Summary of Product Characteristics (SPC)

Product Information

Name of the Product: Metronidazole infusion 500mg/100ml PP

Applicant:

Name: Shijiazhuang No.4 pharmaceutical Co., Ltd.

Production Address: Yangzi Road, Economic & Technological Development Zone, Shijiazhuang City, Hebei Province, China;

Official Address: No. 518 East Huaian Road, Hi-tech Industrial Development Zone, Shijiazhuang City, Hebei Province, China;

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Metronidazole Intravenous Infusion 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle of Metronidazole Injection contains 500mg Metronidazole and 800mg Sodium Chloride, Water for injection 100ml q.s.

3. PHARMACEUTICAL FORM

Solution for intravenous infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Metronidazole is mainly used in the treatment of anaerobe bacterial infection.

4.2. Posology and method of administration

Doses for the adult In the treatment of anaerobic bacteria infections, administer by intravenous drip according to 1g/70kg for the first time, and calculate the does according to 7.5mg/kg during the course of treatment, and interval time is 6~8hours.

2. Doses for the children in the treatment of anaerobic bacteria infection, the doses are similar with that of the adult.

4.3. Contraindications

Forbid to use the medicine for the patients with the diseases in central nervous system and blood.

Indication for women in pregnant and suckle

Forbid to use this medicine for women in pregnant and suckle.

The dose of Metronidazole Injection should be reduced by half for the patients with renal impairment.

The drug has the function of increasing the efficiency of anticoagulants such as Warfarin.

The patients are not allowed to drink during the treatment.

The treatment should be stopped while motorial irregularity and symptom of central nervous system occur.

4.4. Special warnings and special precautions for use

Precautions: (1)The metabolites of this product make urine dark red. (2) The dose should be reduced when this product used for patients with severe hepatic diseases. (3) Alcoholic beverages should not be consumed during metronidazole therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. (4) The osmolarity of this product should be 260~340mOsmol/kg.

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

（1）Metronidazole may increase the anticoagulant effect of warfarin and other oral anticoagulants resulting in a prolongation of prothrombin time. (2) The simultaneous administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported. (3) The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma

clearance of metronidazole. Dose should be adjusted according to the test result of plasma concentration.（4）The alcoholic patients who are using metronidazole and disulfiram concurrently can lead to psychotic reactions. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks. (5) This product can interfere aminotransferase and LDH measurement results, make cholesterol, triglyceride levels decreased.

4.6. Fertility, pregnancy and lactation

This product has been observed in animal experiments for mutagenesis, and pregnant and lactating women are prohibited.

4.7. Effects on ability to drive and use machines

No studies have been performed on the effects of Metronidazole on the ability to drive or use machines.

4.8. Undesirable effects

15~30% of the cases were reported side-effect, and adverse reactions frequently associated with Metronidazole include: Digestive tract reaction such as nausea, vomiting, and diarrhea stomach pain or cramps, anorexia; Symptoms of nerve system include headache and swirl; Abnormal sensation, numb limbs and tense tendons, ataxia, and multiple neuritis occasionally happen; Over high dose can cause convulsion. Few cases have the symptoms such as urticaria, moisst, pruritus, cystitis, dysuresia, change in taste sensation and decreased white cell. But the abovementioned symptoms are all reversible and recover after the administration.

4.9 Overdose

Large doses can cause convulsions.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: J01XD01

Pharmacotherapeutic group: Metronidazole is mainly used in the treatment of anaerobe bacterial infection.

Mode of action:

Potent Nitro-imidazole derivative. The exact mechanism of action of metronidazole is unknown. At physiologic pH, metronidazole is un-ionized and taken up readily by anaerobic organisms. The drug then undergoes intracellular chemical reduction via mechanisms unique to anaerobes. Reduced metronidazole interacts with DNA and inhibits nucleic acid synthesis, leading to cell death. Metronidazole is equally effective against dividing and nondividing cells.

The nitroimidazole antibiotic metronidazole has a limited spectrum of activity that encompasses various protozoans and most Gram-negative and Gram-positive anaerobic bacteria. Many clinicians still consider metronidazole to be the 'gold standard' antibiotic against which all other antibiotics with anaerobic activity should be compared.

5.2 Pharmacokinetic properties

The peak value is observed 20mins after administering by intravenous drip and binding rate with protein <5%. After absorption Metronidazole distributes widely in all kinds of tissues and body liquids, and pass easily blood brain barrier to the tissues such as saliva, placenta, bile, latex, ammiotic fluid, semen, urine, purulence, cerebrospinal fluid and etc. It is reported that the concentration in placenta, latex, bile is similar with that in plasma. For the healthy people the concentration of Metronidazole in the cerebrospinal fluid is about 43% of that in the plasma, and the effective concentration can remain 12hours. 60~80% of the preparation is excreted via kidney, about 20% of Metronidazole is excreted unchanged in the urine, the other is excreted in the urine as the products of metabolism (25%- glucuronicacid combo, 14%-other kinds of products of metabolism). 10% of Metronidazole is excreted in the dejection, and 14% is excreted from skin.

Absorption

Oral doses of MZ are absorbed rapidly and almost completely in the human organism. MZ diffuses well into nearly all body tissues, including the central nervous system, and spreads widely throughout the body. Peak serum levels are generally reached in about 1 h after ingestion. Its half-life is about 8 h and within 24 h after intake the level of MZ in blood is markedly low. MZ binds to plasma proteins at a degree of less than 20%.

MZ penetrates the blood-brain or bloodcerebrospinal fluid barrier and can be found in the human female reproductive organs, aqueous humors, prostate glands and seminal vesicles.

Distribution

Metronidazole is widely distributed into most body tissues and fluids including bone, bile, saliva, pleural fluid, peritoneal fluid, vaginal secretions, seminal fluid, CSF, and cerebral and hepatic abscesses. Distribution is similar whether the drug is administered orally or by IV infusion. Concentrations of metronidazole in CSF are reported to be 43% of concurrent plasma concentrations in patients with uninflamed meninges and equal to or greater than concurrent plasma concentrations of the drug in patients with inflamed meninges. The drug also distributes into erythrocytes. Limited data suggest that the volume of distribution of metronidazole may be reduced in geriatric individuals as compared with younger individuals, perhaps as a result of decreased erythrocyte uptake of the drug in such patients. Metronidazole is less than 20% bound to plasma proteins.

Metabolism

The metabolism of metronidazole was studied in microsomes isolated from livers of human kidney donors.The formation of the major in vivo metabolite, hydroxymetronidazole, proceeded according to biphasic kinetics, suggesting the involvement of at least two enzymatic sites. The affinity constant (Km) of the high affinity site ranged from 140 to 320 microM and metabolism at this site contributed more than 75% of the intrinsic clearance. Thus, at therapeutic doses of metronidazole most of the hydroxylation in vivo should be associated with this site. Antipyrine, cimetidine, alpha-naphthoflavone, caffeine, theophylline, mephenytoin, tolbutamide,

quinidine, acetone and nifedipine were poor inhibitors of the formation of hydroxymetronidazole by human liver microsomes. Propranolol (500 microM) inhibited the hydroxylation rate by 70%. Phenacetin inhibited metronidazole hydroxylation with a competitive inhibition constant (Ki) of 4-5 microM. However, metronidazole did not inhibit the O-deethylation of phenacetin. It is concluded that cytochromes P450 IA2, IIC9, IIC10, IID6, IIE1 and IIIA3 do not contribute significantly to the high affinity hydroxylation of metronidazole in man.

Excretion

MZ in humans is primarily excreted via the renal pathway, mostly in the form of metabolites,to a lesser extent unchanged. The elimination half-life values vary between 6 and 12 h, with an average of about 7 h.About 80% of the compounds is eliminated after hydroxylation to hydroxymetronidazole. Some 6-15% of MZ is excreted in the feces, partly in the form of the active metabolite 1-(2-hydroxyethyl)-2-carboxyl-5-nitroimidazole.

The presence of MZ is also detectable in other body fluids, including vaginal secretions and seminal fluids, bile, saliva, sweat.It is also excreted via breast milk, with a half-life of about 9 h.

5.3 Preclinical safety data

Carcinogenesis

Metronidazole (MTZ, 1-[2-hydroxyethyl]-2-methyl-5-nitroimidazole), an antiparasitic and antibacterial compound, is one of the world's most used drugs. MTZ is potentially carcinogenic to humans due to the following facts: it is a proven mutagen in bacterial systems, it is genotoxic to human cells and also, it is carcinogenic to animals. However, due to inadequate epidemiological evidence, it is not considered as a risk factor for cancer in humans. As it will be discussed here, the existing population studies are deficient since they have not included sufficient sample size, the follow-up time has not been long enough, and the individual sensitivity to the drug might have been acting as a confounding factor. Due to the increasing use of this drug, more and improved studies are needed to elucidate its mechanism of genotoxicity and its carcinogenic potential.

Reproductive toxicity

The reproductive toxicology of metronidazole was studied in rats. Male Charles River Crl:CD(S-D)BR rats (10/group) were treated with metronidazole as a dietary admixture at doses of 0 (control), 25, 100, and 400 mg/kg/day for 8 weeks. The reversibility of effects after a 312 months recovery period was determined in separate groups of 10 control and 10 rats treated with 400 mg/kg/day of metronidazole. After 2 and 4 weeks of metronidazole treatment, mating performance and fertility in treated and control animals were comparable. After 6 weeks of treatment, all high-dose rats were infertile; however, fertility in low- and middose rats was not affected. High-dose male rats killed after 8 weeks of treatment showed markedly decreased testicular and epididymal weights, and markedly decreased testicular spermatid counts and epididymal sperm counts. Most of the few epididymal sperm present in high-dose rats were viable, but morphologically abnormal. Histologically, severe degeneration of the seminiferous epithelium was observed in the testes of high-dose rats; the tubules were generally devoid of primary or secondary spermatocytes and spermatids.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial: 36 months.

After opening: To be used immediately.

6.4 Special precautions for storage

Protect from light and store in well-closed containers.

6.5 Nature and contents of container

Metronidazole and Sodium Chloride Injection (100 ml:0.5g:0.8g) is presented in polypropylene (PP) bottles.The polypropylene (PP) bottles Should be transparent, bright and clean, internal and external should not be visible to the foreign body.100 bottles are packed in a Carton.

6.6 Special precautions for disposal and other handling

Intravenous administration

Vial	**Diluent (ml)**
500 mg	100

For single use only. Discard any remaining solution.

Metronidazole and Sodium Chloride Injection should be infused at a rate of no more than 10 ml/min.

7. MARKETING AUTHORISATION HOLDER

Shijiazhuang No.4 Pharmaceutical Co.,Ltd.

Address: No. 518 East Huaian Road, Hi-tech Industrial Development Zone, Hebei, China

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

Registration number in China:

GUOYAOZHUNZI H13022486

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT