SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

POLGYL 0.5% Solution for I.V. Perfusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Each 100 ml PVC or PP bag contains 500 mg metronidazole.

Excipients:
Disodium phosphate 150 mg
Sodium Chloride 740 mg
See section 6.1 for other excipients.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, bright, pale yellow sterile isotonic solution for intravenous infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of medical and surgical infections caused by anaerobic bacteria sensitive against metronidazole,
- For prophylaxis in surgical procedures bearing the risk of anaerobic infection development,
- Serious intestinal and hepatic amebiasis.

4.2 Posology and method of administration

Posology/ Frequency and period of administration:
a. Treatment of the medical and surgical infections caused by sensitive anaerobic bacteria:

Adults: 1 – 1,5 g/day intravenously in 2 or 3 equal doses

Children: 20–30 mg/kg/day for children between 8 weeks and 12 years of age intravenously in one single dose or 7,5 mg/kg every 8 hours. The daily dose can be increased up to 40 mg/kg depending on the severity of infection. Period of treatment is generally 7 days.

Children younger than 8 weeks: Single dose of 15 mg/kg per day or 7,5 mg/kg every 12 hours. Metronidazole accumulation can be seen within the first week of life in neonates with gestational ages smaller than 40 weeks. Therefore, monitoring the serum metronidazole concentrations in the first few days of the treatment can be required. Once status of the patient allows oral intake, the treatment must continue with same doses given orally.

b. Treatment with prophylactic purposes in surgical procedures bearing the risk of anaerobic infection development:
Metronidazole must be combined with a drug effective against enterobacteria in this indication.

Adults: 500 mg administered right before the operation and at hours 8 and 16 through intravenous infusion (to be completed within 30-60 minutes)

Children younger than 12 years of age: 20-30 mg/kg in one single dose 1-2 hours before surgery.

Neonates with gestational ages smaller than 40 weeks: 10 mg/kg in one single dose before surgery.

c. Severe intestinal amebiasis:
Adults: 1,5 g/day (e.g. 3 intravenous infusions of 500 mg per day)

Children older than 10 years of age: 400-800 mg three times per day for 5-10 days

Children between 7 and 10 years of age: 200-400 mg three times for 5-10 days

Children between 3 and 7 years of age: 100-200 mg four times a day for 5-10 days

Children between 1 and 3 years of age: 100-200 mg three times a day for 5-10 days

Alternatively, dose can be adjusted according to body weight. The daily dose is 35-50 mg/kg divided into three for 5 to 10 days. The daily dosage must not exceed 2400 mg.

Abscess drainage must be applied in hepatic amebiasis together with metronidazole therapy.

Route of administration:
5 mL will be injected per minute.

Special populations:
Renal/ hepatic impairment:
Dose and frequency of administration must be adjusted in severe hepatic failure based on the level of failure and serum levels of metronidazole. See Section 4.4 for renal failure.

Paediatric population:
Explained above

Geriatric population:
Careful use is recommended in the elderly population. Careful attention is particularly required in high dosages.

4.3 Contraindications

This drug is contra-indicated in individuals hypersensitive against imidazole derivatives or the inactive ingredients.

4.4 Special warnings and precautions for use

- Long-term use of POLGYL in treatment must be evaluated carefully (see: section 5.3). Regular blood tests must be carried out in use longer than planned, and particularly leukocyte count must be monitored, and development of neuropathy must be watched.

- Because of the risk of exacerbation of neurologic symptoms, it must be used carefully in patients with active or chronic peripheral or central neurological disorders.

- Since it can cause a disulfiram-like reaction, patients must be warned not to take alcohol during the treatment and for at least two days after the treatment is stopped.

- It must be used carefully in patients with blood dyscrasia findings or amnesia. Leukocyte counts must be taken before and after the treatment. Whether or not continuing the treatment in patients with blood dyscrasia or those treated with high dosages and/or in long-term must be decided according to the severity of the infection. Adverse reactions must be monitored in treatments for periods longer than 10 days.

- Metronidazole must be used carefully in hepatic encephalopathy cases. The daily dose must be reduced to one-thirds and must be used as one single dose.

- It can cause dark urine because of their metabolites; patients must be warned about this.

- Oral, vaginal or intestinal candidiasis can develop after intravenous metronidazole use.

- It has no direct effect on aerobic and facultative anaerobic bacteria.

- There is the possibility of residual gonococcal infection after the elimination of *Trichomonas vaginalis*.

- Elimination half-life of metronidazole will not change in renal failure; therefore, there will be no need to reduce the metronidazole dosage. However, metabolites of metronidazole will be retained in these patients. The clinical importance of this is unknown.

- Metronidazole and metabolites are effectively removed with a dialysis period of 8 hours in patients receiving hemodialysis therapy. Therefore, metronidazole must be re-administered right after hemodialysis.

- There are no routine dose adjustments for patients with renal failure and receiving intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).

- Therapy must be stopped if ataxia, vertigo, hallucinations or confusion is seen.

- Metronidazole potentiates the effect of vecuronium, which is used to create non-depolarizing neuromuscular block.

- Although metronidazole has been found to be carcinogen in a certain mouse species, this effect have not been shown in rat and hamster species. This preparation has no such effect in humans.

- Based on the insufficiency of evidences mutagenicity risk in humans (see: section 5.3), use of POLGYL in periods longer than usual must be evaluated carefully.

This medicinal product contains 13 mmol sodium per each 100 ml. This should be considered for patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

- *Disulfiram:* Psychotic reactions have been reported in individuals who use disulfiram together with metronidazole.

- *Alcohol:* Alcoholic drinks or alcohol containing drugs must be avoided to prevent disulfiram-like reaction (flushing in the face and neck area, vomiting, tachycardia) during the treatment and for at least 2 days after the termination of treatment.

- *Varfarine:* Since metronidazole increases the destruction of oral anticoagulants in the liver, the effects of these preparations and risk of hemorrhage can be increased in concomitant use. Therefore, prothrombin levels must be checked with close intervals in combined use, and the oral coagulant dose to be administered must be adjusted.

- *Lithium:* Plasma levels of lithium can increase when used with metronidazole. Therefore, plasma concentrations of lithium, creatinine and electrolytes must be monitored in patients that metronidazole is administered while under lithium therapy.

- *Cyclosporine:* Serum levels of cyclosporine can increase. If concomitant use with metronidazole is required, serum cyclosporine and creatinine levels must be followed closely.

- *Phenitoin-phenobarbital:* Elimination of *m*etronidazole can increase, and its serum levels can decrease.

- *5-fluoro-urasil:* Excretion of 5-fluoro-urasil will decrease when used together with metronidazole, and its toxic effects will increase consequently.

- *Busulfan:* Since metronidazole will increase the plasma busulfan concentration, it can cause serious busulfan toxicity.

Interaction with laboratory tests: Metronidazole can cause changes in AST (SGOT), ALT (SGPT), LDH, triglycerides or glucose tests measured using the ultraviolet absorbance method.

Additional information related the special populations
Pediatric population:
It can be used in children from 8 weeks of age.

4.6 Pregnancy and lactation

General recommendations
Pregnancy category: B (during the 2nd and 3rd trimesters).

Women of childbearing potential /Contraception
It must not be used within the first trimester.

Pregnancy
Information on the safety of metronidazole is insufficient. It must not be administered during pregnancy unless it use is absolutely necessary. If its use is unavoidable, then short-term regimes with lower doses are recommended.

Lactation
Metronidazole must not be used by lactating mothers, because it is excreted in the breast milk.

Fertility
Metronidazole has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells in humans *in vivo*, there was inadequate evidence of mutagenic effect of metronidazole (See section 5.3).

4.7 Effects on ability to drive and use machines

Patients must be warned that confusion, hallucinations and temporary visual impairments can develop (see: section 4.8), and they should not drive or use machines if such symptoms develop.

4.8 Undesirable effects

Adverse effects that relation with metronidazole treatment has been defined by accepting such relation is probable as a minimum after evaluating the available data reported in clinical trials more frequently as compared to placebo are listed below with the following classification:

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), and unknown (cannot be estimated from the available data)

Blood and lymphatic system disorders
Very rare: Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Unknown: Leukopenia

Immune system disorders
Rare: Anaphylaxis
Unknown: Angioedema, urticaria, fever

Metabolism and nutrition disorders
Unknown: Anorexia

Psychiatric disorders
Very rare: Psychotic disorders including confusion and hallucinations
Unknown: Depressive status

Nervous system disorders
Very rare: Encephalopathy that can improve with the withdrawal of the drug (e.g., confusion, headache, hallucinations, paralysis, light sensitivity, motility disorders, opisthotonus) and sub-acute cerebellar syndrome (e.g., ataxia, dysarthria, gait disorder, nistagmus and tremor). Dizziness, vertigo, convulsions, headache.

Unknown: Peripheral sensory neuropathy and temporary epileptiform convulsions have been reported during intense and/or long-term metronidazole treatment. Neuropathy had disappeared in many cases with the stopping of treatment or reducing the dosage. Aseptic meningitis

Eye disorders
Very rare: Visual impairments including diplopia or myopia, mostly temporary, blurred vision, decreased visual acuity, changes in color image
Unknown: Optic neuropathy/neuritis

Gastrointestinal disorders
Unknown: Gastrointestinal disorders including taste changes, oral mucositis, coated tongue, tongue discoloration / fuzz, nausea, vomiting, epigastric pain and diarrhea. Pancreatitis which is reversible.

Hepatobiliary disorders
Very rare: increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice on drug withdrawal. Cases of liver failure

requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders
Very rare: Rashes, pustular rashes, itching, facial flushing
Unknown: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis

Musculoskeletal and connective tissue disorders
Very rare: Myalgia, arthralgia

Renal and urinary disorders
Very rare: Dark urine (related to metronidazole metabolites)

General disorders and administration site conditions
Fever

4.9 Overdose and treatment
Overdose symptoms include vomiting, ataxia and disorientation.
There is no specific antidote. Symptomatic and supporting treatment must be administered.

5. PHARMACOLOGIC PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemically used antibacterials
ATC code: J01XD01

Effect mechanism
Metronidazole is an antibiotic included in the 5-nitroimidazole group. It has bactericidal, amebicide and trochomonocide effects. Its antimicrobial action mechanism is not yet known.

It is not in ionized form at physiologic pH, and is introduced in the cells by anaerobic microorganisms and cells. It is reduced to its polar metabolites, which do not have nitro groups and have not been clearly defined yet, in the cells with electron transport proteins with low reduction-oxidation potential. It is thought that the reduced metabolites make antimicrobial effects by inhibiting the nucleic acid synthesis and impairing the DNA. Metronidazole is equally effective on the dividing and not dividing cells. I*n vitro and in vivo* studies have shown the direct anti-inflammatory effects of metronidazole through the effects on neutrophil motility, formation of lymphocytes and cellular immunity.

Antibacterial effect spectrum of metronidazole:
Anaerobic bacteria:
Metronidazole is effective on many bacteria *in vitro*: *Bacteroides fragilis, B. bivius (Prevotella bivia), B. disiens (Prevotella disiens), B. distasonis, B. gingivalis, (Porphyromonas gingivalis), B. intermedius (Prevotella intermedia), B. melaninogenicus (Prevotella meloninogenica), B. oralis (Prevotella oralis), B. ovatus, B. thetaiotaomicron, B.*

vulgatus, B. asaccharolyticus (Porphyromonas asaccharolytica), B. ureolyticus, Fusobacterium and *Veillonella*.

Some species of *Mobiluncus* (motile and anaerobic species and species with tortuous rods) are *in vitro* inhibited with metronidazole, while other species are accepted as resistant.

The Gram-positive anaerobic cocci that the drug is effective on include *Clostiridium, C. difficile, C. perfringens, Eubacterium, Peptococcus and Peptostreptococcus*; while *Actinomyces, Lactobacillus, Propionibacterium acnes, P. avidum and P. granulosum* are accepted as resistant.

Other microorganisms:
Metronidazole is ineffective against *Campylobacter fetus in vitro*. *Gardnerella vaginalis (Haemophilus vaginalis)* is sensitive against metronidazole at high doses. *In vitro* studies have shown that metronidazole is ineffective against fungi.

Resistance
Some species of *Trichomonas vaginalis* have developed resistance against metronidazole. *Bacteroides fragilis* and other anaerobic bacteria can also become resistance rarely after long-term use. Resistance against metronidazole can be related to weak cellular penetration and/or nitroreductase activity.

5.2 Pharmakokinetic properties
General properties
Absorption:
Since it is administered through injection, the entire portion of the administered drug will be transferred to the body.

Distribution:
The mean serum level obtained after intravenous infusion of the solution containing 500 mg metronidazole in 20 minutes is 18 mcg/mL. Serum level is maintained by repeating the same dosage is injected intervals of 8 hours. The serum level obtained by repeating to dose with 12-hour intervals, however, is 13 mcg/mL. Its half-life in plasma is 8-10 hours. Protein binding rate is low (less than 10%). Distribution is rapid and concentrations in lungs, kidneys, liver, skin, bile, cerebrospinal fluid, saliva, seminal fluid and vaginal secretions. Metronidazole is transported to the placenta and breast milk.

Biotransformation:
It is metabolized in the liver and is found in high concentrations in the liver and bile. Metronidazole is metabolized in the body to two metabolites that have antibacterial activity.

- "Alcoholic" metabolite is the primary metabolite. The bactericidal effect against anaerobic bacteria is 30% of the effect of metronidazole. Elimination half-life is about 11 hours.

- "Acidic" metabolite is found in small amounts and has bactericidal effect equivalent to 5% of metronidazole.

Elimination:
Excretion is mainly through urine (40-70% of metronidazole excreted un changed); therefore, urine can turn to dark read.

Linearity/ nonlinear conditions:
There is no information related to dose linearity.

5.3 Pre-clinic safety data
It has been shown that metronidazole is carcinogenic in mice and rats following chronic oral administration. However, negative results have been obtained in similar studies carried out on hamsters. No clear evidence related to the increase in carcinogenicity risk in humans has been obtained in the epidemiologic studies. Therefore, long-term use of POLGYL in treatment must be evaluated carefully.

It has been shown *in vitro* that metronidazole is mutagenic in bacteria. Sufficient data on its mutagenic effects have been obtained *in vivo* human cell culture studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate
Sodium chloride
Citric acid monohydrate
Water for injection

6.2 Incompatibilities
Clarity of the solution must be confirmed to determine that the solutions to be used together will not cause any incompatibility.

POLGYL must not be mixed with cefamendole naftate, cefoxitin sodium, 10% dextrose, sodium lactate and penicillin G potassium.

6.3. Shelf-life
36 months

6.4 Special precautions for storage
It must be kept at room temperature under 25 °C and in a place without direct light.

6.5 Nature and contents of the packaging
POLGYL 0.5% solution for I.V. perfusion: In 100-ml PVC and PP bags with and without sets containing 0.5g/100ml metronidazole.

6.6 Destruction of the residual materials human medicinal product and other special precautions

The unused or waste products must be discarded according to the "Regulation Related to the Control of Medical Wastes" and the "Regulation Related to the Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORISATION HOLDER

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