SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BIOFLEKS METROSEL 0.5% IV Solution for Perfusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 100 ml solution contains 500 mg metronidazole.

Excipients:
Disodium phosphate 150 mg
Sodium Chloride 740 mg

For other excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection, perfusion
Clear, bright, pale yellow, sterile, isotonic solution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- It is indicated in the treatment of medical and surgical infections caused by anaerobic bacteria sensitive to metronidazole,
- For prophylaxis in surgical interventions with anaerobic infection development risk,
- Severe intestinal and hepatic amoebiasis.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

a) Treatment of medical and surgical infections caused by anaerobic bacteria sensitive to metronidazole:

Adults: intravenously 2 or 3 equal doses of 1-1.5 g / day.
Children: Intravenously, as a single dose of 20-30 mg/kg/day or 7.5 mg/kg every 8 hours in children aged between 8 weeks to 12 years. Depending on the severity of the infection, daily dose can be increased up to 40 mg/kg. Treatment period is usually 7 days.
Children younger than 8 weeks: Single dose of 15 mg/kg or 7.5 mg/kg once every 12 hours. Metronidazole accumulation may be seen in newborns with gestational age below 40 weeks, during the first week of their lives. Therefore, the serum concentration of metronidazole may need to be monitored during the first few days of treatment. After the patient becomes able to take oral medication, the treatment should be continued orally at the same doses.

b) Treatment for prophylaxis in surgical interventions with anaerobic infection development risk:

In this indication metronidazole should be combined with a drug effective against enterobacteria.
Adults: Immediately before surgery and after 8 and 16 hours from the surgery, 500 mg by intravenous infusion (in 30-60 minutes)
Children younger than 12 years: A single dose of 20-30 mg/kg, 1-2 hours prior to surgery.
Newborns with gestational age below 40 weeks: A single dose of 10 mg/kg before the operation.

c) Severe intestinal amoebiasis:

Adults: 1.5 g/day (e.g., 3 intravenous infusions of 500 mg/kg per day)
Children over 10 years: 400-800 mg 3 times per day for 5-10 days
Children between 7-10 years: 200-400 mg 3 times per day for 5-10 days
Children between 3-7 years: 100-200 mg 4 times per day for 5-10 days
Children between 1-3 years: 100-200 mg 3 times per day for 5-10 days

Alternatively, the dose can be adjusted according to body weight. 3 divided doses of 35 to 50 mg/kg per day for 5-10 days. Daily dose should not exceed 2400 mg.

In hepatic amoebiasis, abscess drainage should be implemented together with the metronidazole treatment during the abscess period.

Method of administration:
It is applied as an injection of 5 ml per minute.

Additional information regarding special populations:

Renal/Hepatic impairment:
In severe hepatic failure, dose and frequency of administration should be adjusted according to the severity of the failure and serum levels of metronidazole. For kidney failure *See* Section 4.4.

Pediatric population:
It is given above.

Geriatric population:
It is recommended to be used with caution in the elderly. Attention should be exercised especially in high doses.

4.3 Contraindications
It is contraindicated in patients with hypersensitivity to imidazole derivatives or the excipients.

4.4 Special warnings and precautions for use

- Long-term use of metronidazole therapy should be carefully evaluated (see section 5.3). Regular blood testing should be done when used longer than planned, particularly being cautious for development of neuropathy by monitoring the leukocytes.

- Due to the risk of aggravation of neurological symptoms, it should be used with caution in patients with active or chronic peripheral or central neurological disorders.
- As it may cause a disulfiram-like reaction, patient should be warned not to take alcohol during treatment and at least for two days after the treatment is discontinued.
- It should be used with caution in patients with a history or symptoms of blood dyscrasia. Leukocyte count should be performed before and after treatment. In cases with blood dyscrasia or with high dose and/or prolonged treatment, decision to continue the treatment should be made depending on the severity of the infection. Treatments longer than 10 days should be monitored for adverse reactions.
- Metronidazole should be used carefully in hepatic encephalopathy cases. Daily dose should be reduced to one third and applied as a single dose.
- Metabolites can darken the color of urine; patients should be informed about it.
- After intravenous metronidazole use, oral, vaginal or intestinal candidiasis may develop.
- As the preparation contains 28 mEq sodium in each gram, it should be used with caution in patients receiving corticosteroids, patients on a controlled sodium diet and patients with a predisposition to edema.
- It has no direct activity against aerobic and facultative anaerobic bacteria.
- A gonococcal infection is likely to persist after *Trichomonas vaginalis* is eliminated.
- The elimination half-life of metronidazole does not change in patients with renal failure. Thus, there is no need to reduce the dose of metronidazole. However, metronidazole metabolites remain in these patients. The clinical relevance is not known.
- In patients undergoing hemodialysis, metronidazole and its metabolites are removed effectively in a dialysis period of 8 hours. Thus, metronidazole should be applied again immediately after hemodialysis, no routine dose adjustment is necessary in patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).
- Treatment should be discontinued if ataxia, vertigo, hallucination or confusion is observed.
- Metronidazole, potantialises vecuronium used to create non-depolarizing neuromuscular blockage.
- Metronidazole was found to be carcinogenic in a certain mice species, however this effect could be demonstrated in rat and hamster species. The preparation has no such an effect on people
- Due to lack of evidence of mutagenicity risk on people (see section 5.3), use of metronidazole for a longer period than usual should be carefully evaluated.

4.5 Interaction with other medicinal products and other forms of interaction

- *Disulfiram:* Psychotic reactions were reported in patients taking disulfiram together with metronidazole.

- *Alcohol:* In order to avoid disulfiram-type reactions (redness of the face and neck, vomiting, tachycardia), alcoholic beverages or drugs containing alcohol should not be used during treatment and for at least 2 days after treatment.
- *Warfarin:* As metronidazole reduces the degradation of oral anticoagulants in the liver, when used together, the effects of these drugs and risk of hemorrhage may increase. Therefore, in combined use, prothrombin levels should be checked at frequent intervals and oral anticoagulant dose should be adjusted.
- *Lithium:* Metronidazole may increase the plasma levels of lithium when used together. Therefore, when metronidazole is administered in patients undergoing lithium treatment, plasma concentrations of creatinine and electrolytes should be monitored.
- *Cyclosporine:* Elevations in serum levels of cyclosporine may occur. If co-administration with metronidazole is required, serum cyclosporine and creatinine levels should be closely monitored.
- *Phenytoin-phenobarbital:* Elimination of metronidazole may increase and serum levels may decrease.
- *5-fluoro-uracil:* When used together with metronidazole, excretion of 5-fluoro-uracil decreases and thus its toxic effects increases accordingly.
    - *Busulfan:* As metronidazole increases plasma busulfan amount, it can cause serious busulfan toxicity.

Laboratory Test Interactions: Metronidazole, when measured using ultraviolet absorbance method, may cause changes in AST (SGOT), ALT (SGPT), LDH**,** triglycerides, or glucose measurements.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: B (in 2nd and 3rd trimesters)

Women of child bearing potential/Birth control (contraception)
It should not be used in the first trimester.

Pregnancy
Information on the safety of metronidazole in pregnancy is inadequate. It should not be given during pregnancy except in cases where it is absolutely necessary. If use is unavoidable, short-term and low-dose regimen is recommended.

Lactation period
It should not be used by nursing mothers as metronidazole passes into breast milk.

Reproductivity/Fertility
See section 5.3

4.7 Effects on ability to drive and use machines
Patients should be warned about the possibility of developing confusion, hallucinations, convulsions and temporary visual disorders (see section 4.8) and if these symptoms occur, they should not drive or use machines.

4.8 Undesirable effects

Adverse effects considered to be possibly caused by metronidazole treatment, defined by the higher frequency of reporting in clinical studies compared to placebo and the result of evaluation in terms of causality of data, are listed below using the following classification:

Very common ≥1/10; common ≥1/100 - <1/10; uncommon ≥1/1000 - <1/100; rare ≥1/10000 - <1/1,000; very rare <1/10,000; 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: Depressed mood

Nervous system disorders

Very rare: Encephalopathy which can be resolved if the drug is discontinued (e.g., confusion, headache, hallucinations, paralysis, light sensitivity, movement disorders, stiff neck) and subacute cerebellar syndrome (e.g., ataxia, dysarthria, gait disturbances, nystagmus and tremor). Drowsiness, dizziness, convulsions, headache
Unknown: Intense and/or prolonged peripheral sensory neuropathy or transient epileptiform seizures have been reported during treatment with metronidazole. Neuropathy had resolved in many cases when the treatment was stopped or the dosage was reduced
Aseptic meningitis

Eye disorders

Very rare: Vision disorders, such as diplopia or myopia, mostly temporary
Unknown: Optic neuropathy/neuritis

Gastrointestinal disorders

Unknown: Taste changes, oral mucositis, coated tongue, nausea, vomiting, gastro-intestinal disorders such as epigastric pain and diarrhea. Reversible pancreatitis cases.

Hepato-biliary disorders

Very rare: Increase in liver enzymes (ALT, AST, ALP), cholestatic hepatitis with jaundice or mixed hepatitis and hepatocellular liver damage have been reported. In patients treated with metronidazole in combination with other antibiotics, hepatic failure requiring liver transplantation has been reported.

Skin and subcutaneous tissue disorders
Very rare: Skin rash, pustular rash, itching, reddening of the face (flushing)
Unknown: Erythema multiforme

Musculoskeletal disorders, connective tissue and bone disorders
Very rare: Myalgia, arthralgia

Renal and urinary disorders
Very Rare: Darkening of the urine color (due to metronidazole metabolite)

General disorders and administration site conditions
Fever

4.9 Overdose and treatment
Overdose symptoms are; vomiting, ataxia and disorientation. There is no specific antidote. Symptomatic and supportive treatment should be applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic group: Anaerobicides ATC code: J08B0

Mechanism of action
Metronidazole is an antibiotic from the 5-nitroimidazole group. It has bactericidal, amoebicidal and trichomonocidal effects. Its antimicrobial action mechanism is not yet known. It is not ionized at physiological pH, it is taken up by anaerobic microorganisms and cells. It is reduced to not yet completely defined polar metabolites in the cells by electron transport proteins without nitro groups which have low redox potential. The reduced metabolites are believed to create and antimicrobial effect by inhibiting nucleic acid synthesis and disrupting DNA. Metronidazole is effective in dividing and non-dividing cells at the same level. *In-vitro* and *in-vivo* studies have demonstrated the direct anti-inflammatory effect of metronidazole with its effects on neutrophil motility, lymphocyte formation and cellular immunity.

Antibacterial effect spectrum of metronidazole

Anaerobic bacteria:

Metronidazole, is effective against many bacteria *in vitro: Bacteroides fragilis, B. bivius, (Porphyromonas gingivalis), B. disiens (Prevotella disiens), B. distasoni, B. gingivalis (Porphyromonas gingivalis), B. intermedins (Prevotella intermedia), B. melaninogenicus (Prevotella meloninogenica), B. oralis (Prevotella oralis), B. ovatus, B.thetaiotaomicron, B. vulgatus, B. asaccharolytİcus (Porphyromonas asaccharolytica), B. ureolyticus, Fusobacterium and Veillonella. Some species of mobiluncus* (motile, anaerobic and corrugated rod forms) is inhibited by metronidazole *in-vitro.* Other types are considered resistant.
Anaerobic Gram-positive cocci that the drug is effective against; *Clostridium, C. difficile, C. perfringens, Eubaeterium, Peptococcus and Peptostreptococcus. Actinomyces, Lactobacillus,*

Propionibacterium acnes, P. avidum and P. granulosum are known to be resistant.

Other microorganisms:
Metronidazole is effective against *Campylobacter fetus in-vitro*. *Gardnerella vaginalis (Haemophilus vaginalis)* is sensitive to high doses of metronidazole. Metronidazole was found to be ineffective against fungi in *in-vitro* studies.

Resistance
Some species of Trichomonas vaginalis have developed resistance to metronidazole. After long-term use, Bacteroides fragilis and other anaerobic bacteria can develop resistance as well. Resistance to metronidazole, may be due to poor cellular penetration and/or nitroreductase activity.

5.2 Pharmacokinetic properties

Absorption:
As it administered by injection, all of the drug is transferred to the body.

Distribution:
Mean serum levels obtained after 20 minutes of intravenous perfusion with solution containing 500 mg metronidazole is 18 mcg/ml. When the same dose is repeated 8 hours apart, serum levels are maintained. When it is repeated 12 hours apart, serum level is 13 mcg/ml. The plasma half-life is 8-10 hours. Protein binding is low (less than 10%). Distribution is fast and it concentration in lungs, kidneys, liver, skin, bile, cerebrospinal fluid, saliva, seminal fluid and vaginal secretions is high. Metronidazole passes into breast milk and placenta.

Biotransformation:
It is metabolized in the liver and it is found in high concentrations in the liver and bile. Metronidazole is metabolized into two metabolites with antibacterial activity in the body. - "Alcohol" metabolite is the primary metabolite. Its bactericidal effect against anaerobic bacteria is 30% of the effects of metronidazole. Elimination half-life is about 11 hours.
- "Acid" metabolite is present in small amounts and has 5% of the bactericidal effect of metronidazole.

Elimination:
It is excreted mainly through urine (excreted unchanged metronidazole 40-70%), and therefore urine can turn a red-brown color.

Linearity/non-linearity:
There is no information on dose linearity.

5.3 Pre-clinical safety data

Metronidazole was shown to be carcinogenic in mice and rats, after chronic oral administration. However, similar studies in hamsters gave negative results. Epidemiological studies did not demonstrate any clear evidence of increased carcinogenic risk in humans. Therefore, long-term metronidazole therapy should be carefully evaluated. Metronidazole was

shown to be mutagenic in bacteria *in-vitro*. No sufficient findings were obtained for mutagenic effects in *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

The mixture should be clear to ensure that the solutions used together do not cause any incompatibilities.
Metronidazole should not be mixed with cefamandol-naphthate, cefoxitin sodium, 10% dextrose, sodium lactate, penicillin G potassium.

6.3 Shelf life

24 months

6.4 Special precautions for storage

It should be stored at room temperature between 15° - 30°C.
It should not be used if the solution is not clear, the bag contains foreign substances or it is damaged.
The remaining part of the used solution should not be used again.

6.5 Nature and contents of container

BIOFLEKS METROSEL 0.5% IV Solution for Perfusion, in 100 ml PVC Bag with two outputs, with protective HDPE Overpouch containing 0.5 g/100 ml of metronidazole, with or without sets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with "Regulation on Control of Medical Wastes" and "Regulation on Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

202 / 20

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 14.03.2003
Date of authorization renewal: 19.08.2009

10. DATE OF REVISION OF THE SmPC

14.12.2013.