis.
Eye disorders	Rare: Transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity. Not known: Optic neuropathy/neuritis.
Ear and labyrinth disorders	Not known: Hearing impairment/hearing loss (including sensorineural), tinnitus.
Gastrointestinal disorders	Common: Diffuse gastro-intestinal disturbances, metallic taste. Rare: Pancreatitis, vomiting, diarrhoea, oral mucositis, epigastric pain, nausea, anorexia, taste disorders. Not known: Tongue discoloration/furred tongue.
Hepatobiliary disorders	Very rare: Cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice.
Skin and subcutaneous tissue disorders	Rare: Erythema multiforme, pustular eruptions, exanthema, urticaria, itching, flushing. Not known: Fixed drug eruption, acute generalised exanthematous pustulosis, Steven-Johnson syndrome, toxic epidermal necrolysis.
Renal and urinary disorders	Rare: Darkening of urine.
General disorders and administration site conditions	Rare: Fever.
Investigations	Rare: Increase in liver enzymes (AST, ALT, alkaline phosphatase).

Cases of hepatic failure have been reported in patients treated with metronidazole in combination with other antibiotics.
Blood cell changes are very rare and usually reversible, but fatal cases have been reported.
Peripheral sensory neuropathy has been reported in association with long-term treatment with high total doses (more than 30 g). After discontinuation of the treatment, slow regress of the neuropathy is obtained, in some cases incomplete.
Rare and reversible cases of pancreatitis have been reported.
Very rare cases of encephalopathy have been reported. These were reversible upon discontinuation of the treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.*

4.9 Overdose

Toxicity:
Limited experience of acute overdosing but acute toxicity is probably low. 400 mg to a 3 years old child, maximum 2,8 g to a 4 years old child (activated charcoal was given) and 12 g to adult did not give any symptoms.

Symptoms:

It is possible that the side effects described e.g. gastrointestinal disorders, dizziness, lethargy, headache, dysarthria, neuropathy, seizures, metallic taste, darkening of the urine may occur. Symptoms have been limited to vomiting, ataxia and slight disorientation.

Treatment:
In case of suspected massive overdose, symptomatic and supportive treatment should be instituted. There is no specific antidote for metronidazole overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals
ATC code: P01AB01.

Metronidazole is a nitroimidazole derivative with an inhibitory effect on mainly strict anaerobic bacteria. Metronidazole is a prodrug. Under anaerobic conditions nitroso radicals acting on DNA are formed from metronidazole by the microbial pyruvate ferredoxinoxidoreductase, with oxidation of ferredoxin and flavodoxin. Nitroso radicals form adducts with base pairs of the DNA, thus leading to breaking of the DNA chain and consecutively to cell death.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (version 11.0, 01-01-2021) are as follows:

	MIC breakpoints (mg/L)	
	S≤	R>
Gram-positive anaerobes[1]	4	4
Gram-negative anaerobes	4	4
Clostridioides difficile	2	2
Helicobacter pylori	8	8

[1] Except Clostridioides difficile

Antibacterial spectrum

Susceptible	Peptostreptococcus *Clostridium* including *Clostridium perfringens* and *Clostridioides difficile* *Bacteroides* including *Bacteroides fragilis* *Fusobacteria* *Prevotella* *Gardnerella vaginalis* *Helicobacter pylori*
Resistant	Aerobic bacteria Microaerophilic streptococci *Actinomyces* *Arachnia* *Propionibacteria*

Resistance is rare (<1%) among anaerobic bacteria.

Cross resistance with tinidazole occurs. Resistance is common (>10%) among Helicobacter pylori.

The resistance situation varies geographically and information about the local resistance conditions should be obtained by a local microbiological laboratory.

Spectrum of protozoa

Susceptible	*Entamoeba histolytica* *Giardia intestinalis*

	Trichomonas vaginalis

Resistance of these protozoa to nitromidazoles has not been reported except for single strains of Trichomonas vaginalis.

5.2 Pharmacokinetic properties

Orally administered metronidazole is almost completely absorbed, peak plasma concentration is reached after 1-3 hours, single doses of 200 mg, 400 mg and 2 g provide serum levels of about 5, 10 and 40 µg/ml, respectively.

At recommended dose, metronidazole is distributed to tissues and body fluids, including the cerebrospinal fluid, at concentrations that usually exceed the smallest inhibitory concentration for anaerobic bacteria. Metronidazole is partially metabolized by oxidation and hydroxylation and also conjugated with glucuronic acid.
The half-life is approximately 8 hours in adults and children over 8 weeks of age. In younger and premature children a slower metabolism has been shown, resulting in about 3 times longer half-life. The active metabolite hydroxy-metronidazole has a half-life of 10-13 hours in adults. Excretion of unchanged metronidazole and its metabolites occurs mainly via the urine. A minor portion is eliminated via the bile.

5.3 Preclinical safety data

Mutagenic and tumorigenic potential
Metronidazole has shown to be carcinogenic in mice and rats. However, similar studies in hamster have given negative results and epidemiological studies in humans have provided no evidence of an increased carcinogenic risk in humans.

Metronidazole has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells *in vitro* as well as in rodent and in humans *in vivo*, the results have not been unambiguous in terms of mutagenic effects. Due to inconsistent results, the use of <Invented name> for longer treatment durations than those recommended should be carefully considered (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Calcium hydrogen phosphate
Maize starch
Povidone
Magnesium stearate
Tablet coating:
Macrogol
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

200 mg film-coated tablets:
PVC/PVD/Al blisters of 21 tablets

400 mg film-coated tablets:
PVC/PVD/Al blisters of 14, 20 and 30 tablets
HDPE bottle with polypropylene cap of 100 and 105 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2023-01-31

<[To be completed nationally]>