SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

TROZ METRONIDAZOLE 400MG

This information is intended for use by health professional

1. Name of the medicinal product TROZ 400 TABLETS

2. Qualitative and quantitative composition

Each uncoated tablet contains

METRONIDAZOLE 400MG

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Yellow-colored, round biconvex, 13 mm uncoated tablets with 'GOL' engraved on one side and break line on the other.

4. Clinical particulars

4.1 Therapeutic Indications

Metronidazole is indicated for the treatment and prophylaxis of infections caused by anaerobic bacteria and susceptible protozoa. Its therapeutic indications include, but are not limited to:

- **Treatment of Anaerobic Bacterial Infections**, including:
  - Intra-abdominal infections (e.g., peritonitis, abscesses)
  - Pelvic infections (e.g., endometritis, bacterial vaginosis)
  - Skin and soft tissue infections
  - Central nervous system infections (e.g., brain abscess)
  - Dental infections (e.g., acute necrotizing ulcerative gingivitis)
- **Treatment of Protozoal Infections**, including:
  - **Trichomoniasis**: Treatment of trichomonas vaginal infections in females and urethritis in males caused by *Trichomonas vaginalis*
  - **Giardiasis**: Treatment of intestinal infections caused by *Giardia lamblia*
  - **Amoebiasis**: Treatment of intestinal and hepatic infections caused by *Entamoeba histolytica*
- **Adjunctive therapy in the eradication of *Helicobacter pylori*** in combination with other antibiotics and proton pump inhibitors, as part of triple or quadruple therapy regimens.
- **Prophylaxis of anaerobic infections** in surgical procedures with a high risk of contamination, especially in gastrointestinal or gynecological surgeries.

4.2 **Posology and method of administration**

Posology (Dosage)

The recommended dosage of Metronidazole varies depending on the **type and severity of infection, patient age and weight,** and **national/international treatment guidelines.**
is available as tablets, allowing for flexible dose adjustment and suitability for both adult and paediatric populations.

Adults and Adolescents (≥12 years)

INDICATION	Typical Dosage Using 400 mg Tablets	Duration
Anaerobic bacteria infection	2 tablet every 8 hours	7-10 days
Trichomoniasis	10 tablets (2 g) as a single dose or 2 tablets twice daily	Single dose or 7 days
Giardiasis	10 tablets (2 g) once daily or 2 tablets three times daily	3–5 days
Amoebiasis (intestinal/hepatic)	4 tablets (800 mg) three times daily	5–10 days
Bacterial vaginosis	2–3 tablets (400–600 mg) twice daily	2–3 tablets (400–600 mg) twice daily
H. pylori eradication	2 tablets (400 mg) twice daily in combination regimens	7–14 days
Surgical prophylaxis	5–10 tablets (1–2 g) 1–2 hours before surgery	Single dose

Special Populations & Administration

- **Renal & Hepatic Impairment**: Adjust dosing or extend intervals based on clinical judgment.
- **Pregnancy**: Avoid during the **first trimester** unless no alternative is available.

Method of administration

400 mg is administered orally.

- Tablets should be swallowed whole with a sufficient quantity of water.
- The medication can be taken with or without food. However, taking it with meals is recommended to minimize gastrointestinal side effects such as nausea or a metallic taste.
- For patients with swallowing difficulties, the 400 mg tablet may be crushed and dispersed in a small amount of water immediately prior to administration. The entire mixture should be consumed promptly to ensure full dosing.

400 mg is suitable for both adults and children, and its lower strength provides greater flexibility for weight-based dosing, especially in paediatric or elderly populations.

4.3 **Contraindications**

Use of **® 400 mg (Metronidazole)** is contraindicated in the following cases:

1. **Hypersensitivity to Metronidazole or Other Nitroimidazoles**
    - Patients with a known history of hypersensitivity or allergic reactions to metronidazole or other nitroimidazole derivatives (e.g., tinidazole).
2. **First Trimester of Pregnancy**
    - The use of metronidazole is contraindicated during the first trimester of pregnancy unless clearly necessary and prescribed by a physician after a benefit–risk assessment.
3. **Use with Alcohol or Products Containing Propylene Glycol**
    - Concomitant use of metronidazole with alcohol or propylene glycol-containing preparations is contraindicated due to the risk of a **disulfiram-like reaction** (flushing, nausea, vomiting, tachycardia).
4. **Active Central Nervous System (CNS) Disease**

- Patients with active neurological disorders such as **epilepsy, peripheral neuropathy**, or **a history of metronidazole-induced neurotoxicity** should avoid use, except under specialist supervision.

5. Severe Hepatic Impairment (without dosage adjustment)

- In patients with severe liver dysfunction, where dosage adjustment is not possible or monitoring is inadequate, use may be contraindicated due to accumulation and increased risk of neurotoxic effects.

4.4 Special warnings and precautions for use

The following warnings and precautions should be considered before initiating treatment with **400 mg (Metronidazole)**:

1. Neurological Effects

- **Peripheral neuropathy, seizures**, and **encephalopathy** have been reported, particularly with **high doses** or **prolonged use**.
- Treatment should be discontinued immediately if **neurological symptoms** (e.g., numbness, tingling, unsteadiness, confusion) occur.
- Caution is advised in patients with **existing CNS disorders** or those receiving metronidazole for longer than 10 days.

2. Hepatic Impairment

- Metronidazole is extensively metabolized in the liver; **accumulation may occur in patients with hepatic dysfunction,** increasing the risk of toxicity.
- In cases of **severe liver disease**, dosage adjustment and close clinical monitoring are recommended.

3. Use in Patients with Blood Dyscrasias

- Metronidazole should be used with caution in patients with **active or a history of hematologic disorders**, such as **leukopenia.**
- Regular blood counts are advisable during prolonged therapy.

4. Alcohol and Propylene Glycol Interaction

- Concurrent use of alcohol or propylene glycol-containing products is **strictly contraindicated** during therapy and for **at least 48 hours after the last dose**, due to the risk of a **disulfiram-like reaction** (flushing, nausea, vomiting, tachycardia).

5. Use during Pregnancy and Lactation

- Use in the **first trimester of pregnancy** is contraindicated unless clearly necessary.
- Caution should be exercised in the **second and third trimesters**; benefit–risk assessment is essential.
- Metronidazole is **excreted in breast milk**; temporary interruption of breastfeeding may be considered during high-dose or prolonged therapy.

6. Renal Impairment

- Although dose adjustment is usually not necessary in patients with mild-to-moderate renal impairment, caution is advised in **end-stage renal disease** and during **dialysis,** as accumulation of metabolites may occur.
- Dosing should preferably be scheduled **after dialysis sessions.**

7. Prolonged or Repeated Use

- Prolonged or repeated courses should be avoided unless absolutely necessary, as **cumulative exposure increases the risk of neurotoxicity and carcinogenicity** (observed in animal studies).

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

Metronidazole has the potential to interact with various drugs and substances, which may alter its efficacy or increase the risk of adverse effects. Caution is advised when co-administering **400 mg** with the following:

1. Alcohol and Propylene Glycol

- Concomitant use of **alcohol** or **propylene glycol-containing products** is contraindicated due to the risk of a **disulfiram-like reaction**, which may include flushing, nausea, vomiting, abdominal cramps, headache, and tachycardia.
- Patients should abstain from alcohol **during treatment** and for **at least 48 hours after the last dose.** 2. Disulfiram

- Concurrent administration with **disulfiram** may cause **acute psychotic reactions or confusion.**
- Use is contraindicated within **2 weeks of disulfiram therapy**.

3. Warfarin and Other Oral Anticoagulants

- Metronidazole may **enhance the anticoagulant effect** of warfarin and other coumarin-type agents by **inhibiting hepatic metabolism,** leading to an increased risk of bleeding.
- Prothrombin time or INR should be monitored closely, and dosage of anticoagulants may need adjustment.

4. Lithium

- Metronidazole may **increase serum lithium levels** when used concurrently.
- Plasma lithium levels, renal function, and signs of lithium toxicity should be monitored if coadministration is necessary.

5. Cyclosporine

- Co-administration may result in **elevated cyclosporine levels**. Monitoring of cyclosporine levels and renal function is recommended.

6. Phenobarbital and Phenytoin
   These **enzyme-inducing anticonvulsants** may **reduce plasma concentrations** of metronidazole, potentially decreasing its effectiveness.

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7. Cimetidine

   - May **inhibit the metabolism of metronidazole**, leading to elevated serum concentrations and an increased risk of adverse effects such as neurotoxicity.

8. 5-Fluorouracil (5-FU)

   - Metronidazole may **reduce the clearance** of 5-FU, leading to increased toxicity. Close monitoring is advised.

9. Busulfan

   - Plasma levels of busulfan may increase significantly with metronidazole, leading to **lifethreatening toxicity**. The combination should be avoided.

10. Oral Contraceptives

    - Although the evidence is limited, some reports suggest that metronidazole may **reduce the effectiveness** of hormonal contraceptives. Additional contraceptive methods should be considered during therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

- **First Trimester:**
  The use of **(Metronidazole)** is **contraindicated during the first trimester of pregnancy** unless the potential benefits outweigh the risks. Although animal studies have shown evidence of carcinogenicity, human data are limited and inconclusive. Therefore, the drug should only be used if no safer alternatives are available and the infection is potentially life-threatening.
- **Second and Third Trimesters:**
  Metronidazole may be used in the **second and third trimesters** under close medical supervision. A thorough **benefit–risk assessment** should be conducted prior to initiation, especially in prolonged or high-dose regimens.

Lactation

- Metronidazole **is excreted in breast milk** and may reach concentrations similar to maternal plasma levels.
- Although short-term use is generally considered compatible with breastfeeding, caution is advised, especially with **high-dose or prolonged therapy**, due to potential effects on the infant's gut flora and rare risk of candidiasis or diarrhea.
- Where prolonged or high-dose therapy is required**, temporary interruption of breastfeeding or use of alternative agents** may be considered.

Fertility

There is **no conclusive evidence** that metronidazole affects human fertility.

- However, some animal studies have shown **reversible effects on spermatogenesis** at high doses. The clinical relevance of these findings in humans remains uncertain.

4.7 Effects on ability to drive and use machines Not applicable.

4.8 Undesirable effects

(Metronidazole), like all medicinal products, may cause adverse effects. Most are **mild and transient**, but some may be **serious or require discontinuation** of therapy. The frequency categories below are based on clinical trial data and post-marketing reports.

Very Common (≥1/10):

- Nausea
- Metallic taste in the mouth

Common (≥1/100 to <1/10):

- Vomiting
- Diarrhoea
- Anorexia
- Abdominal discomfort
- Headache
- Dizziness

Uncommon (≥1/1,000 to <1/100):

- Oral mucositis
- Glossitis (inflammation of the tongue)
- Darkening of urine (due to metabolites; harmless)

Rare (≥1/10,000 to <1/1,000):

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Peripheral neuropathy (tingling or numbness in hands/feet) Seizures

Very Rare (<1/10,000):

- Hepatotoxicity (including cholestatic hepatitis and elevated liver enzymes)
- Encephalopathy
- Cerebellar symptoms (ataxia, dysarthria)
- Optic neuropathy or visual disturbances
- Psychotic disorders, confusion, hallucinations
- Severe cutaneous adverse reactions (SCARs), including **Stevens–Johnson syndrome and toxic epidermal necrolysis**

Not Known (cannot be estimated from available data):

- Anaphylactic reactions
- Agranulocytosis
- Leukopenia
- Pancreatitis
- Taste disturbance (dysgeusia)
- Depression and mood changes

Reporting of Suspected Adverse Reactions:

Healthcare professionals are encouraged to report any suspected adverse reactions to the **National Pharmacovigilance Centre** or to **NAFDAC** through official reporting channels. Regular submission of **Periodic Safety Update Reports (PSURs)** is also required by Marketing Authorization Holders to ensure continuous monitoring of the drug's safety profile.

4.9 Overdose

Symptoms of Overdose:

Overdose with **(Metronidazole)** is rare but can occur, particularly with accidental ingestion or intentional misuse. Reported symptoms are generally consistent with dose-dependent toxicity and may include:

- Nausea and vomiting
- Dizziness or ataxia
- Abdominal pain
- Headache
- Metallic taste
- Confusion or agitation
- Seizures
- Peripheral neuropathy
- Encephalopathy (especially in prolonged or high-dose exposure)

Very high doses (≥12 g/day) have been associated with central nervous system toxicity, including seizures and cerebellar dysfunction.

Management of Overdose:

There is **no specific antidote** for metronidazole overdose. Management is **supportive and symptomatic,** and may include:

- Inducing emesis or performing **gastric lavage** (if within 1 hour of ingestion and clinically appropriate)
- **Activated charcoal** may be considered to limit further absorption
- **Intravenous fluids** to maintain hydration and support renal clearance
- **Monitoring of neurological status**, particularly for signs of seizures or encephalopathy
- In severe cases, **haemodialysis** may be considered, as metronidazole is moderately dialyzable Prognosis:

Most patients recover fully with supportive care. However, **neurological symptoms** may take **several days to weeks** to resolve, depending on the dose ingested and the duration of exposure.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Antibacterials for systemic use – Nitroimidazole derivatives **ATC code:** J01XD01

Mechanism of Action:

Metronidazole, the active ingredient in ®, is a synthetic **nitroimidazole** compound with broadspectrum activity against **obligate anaerobic bacteria** and **protozoa**.

- Metronidazole is **inert in its parent form** and becomes active only after **reduction of its nitro group** by intracellular electron transport proteins within susceptible organisms (e.g., ferredoxins).
- The resulting **reactive intermediates** bind to DNA, causing **strand breakage**, inhibition of nucleic acid synthesis, and ultimately **cell death.**

Spectrum of Activity:

Metronidazole is effective against:

- **Anaerobic bacteria**, including:
  - *Bacteroides fragilis* group ○ *Clostridium* species (excluding *C. difficile* as first-line treatment in severe cases) ○ *Peptostreptococcus*, *Fusobacterium* spp.
- **Protozoa**, including:
  - *Entamoeba histolytica* ○ *Giardia lamblia* ○ *Trichomonas vaginalis*

Antimicrobial Activity (In Vitro):

Metronidazole exhibi**ts bactericidal activity** against anaerobes at low concentrations (generally MIC < 8 µg/mL). It has **no activity against aerobic or facultative anaerobic bacteria**.

Clinical Efficacy:

Metronidazole has demonstrated high clinical cure rates in:

- **Trichomoniasis** (as a single 2 g dose or 7-day regimen)
- **Giardiasis and amoebiasis**
- **Intra-abdominal and pelvic infections**
- **Dental and periodontal infections**
- **Bacterial vaginosis**
- As part of **triple therapy** for *H. pylori* eradication

5.2 Pharmacokinetic Properties

Metronidazole is well absorbed, widely distributed, and extensively metabolized, supporting its effectiveness in treating systemic and tissue-level anaerobic and protozoal infections.

Absorption:

- Metronidazole is **rapidly and almost completely absorbed** after oral administration, with **bioavailability approaching 100%.**
- Peak plasma concentrations are typically reached **within 1–2 hours** following administration of a single **400 mg tablet**.
- Food may **delay the rate** but does **not reduce the extent** of absorption.

Distribution:

- Metronidazole is widely distributed in body tissues and fluids, including:
  - **Cerebrospinal fluid**
  - **Liver** ○ **Lung** ○ **Saliva** ○ **Bile** ○ **Vaginal secretions**
- It readily crosses the **placenta** and is present in **breast milk**. Plasma protein binding is low (~10–20%).

Metabolism:

- Metronidazole is **extensively metabolized in the liver** via oxidation, side-chain hydroxylation, and glucuronidation.
- The primary active metabolite, **hydroxy-metronidazole**, retains antimicrobial activity and contributes to the overall therapeutic effect.

Elimination:

- The elimination half-life is approximately **8 hours** in healthy adults.
- **60–80%** of the administered dose is excreted in the urine, primarily as metabolites (20–40% as unchanged drug).
- A small portion is eliminated via the **faeces.**

Special Populations:

- **Hepatic Impairment:** Clearance is reduced, and the half-life prolonged. Dose adjustment may be required.
- **Renal Impairment:** Accumulation of metabolites may occur in severe renal failure, though metronidazole itself is not significantly affected. Dialysis may remove both the parent drug and metabolites.
- **Elderly:** Pharmacokinetics are generally unchanged, although caution is advised due to agerelated changes in liver and kidney function.

5.3 Preclinical safety data

Not available

6. Pharmaceutical particulars

6.1 List of excipients ***Tablet core:***

Lactose Monohydrate, Corn starch, Gelatin bloom, Tartrazine yellow, Magnesium stearate.

6.2 Incompatibilities Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in the original package to protect from moisture.

Do not store above 30°C.

6.5 Nature and contents of container

Tablet are packed in PVC and Foil blisters of 10 tablets per blister.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

GLOBAL ORGANICS LTD, PLOT NO 868, KM 34 AJEGUNLE BUS-STOP, LAGOS ABEOKUTA EXPRESSWAY, LAGOS STATE.