METROZINE
(Metronidazole)

200 mg & 400 mg

Syrup & Tablets

WARNING

Metronidazole has been shown to be carcinogenic in mice. Unnecessary use of the drug should be avoided. Its use should be reserved for the indicated conditions.

COMPOSITION

Tablets

Each film-coated tablet contains:
Metronidazole ……400 mg

Each film-coated tablet contains:
Metronidazole…… 200 mg

Syrup

Each 5ml contains:
Metronidazole benzoate equivalent to Metronidazole B.P….. 200mg

THERAPEUTIC INDICATIONS

Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.
Metronidazole is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides*, Fusobacteria, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*. It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*.

Metronidazole is indicated in adults and children for the following indications:
1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.
2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.
3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).
5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
6. Giardiasis.
7. Acute ulcerative gingivitis.
8. Anaerobically-infected leg ulcers and pressure sores.
9. Acute dental infections (e.g. acute pericoronitis and acute apical infections).

DOSAGE AND ADMINISTRATION

***Prophylaxis against anaerobic infection* (especially colorectal and gynecological surgery)**

Adults
400 mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.
Children
Children < 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery Newborns with a gestation age < 40 weeks: 10mg/kg body weight as a single dose before operation

***Treatment of established Anaerobic infections*:**
The duration of a course of Metronidazole treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.
Adults
800 mg followed by 400 mg 8 hourly.

Children

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.
Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours. In newborns with a gestation age < 40 weeks, accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Protozoal and other infections:

Dosage is given in terms of metronidazole or metronidazole equivalent

	Duration of dosage in days	Adults and children over 10 years	Children		
			7 to 10 years	3 to 7 years	1 to 3 years
Urogenital trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently	7 or	2000mg as a single dose or 200 mg three times daily or	40mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2-3 doses; not to exceed 2000mg/dose		
	5-7	400mg twice daily			
Bacterial vaginosis	5-7 or	400 mg twice daily			
	1	2000mg as a single dose			
Amoebiasis (a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three times daily	200 mg four times daily	200 mg three times daily
(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5-10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(d) Symptomless cyst passers	5-10	400-800 mg three times daily	200-400 mg three times daily	100-200 mg four times daily	100-200 mg three times daily
	Alternatively, doses may be expressed by body weight 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day				
Giardiasis	3	2000mg once daily or	1000mg once daily	600-800 mg once daily	500 mg once daily
	5	400mg three times daily or			
	7-10	500mg twice daily			
	Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.				
Acute ulcerative gingivitis	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
Acute dental infections	3-7	200 mg three times daily			
Leg ulcers and pressure sores	7	400 mg three times daily			

Children and infants weighing less than 10 kg should receive proportionally smaller dosages.
Elderly: Metronidazole is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.

Eradication of Helicobacter pylori in pediatric patients:
As a part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.

CONTRAINDICATIONS

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Encephalopathy and peripheral neuropathy
Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.
Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible. Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity. Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis
Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.
The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Risk of Hepatotoxicity and Death in Patients with Cockayne Syndrome
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. Obtain liver function tests prior to the start of therapy, within the first 2–3 days after initiation of therapy, frequently during therapy and after end of treatment. Discontinue metronidazole if elevation of liver function tests occurs, and monitor liver function tests until the baseline values are reached.
Advise patients with Cockayne syndrome to stop taking metronidazole immediately if they experience any symptoms of potential liver injury, such as abdominal pain, nausea, change in stool color or jaundice, and to contact their healthcare provider.

Precautions

Hepatic Impairment
Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. For patients with severe hepatic impairment (Child-Pugh C), a reduced dose of metronidazole is recommended. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed but these patients should be monitored for metronidazole associated adverse events.
Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Renal Impairment
Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended

Fungal Superinfections
Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Use in Patients with Blood Dyscrasias
Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

Drug-Resistant Bacteria and Parasites
Prescribing metronidazole in the absence of a proven or strongly suspected bacterial or parasitic infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria and parasites.

Interaction with Alcohol
Discontinue consumption of alcoholic beverages or products containing propylene glycol while taking metronidazole and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Treatment of Bacterial and Parasitic Infections
Patients should be counseled that metronidazole should only be used to treat bacterial and parasitic infections. Metronidazole does not treat viral infections (*e.g.,* the common cold). When metronidazole is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Metronidazole in the future.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Tumors affecting the liver, lungs, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.
Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m^2 (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.
Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage.
Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up at 400 mg/kg/day (similar to the maximum recommended clinical dose, based on body surface area comparisons) for 28 days. However, rats treated at the same dose for 6 weeks or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in most rats after an eight-week, drug-free recovery period.

DRUG INTERACTIONS

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.
Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.
Patients receiving phenobarbital or phenytoin metabolize metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.
Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.
Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

PREGNANCY AND LACTATION

There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. Nevertheless Metronidazole, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

Effects on ability to drive and use machines

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

ADVERSE DRUG REACTIONS

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).
Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Blood and lymphatic system disorders:
Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known: leucopenia.

Immune system disorders:
Rare: anaphylaxis
Not known: angioedema, urticaria, fever.

Metabolism and nutrition disorders:
Not known: anorexia.

Psychiatric disorders:
Very rare: psychotic disorders, including confusion and hallucinations. Not known: depressed mood

Nervous system disorders:
Very rare:
• encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.
• drowsiness, dizziness, convulsions, headaches
Not known:
• during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.
• aseptic meningitis

Eye disorders:
Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient.
Not Known: optic neuropathy/neuritis

Ear and labyrinth disorders:
Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

Gastrointestinal disorders:
Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:
Very rare:
• increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible 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: skin rashes, pustular eruptions, acute generalized exanthematous pustulosis, pruritis, flushing
Not known: erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia.

Renal and urinary disorders:
Very rare: darkening of urine (due to metronidazole metabolite).

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. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific antidote for metronidazole overdosage. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01X D01
Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardia lamblia* and against anaerobic bacteria.

Pharmacokinetic properties

Metronidazole is rapidly and almost completely absorbed on administration of Metronidazole tablets; peak plasma concentrations occur after 20 min to 3 hours.
The half-life of metronidazole is 8.5 ± 2.9 hours. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants

PRECLINICAL SAFETY DATA

Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear 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 or humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative

PRESENTATION

Metrozine 200mg Tablets are available in blister pack of 100 Tablets.
Metrozine 400mg Tablets are available in blister pack of 100 Tablets.
Metrozine 200mg/5ml suspension is available in 90ml.

INSTRUCTIONS

-To be sold on the prescription of a registered medical practitioner only.

-Protect from sunlight, moisture and heat.

-Store below 30°C.

-Keep all medicines out of sight and reach of children.

-Shake well before use.

REGISTRATION NUMBER

Metrozine 200mg Tablets : 010932 (Mfg. U.S.P. Specs)

Metrozine 400mg Tablets : 010931 (Mfg. U.S.P. Specs)

Metrozine Suspension : 010933 (Mfg. B.P. Specs)

Manufacturing License No. : 000647

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited,

32-Km, Multan Road, Lahore – Pakistan

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