SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

METROKRIS® 200 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each METROKRIS® 200 tablet contains Metronidazole 200 mg

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oral Tablets. Yellow coloured, round uncoated tablet, one side middle line and other side embossed with METROKRIS 200.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The therapeutic indications of metronidazole are based on its antiparasitic and antibacterial activity and pharmacokinetic properties. They consider both the clinical studies carried out with the medicinal product, and its position in the range of currently available anti-infectives. Its use is limited to the treatment of infections caused by microorganisms which have been shown to be susceptible to the drug:

- amebiasis,
- urogenital trichomoniasis,
- nonspecific vaginitis,
- giardiasis,
- curative treatment of medical and surgical infections caused by susceptible anaerobes,
- replacement therapy after curative treatments given by injection of infections caused by susceptible anaerobes.

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

4.2. Posology and method of administration

Posology

- Amebiasis o Adults

1.50 g/day as 3 divided doses.

Children

30 to 40 mg/kg/day as 3 divided doses.

In patients with amoebic liver abscess, abscess drainage should be performed in conjunction with metronidazole therapy.

Treatment duration is 7 consecutive days.

- Trichomoniasis

In women (urethritis and vaginitis due to Trichomonas), preferably, 10-day treatment combining the following:

0.50 g/day by oral route as 2 divided doses

1pessary/day.

It is important that the partner be treated concomitantly, regardless of whether there are clinical signs of Trichomonas vaginalis infestation, even without a positive laboratory test result.

In men (urethritis due to Trichomonas):

0.50 g by oral route as 2 divided doses for 10 days.

In exceptional cases, it might be necessary to increase the daily dose to 0.750 g or 1 g.

- Giardiasis

Adults

0.750 g to 1 g/day for 5 consecutive days.
Children:
From 2 to 5 years of age: 250 mg/day.
From 5 to 10 years of age: 375 mg/day.
From 10 to 15 years of age: 500 mg/day.
• Nonspecific vaginitis
500 mg twice daily for 7 days.
The patient's partner should be treated at the same time.
• Treatment of infections caused by anaerobes (as first-line or replacement treatment)
Adults:
1 g to 1.5 g/day.
Children:
20 to 30 mg/kg/day.
Method of administration:
Oral use.

4.3. Contraindications

Hypersensitivity to metronidazole or to imidazole or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Hypersensitivity / Skin and appendages

Allergic reactions, including anaphylactic shock, can occur and be life-threatening (see Section 4.8). In this case, treatment with metronidazole must be discontinued and appropriate medical treatment initiated. If, at the start of treatment, patients experience generalized erythema with fever and pustules, acute generalized exanthematous pustulosis should be suspected (see Section 4.8). If this occurs, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated. Severe skin reactions have been reported with metronidazole, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or Lyell syndrome) and acute generalized exanthematous pustulosis. Patients must be informed of the signs and symptoms of these conditions and the skin should be closely monitored.
If any signs or symptoms of Stevens-Johnson syndrome, toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) or acute generalized exanthematous pustulosis (see Section 4.8) occur, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated.
Central nervous system

If symptoms indicative of encephalopathy or cerebellar syndrome appear, patient management should be immediately reassessed, and metronidazole treatment discontinued. Cases of encephalopathy have been reported as part of post-marketing surveillance of the drug. Cases of MRI changes associated with encephalopathy have also been observed (see Section 4.8). Damage is most often located in the cerebellum (particularly in the dentate nucleus) and in the splenium of the corpus callosum. Most cases of encephalopathy and MRI changes are reversible on treatment discontinuation. Very rare cases of fatal outcome have been reported.
Patients should be monitored for warning signs of encephalopathy, and exacerbation of symptoms in patients with CNS disorders. If aseptic meningitis occurs during treatment, rechallenge with metronidazole is not recommended, and an assessment of the benefit/risk ratio should be done for patients with serious infection. Peripheral nervous system.
Patients should be monitored for warning signs of peripheral neuropathy, particularly in long-term treatment or in patients with severe, chronic or progressive peripheral neurological disorders.
Psychiatric disorders
From administration of the first doses, patients may experience psychotic reactions, including self

endangering behaviour, particularly if they have a history of psychiatric disorders (see Section 4.8). If this happens, metronidazole must be discontinued, the physician informed, and appropriate therapeutic measures instituted immediately.
Haematological effects

In patients who have a history of haematological disorders or who are receiving high-dose and/or long-term treatment, regular blood tests, and particularly leukocyte counts, should be performed.
In patients with leukopenia, continued treatment will depend on how serious the infection is.
Interaction with other medicinal products
Concomitant use of metronidazole and alcohol is not recommended (see Section 4.5).
Concomitant use of metronidazole and busulfan is not recommended (see Section 4.5).
Concomitant use of metronidazole and disulfiram is not recommended (see Section 4.5).
Interactions with laboratory tests

Metronidazole may immobilize treponemes, and thus lead to false positive results for the Nelson test.
Cases of severe hepatotoxicity/acute liver failure of very rapid onset after treatment initiation, including cases with fatal outcome, have occurred in patients with Cockayne syndrome who were administered medicinal products containing metronidazole intended for systemic use. In this population, metronidazole must therefore be used after thorough evaluation of the benefit/risk ratio and only if no alternative treatment is available. Liver function tests must be performed just before treatment initiation, during treatment and after treatment discontinuation, until liver function values are within the normal range, or until baseline values are reached. If the liver function test values markedly increase during treatment, the medicinal product should be discontinued.

Patients with Cockayne syndrome must be instructed to immediately report any symptoms of potential liver damage to their doctor and to stop taking metronidazole.

4.5. Interaction with other medicinal products and other forms of interaction

Antabuse reaction
Many medicinal products trigger an Antabuse effect with alcohol and their concomitant use with alcohol is not advisable.
Inadvisable combinations
+ Alcohol (beverage or excipient)
An Antabuse effect (hot flushes, erythema, vomiting, tachycardia) may occur. Patients should not consume alcoholic beverages or medicinal products containing alcohol. Alcoholic beverages or medicinal products containing alcohol should not be ingested again until medicinal products have been completely eliminated from the body. The half-life should be used as a reference. + Busulfan
When co-administered with high busulfan doses, metronidazole causes a two-fold increase in plasma busulfan concentrations.
+ Disulfiram
There is a risk of acute psychotic episodes or confusion, reversible on discontinuation of the drug combination. Combinations requiring precautions for use
+ Enzyme-inducing anticonvulsants
Decreased plasma concentrations of metronidazole can occur due to increased liver metabolism by the inducer.
Clinical monitoring is required, and the metronidazole dose may need to be adjusted during and after treatment with the inducer.
+ Rifampicin
Decreased plasma concentrations of metronidazole can occur due to increased liver metabolism by rifampicin. Clinical monitoring is required and the metronidazole dose may need to be adjusted during and after treatment with rifampicin. + Lithium
Increased blood lithium levels can occur, which can reach toxic levels with signs of lithium overdose.

Strict monitoring of blood lithium levels should be performed, and the lithium dose adjusted if necessary.
Combinations to be taken into consideration
+ Fluorouracil (and by extrapolation, tegafur and capecitabine) Increased fluorouracil toxicity can occur due to decreased clearance.
Specific issue: INR imbalance:
Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. The severity of the infection or inflammation, age and general health status of the patient appear to be risk factors. Under these circumstances, it seems difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly fluoroquinolones, macrolides, cyclines, cotrimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy, and lactation

Pregnancy

There is no evidence from animal studies that metronidazole is teratogenic. Therefore, no malformities effect is expected in humans. To date, substances causing malformations in humans have been shown to be teratogenic in animals during well-conducted studies in two species.
In man, analysis of many exposed pregnancies did not seem to show any particular teratogenic or fetotoxic effects of metronidazole. However, only epidemiological studies would make it possible to rule out any risk. Therefore, metronidazole may be prescribed during pregnancy if necessary.
Lactation

Since metronidazole is excreted in breast milk, administration should be avoided in breast-feeding women.

4.7. Effects on ability to drive or use machines

Patients should be warned of the potential risk of dizziness, confusion, hallucinations, and seizures or vision disorders, and should be advised not to drive or operate machines if they experience such symptoms.

4.8. Undesirable effects

Blood and lymphatic system disorders
• neutropenia, agranulocytosis, thrombocytopenia.
Psychiatric disorders
• hallucinations,
• psychotic reactions with paranoia and/or delirium possibly accompanied by suicidal ideation or suicide attempts in some isolated cases (see Section 4.4),
• depressed mood.
Nervous system disorders
• peripheral sensory neuropathy,
• headache,
• dizziness,
• confusion,
• seizures,
• encephalopathy that may be associated with MRI changes, generally reversible upon treatment discontinuation. Very rare cases of fatal outcome have been reported (see Section 4.4),
• sub-acute cerebellar syndrome (ataxia, dysarthria, gait disorders, nystagmus, tremor) (see Section 4.4),
• aseptic meningitis (see Section 4.4).
Eye disorders

• transient vision disorders such as blurred vision, diplopia, myopia, reduced visual acuity, impaired color vision,
• neuropathy / optic neuritis.
Gastrointestinal disorders
• minor gastrointestinal disorders (epigastric pain, nausea, vomiting, diarrhea),
• glossitis with dry mouth, stomatitis, taste disorders, anorexia,
• pancreatitis, reversible on treatment discontinuation,
• discoloration or change in the appearance of the tongue (mycosis).
Hepatobiliary disorders
• elevated liver enzyme levels (AST, ALT, alkaline phosphatase), very rare cases of acute cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported. Isolated cases of hepatocellular insufficiency possibly requiring liver transplantation have been reported.
Skin and subcutaneous tissue disorders
• hot flushes, pruritus, skin rash occasionally with fever,
• urticaria, angioedema, anaphylactic shock (see Section 4.4),
• very rare cases of acute generalized exanthematous pustulosis (see Section 4.4),
• toxic epidermal necrolysis, • Stevens-Johnson syndrome, • fixed drug eruption. Other effects
• urine can appear reddish-brown as water-soluble pigments may be found due to metabolism of the drug.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. Overdose

Administration of up to 12 g as a single dose has been reported in cases of attempted suicide and accidental overdose. The symptoms were limited to vomiting, ataxia and mild disorientation. There is no specific antidote to metronidazole overdose. If massive overdose occurs, symptomatic treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterial, antiparasitic antibiotics belonging to the 5nitroimidazole group, ATC code: J01XD01 — P01AB01 (J: Anti-infectives for systemic use, other antibacterial - imidazole derivatives - P: Antiprotozoals, agents against amebiasis and other protozoal diseases - nitroimidazole derivatives). The MIC breakpoints differentiating susceptible from intermediate strains, and intermediate from resistant strains are as follows: S ≤ 4 mg/L and R > 4 mg/L
The prevalence of acquired resistance in certain species can vary geographically and over time. It is therefore, useful to have local information on the prevalence of resistance, especially in treating severe infections. These data are only guidelines indicating the probability of susceptibility of a bacterial strain to this antibiotic. When the variability of prevalence of resistance of a bacterial species is known in France, it is indicated in the table below:
Category
Prevalence of acquired resistance in France (>10%) (range)
Susceptible species
Gram-negative aerobes
Helicobacter pylori 30%
Anaerobes
Bacteroides fragilis
Bifidobacterium 60-70%
Bilophila
Clostridium

Clostridium difficile
Clostridium perfringens
Eubacterium 20-30%
Fusobacterium
Pepto streptococcus
Porphyromonas
Prevotella
Veillonella
Resistant species
Gram-positive aerobes
Actinomyces
Anaerobes
Mobiluncus
Propionibacterium acnes
Antiparasitic activity
Entamoeba histolytica
Giardia intestinalis
Trichomonas vaginalis

5.2. Pharmacokinetic properties

Absorption
Metronidazole benzoate is gradually hydrolysed as it passes through the gastrointestinal tract. The absorption of metronidazole benzoate is 30% less (area under the curve) than that of metronidazole. Peak plasma concentrations are obtained after four hours following oral administration of the product. At identical doses, metronidazole and metronidazole benzoate do not have significantly different therapeutic results.
The plasma half-life is 6.9 hours by HPLC.
Distribution
• Plasma protein binding is below 10%.
• The drug is rapidly and widely distributed in the lungs, kidneys, liver, skin, bile, CSF, saliva, semen and vaginal secretions.
Metronidazole crosses the placental barrier and is excreted in breast milk.
Biotransformation
Two unconjugated metabolites with antibacterial activity are formed (10%).
Elimination
High concentrations of metronidazole can be found in the liver and bile. Low concentrations of the drug are found in the colon. Metronidazole is poorly excreted in the feces. It is mainly excreted in the urine (40 to 70%, with approximately 20% in unchanged form) causing reddish or brown coloration of the urine.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methyl hydroxybenzoate, propyl hydroxybenzoate, maize starch, Dibasic calcium phosphate, purified talc, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate, colloidal silicon dioxide and tartrazine yellow.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in a cool dry place below 30°C. Protect from direct sunlight. Keep out of reach of children.

6.5. Nature and contents of container

Tablets in PVC/Aluminium Blisters (10x 10).

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Krishat Pharma Ind. Ltd.,
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