# SUMMARY OF PRODUCT CHARACTERISITCS

**1.3.1.1 NAME OF THE MEDICINAL PRODUCT**

COMMERCIAL NAME : GENOGYL-125

INN or GENERIC NAME : Metronidazole Oral Suspension BP

**1.7.3 DOSAGE FORM :** LIQUID ORAL SUSPENSION

**1.3.1.2. QUALITATIVE AND QUANTITATIVE COMPOSITION:**

| Sr. No. | Ingredients |
|---|---|
| 1. | Metronidazole Benzoate |
| 2. | Sucrose |
| 3. | Liquid Glucose |
| 4. | Sorbitol Solution 70% (Non-crystallising) |
| 5. | Glycerol BP |
| 6. | Carmellose Sodium |
| 7. | Colloidal Anhydrous Silica |
| 8. | Sodium Methyl Hydroxybenzoate |
| 9. | Sodium Propyl Hydroxybenzoate |
| 10. | Polysorbate 80 |
| 11. | Sodium Chloride |
| 12. | Citric acid Monohydrate |
| 13. | Sodium Citrate |
| 14. | Essence Vanilla Narda |
| 15. | Pineapple Flavour Singapore |
| 16. | Essence Rose White |
| 17. | Sunset Yellow FCF |
| 18. | Purified Water |

## 1.3.1.4. CLINICAL PARTICULARS

### THERAPEUTIC INDICATIONS:

GENOGYL-125 is indicated in oral treatment of Urogenital Trichomonasis, giardiasis,infections caused by anaerobic bacteria like Bacteroides fragilis and bacterial vaginosis.It is also effective in the treatment of rosacea and Crohn's disease .

### POSOLOGY & METHOD OF ADMINISTRATION:

**POSOLOGY:** As directed by the Physician. Not for use in infants.

**Method of Administration :** Oral Route of Administration

### CONTRAINDICATIONS:

GENOGYL-125 is contraindicated in patients who are hypersensitive to any of the ingredients or any chemically related quinolone antibacterial. GENOGYL-125 should not be used in patients with blood dyscrasias or with active disease of the central nervous system.The use of metronidazole should be avoided during pregnancy, especially the first trimester and whilst breast-feeding.

### SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

All patients receiving metronidazole for more than 10 days should be monitored and treatment discontinued if signs of peripheral neuropathy or CNS toxicity develop.Doses should be reduced in patients with severe liver damage and in patients with renal failure.Concomitant use with alcohol should be avoided.When given in conjunction with alcohol, metronidazole may provoke a disulfiram-like reaction in some individuals.Metronidazole enhances the effect of warfarin.Patients receiving phenobarbitone metabolize metronidazole at a greater rate than normal, reducing the half-life to approximately 3 hours.

### INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

### ACENOCOUMAROL

Oral Metronidazole has been reported to inhibit warfarin metabolism and may be capable of affecting other coumarin anticoagulants as well, resulting in an enhanced anticoagulant effect. Because the maximum concentration (Cmax) of topically administered Metronidazole is

approximately 1% of values seen with oral administration, this interaction is less likely to occur with topical Metronidazole administration. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of treatment with metronidazole and should be reassessed periodically during concurrent therapy. Adjustments of the Acenocoumarol dose may be necessary in order to maintain the desired level of anticoagulation.

**AMPRENAVIR**

Amprenavir oral solution contains a large amount of propylene glycol in the formulation to achieve adequate solubility of Amprenavir. While the acceptable intake of propylene glycol for pharmaceuticals has not been established, certain patient populations may be at risk for propylene glycol accumulation and toxicity, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity and hemolysis. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway and patients being treated concurrently with metronidazole may not be able to adequately metabolize and eliminate propylene glycol. Therefore, the coadministration of Amprenavir oral solution and Metronidazole is contraindicated. Patients should receive Amprenavir oral solution only when Amprenavir capsules or other protease inhibitor formulations are not therapeutic options.

**ANISINDIONE**

Metronidazole has been reported to inhibit warfarin metabolism and may be capable of affecting other coumarin anticoagulants as well, resulting in an enhanced anticoagulant effect. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of treatment with Metronidazole and should be reassessed periodically during concurrent therapy. Adjustments of the anisindione dose may be necessary in order to maintain the desired level of anticoagulation.

**CARBAMAZEPINE**

Significantly increased Carbamazepine serum concentrations and CNS toxicity have been reported in a patient receiving concurrent Metronidazole. The mechanism was thought to be inhibition by Metronidazole of cytochrome P450 aromatic oxidative metabolism of Carbamazepine. Further study is needed to validate this interaction. When Metronidazole and Carbamazepine are coadministered, monitor Carbamazepine serum concentrations and observe patients for signs and symptoms of carbamazepine toxicity (nausea, dizziness, diplopia, CNS effects). Doses of

Carbamazepine may need to be adjusted when Metronidazole is added to or withdrawn from therapy.

**CHOLESTYRAMINE**

Concomitant administration of oral Metronidazole and cholestyramine reduces the absorption of Metronidazole. The bioavailability of Metronidazole was decreased by 21% in a single dose study with healthy volunteers. The dosing regimens for these two drugs should be separated as much as possible.

**CIMETIDINE**

Concomitant Cimetidine and Metronidazole therapy may result in inhibition of Metronidazole metabolism. In six volunteers, Gugler & Jensen (1983) reported an increase in the serum half-life of Metronidazole 400 mg from 6.2 to 7.4 hours and a reduction in clearance of Metronidazole by 30% with the addition of cimetidine 400 mg. This interaction was felt to be due to ability of cimetidine to inhibit cytochrome P-450 enzymes, which are involved in the metabolism of Metronidazole. Patients receiving concurrent cimetidine and Metronidazole therapy should be monitored for an increased incidence of adverse effects with Metronidazole.

**CIPROFLOXACIN**

Serum concentrations of ciprofloxacin and Metronidazole were not altered with coadministration of these two drugs. Metronidazole did not affect the pharmacokinetics or bactericidal activity of oral enoxacin and Fleroxacin or parenteral Ciprofloxacin and Ofloxacin in a single-dose study of healthy volunteers.

**COTRIMOXAZOLE**

A case report from the University of Michigan documents a disulfiram-like reaction including vomiting and flushing when a 16-year-old patient was treated concurrently with intravenous Trimethoprim-Sulfamethoxazole and Metronidazole. The authors concluded that the reaction was likely caused by the 10% ethanol base of the Trimethoprim-Sulfamethoxazole for infusion reacting with Metronidazole. Increased acetaldehyde plasma levels resulting in an increased risk of vomiting, flushing, headaches, tachycardia and hypotension Observe patients for disulfiram-like symptoms including vomiting, flushing, headaches, tachycardia and hypotension. If possible, administer one or both drugs orally.

**PREGNANCY AND LACTATION:**

Metronidazole crosses the placenta and enters fetal circulation rapidly. Although there have been cases reported of fetal malformations occurring in women who had been exposed to Metronidazole,

there is no significant evidence indicating that prenatal use of METRONIDAZOLE in early pregnancy increases the overall risk of birth defects .
METRONIDAZOLE is excreted in breast milk in concentrations approaching those in serum following therapeutic doses. Although no toxic effects on the infant have been observed during breast feeding, the drug should be avoided if possible. When single dose therapy (2 g orally) is amenable (i.e, trichomoniasis), withholding breast feeding for 12 to 24 hours after administration of the dose greatly reduces the amount of drug exposed to the infant during the breast feeding period

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES :**

Metronidazole Suspension may make you feel drowsy, dizzy, confused or affect your vision, cause fits or hallucinations. Make sure you are not affected before you drive, operate machinery or take part in any activities where these may put you or others at risk.

**UNDESIRABLE EFFECT:**

The most common side effects are gastro-intestinal disturbances, especially nausea and an unpleasant metallic taste; abdominal cramps, epigastric discomfort, nausea is sometimes accompanied by headache, anorexia and vomiting. Diarrhoea, dry mouth, a furred tongue, glossitis and stomatitis may also occur. There have been reports of pseudomembranous colitis associated with metronidazole. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities and epileptiform seizures are serious adverse effects on the nervous system that have been associated especially with high doses of metronidazole or prolonged treatment. Weakness, dizziness, ataxia, drowsiness, insomnia and changes in mood or mental state such as depression or confusion have also been reported.
Flushing, dysuria, urticaria and angioneurotic oedema may occur. Temporary moderate leucopenia may occur in some patients receiving Metronidazole. Skin rashes and pruritis occur occasionally.Other side-effects include urethral discomfort and darkening of the urine. Anaphylaxis and raised liver enzymes have been reported.

**OVERDOSE**:

Metronidazole does not seem to be especially toxic in the case of an overdose.
In cases of suicide attempts and accidental overdoses, the following symptoms of an overdose with metronidazole were seen:

- Coordination problems

- Nausea and vomiting.

Studies that used very high doses of the drug during radiation treatment for cancer suggested that an overdose might increase the risk of seizures or nerve problems affecting the hands and feet (such as numbness or paralysis). However, these are also possible Metronidazole side effects, even at normal doses. A Metronidazole overdose is likely to cause problems when taken by mouth or IV, rather than applied to the skin or used vaginally.

The treatment for an overdose will vary and there is no specific antidote. If the Metronidazole overdose was recent and taken by mouth, a healthcare provider may administer certain medicines or place a tube into the stomach to "pump the stomach." Treatment also involves supportive care, which consists of treating the symptoms that occur as a result. For example, supportive treatment options may include:

Fluids through an intravenous line (IV), if necessary

Close monitoring of vital signs, such as heart rate and breathing

Other treatment based on the complications that occur.

It is important that you seek medical attention immediately if you believe that you may have taken too much Metronidazole.

### 1.3.1.5 PHARMACOLOGICAL PROPERTIES

**PHARMACODYNAMIC PROPERTIES:**

**MECHANISM OF ACTION**

Metronidazole is a nitroimidazole antibiotic. Metronidazole has a limited spectrum of activity that includes various protozoans and most Gram-negative and Gram-positive anaerobic bacteria. METRONIDAZOLE appears to selectively produce cytotoxic effects in anaerobes by a reduction reaction, depriving the organism of required reduction equivalents. The complete mode of action of METRONIDAZOLE has not been fully elucidated. The cytotoxic property of METRONIDAZOLE is specific for anaerobic organisms and is thought to be due to intermediate or final products of reduction of the nitro-group of METRONIDAZOLE. Preferential reduction of the 5-nitro group may occur by a ferrodoxin-like system and an anaerobic environment is required for reduction to proceed. Although the drug readily diffuses into both aerobic and anaerobic organisms it remains unchanged in aerobic bacteria. The nitro reduction which takes place in anaerobic bacteria creates a diffusion gradient resulting in a greater uptake of METRONIDAZOLE by these organisms. The specific degradation product of METRONIDAZOLE responsible for the therapeutic effect is not

known. The most probable product is the hydroxylamine derivative. Other investigators postulate that the amino derivative with the imidazole ring cleaved is more likely the cause.
The reduction reaction is a pyruvate phosphoroclastic reaction important to the electron transport proteins, ferredoxins, commonly found in anaerobes. The redox potential of the METRONIDAZOLE reduction is only slightly above that of the electron transport redox potential, thus extensive reduction of METRONIDAZOLE occurs. This is not possible in aerobic systems, in which the redox potential is well above that necessary to promote this reaction. Anaerobic organisms are thus deprived of required reduction equivalents, resulting in loss of the helical structure of DNA, strand breakage and associate impairment of the ability of DNA to function as a template.

**PHARMACOKINETIC PROPERTIES:**

Metronidazole produces peak serum concentrations 1 to 2 hours following oral administration. The drug is metabolized in the liver to an active metabolite and has a half-life of approximately 6 to 11 hours. About 20% of a dose is excreted unchanged in the urine.

**PRECLINICAL SAFETY DATA**

Preclinical Data reveal no special hazard for humans based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

**1.3.1.6. PHARMACEUTICAL PARTICULARS**

**LIST OF EXCIPIENTS:**

Sucrose IHS, Liquid Glucose NF, Sorbitol Solution 70% ( Non-Crystallising) BP, Glycerol BP, Carmellose Sodium BP, Colloidal Anhydrous Silica BP, Sodium Methyl Hydroxy Benzoate BP, Sodium Propyl Hydroxy Benzoate BP, Polysorbate-80 NF, Sodium Chloride BP, Citric Acid Monohydrate BP. Essence Vanilla Narda IHS, Pineapple Flavour Singapore IHS , Essence Rose White IHS , Colour Sunset Yellow FCF IHS & Purified Water BP.

**INCOMPATIBILITIES:** None

**SHELF LIFE:** 36 Months from the date of Manufacturing.

**SPECIAL PRECAUTIONS FOR STORAGE**

Keep the container tightly closed. Protect from light. Store at a temperature not exceeding 30°C. Shake well before use
KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

**NATURE AND CONTENTS OF THE CONTAINER:**
A single bottle containing 100 ml of suspension with 25 mm ROPP cap(Blue/ Silver with GENO logo) fitted with a 10 ml HDPE measuring cup on top of this ROPP cap is packed in a carton with a single packing insert.

**MARKETING AUTHORISATION HOLDER:**
GENO PHARMACEUTICALS LTD.
Pharmaceutical Complex,
Tivim Industrial Estate,
Karaswada, Mapusa, Goa, India,
Phone: +91-832-2257216/17

**INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL:**
For Internal use only. Keep the container tightly closed. Protect from light. Store at a temperature not exceeding 30°C.
SHAKE WELL BEFORE USE
KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

**MARKETING AUTHORIZATION NUMBER :** Mfg. Lic. No.: 52

**NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS:**

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