For the use only of Registered Medical Practitioner

WARNING Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should therefore be avoided. Its use should be reserved for the conditions described in the Indications and Usage section below

1. **Generic Name and Brand Name:**
   Chlorhexidine Gluconate, Metronidazole & Lignocaine Hydrochloride Gel
   Flagyl® Gel

2. **Qualitative and Quantitative Composition:**
   Composition:
   Chlorhexidine Gluconate Solution I.P.
   equivalent to Chlorhexidine Gluconate 1 % w/w
   Metronidazole Benzoate I.P.
   equivalent to Metronidazole 1 % w/w
   Lignocaine Hydrochloride I.P. 2 % w/w
   Gel Base q.s.

   FOR TOPICAL ORAL USE ONLY

3. **Dosage Form & strength**
   Refer section no. 1 & 2

4. **Clinical particulars**

4.1 Therapeutic indication:

For relief in Painful oromucosal conditions, Gingivitis, Periodontitis, and for use in Post periodontal surgery.

4.2 Posology and method of administration

Posology

Always apply FLAGYL GEL, as directed by your physician. It is for external use only. On the affected area, apply a thin layer of this medicine. Use this medicine in the dose and duration as advised by your doctor

Method of Administration:

4.3 Contraindications

FLAGYL GEL is contraindicated in individuals with a history of hypersensitivity to Metronidazole, Chlorhexidine, Lignocaine, or to another local anaesthetic belonging to the amide group or other ingredients of the formulation.

Although the resorbed quantity of lidocaine is clearly lower after local application of the gel than after infiltration anaesthesia or nerve block anaesthesia, systemic effects cannot be completely excluded if resorption conditions are very unfavourable (strongly traumatised mucosa).

Therefore, it is only allowed to be applied under special caution in patients suffering from severe disorders of the conduction system of the heart or acute decompensated cardiac insufficiency and severe kidney or liver diseases.

4.4 Special warnings and precautions for use

Contact with eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication with less frequency or discontinue use.

Metronidazole in FLAGYL GEL is a nitroimidazole. The use of metronidazole has rarely been associated with hematologic adverse effects such as mild, transient leukopenia, thrombocytopenia, and bone marrow aplasia and therefore, should be used with care in patients of, or history of blood dyscrasias.

Metronidazole may be systemically absorbed when applied to the skin or mucosal membranes. A disulfiram-like reaction has been reported in patients who consume alcohol during treatment with oral metronidazole. Symptoms include nausea, vomiting, flushing, sweating, headache, abdominal cramps, and hypotension. Therapy with topical metronidazole should be administered cautiously in patients who might be prone to acute alcohol intake. Patients should be instructed to avoid alcohol-containing products during therapy and for at least 48 hours after the last dose.

Carcinogenicity/Mutagenicity-Metronidazole has been shown to be carcinogenic in the mouse and in the rat. But data from human patients has exemplified the safety of metronidazole.

Central And Peripheral Nervous System Effects

- 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 metronidazoleAseptic 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

Therapy with topical metronidazole should be administered cautiously in patients with or predisposed to seizures or other nervous system abnormalities. Metronidazole therapy should be discontinued promptly if neurologic disturbances occur.

FLAGYL GEL is incompatible with certain ingredients of some toothpastes, Toothpastes should therefore be used first and the mouth rinsed before using FLAGYL GEL, or they should be used at different times of the day.

Chlorhexidine gluconate can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue.
Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques.
Some patients may experience an alteration in taste perception while undergoing treatment with Chlorhexidine gluconate. Rare instances of permanent taste alteration following Chlorhexidine gluconate use have been reported via post-marketing product surveillance.

KIDNEY
FLAGYL GEL should be used with caution in patients with severe renal dysfunction. Consult your doctor before applying for the medicine.

LIVER
Metronidazole may be systemically absorbed when applied to the skin or mucosal membranes. Once absorbed, metronidazole is extensively metabolized by the liver to both pharmacologically active and inactive compounds. The plasma clearance of metronidazole may be decreased and the half-life prolonged in patients with impaired hepatic function.
FLAGYL GEL should be used with caution in patients with advanced liver disease. Consult your doctor before applying for the medicine.

ALLERGY
FLAGYL GEL is not recommended for use if you are allergic to chlorhexidine or metronidazole. lignocaine, methyl hydroxybenzoate, propyl hydroxybenzoate, para-amino benzoic acid or any other ingredients of this medicine.

HEART DISEASE
FLAGYL GEL should be used with caution in patients with heart diseases such as partial or complete heart block. Consult your doctor before applying for the medicine.

OTHERS
Before applying FLAGYL GEL, inform your doctor if you:

Have traumatized (injured) mucosa
Have sepsis (a life-threatening complication of an infection) in the region of the proposed application
Have a poor general health

4.5 Drug Interactions

CHLORHEXIDINE

Chlorhexidine digluconate is incompatible with anionic agents which are usually present in conventional dentifrices. These should therefore be used before the application of the GEL. Rinse the mouth thoroughly with water before using FLAGYL GEL.

METRONIDAZOLE

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

No	Drug	Drug interaction	Remark
1	Busulfan	Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.	
2.	Cyclosporin	Risk of elevation of cyclosporin serum levels.	Serum cyclosporin and serum creatinine should be closely monitored when co-administration is necessary
3.	Disulfiram	Administration of disulfiram and metronidazole has been associated with acute psychoses and confusion in some patients.	These drugs should not be used concomitantly.
4.	5-Fluorouracil	Metronidazole has been reported to reduce the clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.	
5.	Lithium	Concomitant use of lithium and metronidazole may result in lithium intoxication due to decreased renal clearance of lithium. Persistent renal damage may develop.	Frequent monitoring of lithium, creatinine and electrolyte levels and urine osmolality should be done
6.	Oral anticoagulant therapy (Warfarin type)	Metronidazole has been reported to potentiate the anticoagulant effect of warfarin resulting in a prolongation of prothrombin time and increased hemorrhagic risk caused by decreased hepatic catabolism.	Prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole.
7.	Phenytoin or Phenobarbital	The metabolism of metronidazole has been reported to be increased by concurrent administration of phenobarbital or phenytoin.	
8.	Vecuronium	A slight potentiation of the neuromuscular blocking activity of	

		vecuronium has been reported in patients administered metronidazole at a dose of 15 mg/kg.	
9	Alcohol	A disulfiram like reaction may occur when alcohol ingested by a patient taking metronidazole	Ask the patient to avoid alcohol when taking metronidazole

LIGNOCAINE
Relevant clinical interactions are highly unlikely due to the local application and the amount of the gel to be applied. However, in principle the analgesic effect of other local anaesthetics could be increased. Interactions known for lignocaine (antiarrhythmics, beta blockers) are not relevant for oromucosal applications.

Before applying FLAGYL GEL, inform your doctor, if you are applying any of the following medicine:

- Anticoagulants (used to prevent blood clots) such as coumarin derivatives (Ex. warfarin)
- Anti-arrhythmic drugs (used to prevent and treat a heart rhythm that's too fast or irregular) Ex. amiodarone
- Cimetidine (used to treat stomach ulcers)
- Beta-blockers (used to treat high blood pressure)
- General anaesthesia (used to induce unconsciousness during surgery) Ex. propofol, ketamine
- Benzodiazepine, barbiturate (used to treat anxiety and insomnia)

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy:
Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.
Lignocaine is able to cross the placental barrier and may be absorbed by foetal tissue. The potential risk for humans is not known.
No clinical studies with Chlorhexidine in pregnant women have been conducted, so the benefits of using Chlorhexidine should be weighed against the possible harm to the fetus. Reproduction and fertility studies with Chlorhexidine gluconate have been conducted. No evidence of impaired fertility was observed in male and female rats at doses up to 100 mg/kg/day. No evidence of harm to the fetus was observed in rats and rabbits at doses up to 300mg/kg/day and 40 mg/kg/day, respectively.

FLAGYL GEL should be used with caution during pregnancy only if it is necessary. Consult your doctor before applying the medicine.

Breastfeeding:
After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma.
Lignocaine is excreted in breast milk in small quantities.
It is not known whether Chlorhexidine gluconate is excreted in human milk. Cautions should be exercised, and the benefits of use weighed against possible risk to the infant being nursed. In parturition and lactation studies in white rats, no evidence of impaired parturition of toxic effects to suckling pups was observed when Chlorhexidine gluconate was administered at doses over 100 times greater than the recommended daily dose for rinsing.

FLAGYL GEL should be used with caution in breastfeeding women only if it is necessary. Consult your doctor before applying for the medicine.

Use in Pediatrics:
FLAGYL GEL is not generally not recommended for use in children (< 18 years of age) unless considered necessary. Consult your doctor before applying FLAGYL GEL.

Use in Geriatrics:
FLAGYL GEL should be applied with caution in elderly patients (aged 65 years or above). Consult your doctor before applying FLAGYL GEL.

4.7 Effects on ability to drive and use machines

Do not drive or operate machines while applying FLAGYL GEL since it may temporarily affect your ability to drive or operate machines.

4.8 Undesirable effects
Because of the low plasma concentration after local application of the gel, the risk of systemic side effects is low.

The following adverse experiences have been reported with the topical use of Metronidazole-Chlorhexidine combination: burning, irritation, dryness, transient redness, metallic taste, staining of teeth, tingling or numbness of extremities and nausea, glossodynia, oral paraesthesia /hypoaethesia

Oro-mucosal application of lignocaine 2%- Locally administrated lidocaine can cause allergic reactions and, when absorbed, systemic reactions. Occurring and intensity of systemic reactions depend on lidocaine serum concentration (influence of application site and dose), patient's condition, hepatic function, age, body weight, and co-morbidities – heart diseases and hyperthyroidism.

4.9 Overdose
If you or anyone else applies too much of FLAGYL GEL or accidentally swallows it, consult your doctor immediately or visit the nearby hospital. Symptoms of overdose are circumoral paraesthesia (burning, prickling or itching sensation), numbness of the tongue, light-headedness, hyperacusis (unusual tolerance to ordinary environmental sounds), ringing in the ears, visual disturbance,

muscular tremors, generalized & grand mal convulsions (seizures), unconsciousness, hypoxia (low oxygen level), hypercarbia (increased carbon-di-oxide in the blood), apnoea (serious sleep disorder), severe low blood pressure, slow heart rate, irregular heartbeat, arrhythmia and cardiovascular collapse

5. Pharmacological properties

5.1 Mechanism of action

Chlorhexidine kills the microorganisms associated with various mouth and throat infections.Chlorhexidine has also been shown to prevent the formation and buildup of plaque on teeth and helps prevent gingivitis. It can therefore be used as an aid to oral hygiene, particularly in instances where toothbrushing is a problem, e.g following dental surgery.
Metronidazole is classified therapeutically as an antiprotozoal and antibacterial agent. The mechanism by which topical metronidazole acts, is not known but appears to include an antimicrobial and/or anti-inflammatory effect.
Lignocaine is a local anaesthetic of the amide type. It produces a reversible loss of sensation by preventing or diminishing the conduction of sensory nerve impulses near the site of application.

5.2 Pharmacodynamic Properties

Metronidazole is an antiprotozoal and antibacterial agent active against those organisms that are predominant in the subgingival flora in adult periodontitis. Metronidazole has a bactericidal effect against Bacteroides spp., Fusobacterium, Selemonas, Wolinella, Spirochetes, and other anaerobic organisms, but does not affect aerobic bacteria.

Chlorhexidine is a bisbiguanide antiseptic and disinfectant which is bactericidal or bacteriostatic effective against a wide range of Gram negative and Gram positive vegetative bacteria, yeasts, dermatophyte fungi and lipophilic viruses. These include the Candida albicans fungi that causes thrush infections in the mouth e.g after a dental surgery. Infection of these areas increases discomfort and delays healing. It is active against a wide range of important oral pathogens and is therefore effective in the treatment of many common dental conditions.

Lignocaine is a local anaesthetic of the amide type. Lignocaine reversibly inhibits the opening of sodium channels and thus the development of an action potential. The active substance binds on a specific receptor of the sodium channel, inhibiting the ion transport and the development of an action potential. The transmission of nerve impulses is suppressed locally. Pain perception is suppressed. Thin unmylienated nerve fibres are switched off more quickly than thick motoric nerve fibres, Perceptions are switched off in the following order: Pain, temperature, touch and pressure.

5.3 Pharmacokinetic properties

When applied topically there is little if any systemic absorption of metronidazole.
Lignocaine is readily absorbed from mucous membranes and damaged skin producing rapid, local anaesthesia in these areas. Absorption from intact skin is poor. The rate of absorption and amount of dose absorbed is dependent upon concentration, the total dose administered, the specific site of application and the duration of exposure.
Because of its cationic nature, chlorhexidine bonds strongly to skin, mucosa and other tissues and is thus very poorly absorbed. No detectable blood levels have been found following oral use.

6. Nonclinical properties
6.1 Animal Toxicology or Pharmacology

METRONIDAZOLE

Tumors affecting the liver, lungs, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.
Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic,oral administration in mice and rats but not in studies involving hamsters. One study showed a significant enhancement of UV induced skin tumors in hairless mice treated with Metronidazole intraperitoneally (15µg per g body weight and per day for 28 weeks). Although the significance of these studies to man is not clear, patients should be advised to avoid or minimize exposure of Metronidazole treated sited to sun.

Metronidazole has shown mutagenic activity in several in vitro bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneally injection and an increase in chromosome aberrations have been reported in patients with Crohn's disease who are treated with 200 to 1200 mg/day of Metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

CHLORHEXIDINE
Chronic and Sub-chronic Toxicity Studies:
The only consistently observed finding in subchronic and chronic toxicity studies was the accumulation of foamy macrophages in the mesenteric lymph nodes of rats. Based on the following facts: 1) the macrophages did not contain bacteria, indicating that a significant change in the intestinal flora has not occurred 2) the reaction is not associated with increased morbidity or mortality 3) the reaction does not become progressively more severe with continued exposure to Chlorhexidine and 4) the reaction is reversible after administration of Chlorhexidine is discontinued, it was concluded that the lesions did not represent a significant toxic effect.

Carcinogenicity:
No evidence of carcinogenicity was observed in studies in rats in which Chlorhexidine was administered at levels up to 200 mg/kg/day for two years.

Mutagenicity:
No evidence of mutagenicity was observed when Chlorhexidine Gluconate was evaluated by the dominate lethal assay in mice and micronucleus assay in hamsters. Mutagenicity studies, using bacterial cell system, with or without metabolic activation, produced contradictory results, which are unexpected with drugs having antibacterial activity. While Suessmuth et al. (1979) and Ackerman-Schmidt et al. (1982) obtained positive results, Evans et al. (1978) and Sakagami et al. (1988) found no evidence of genotoxicity for chlorhexidine. The clinical significance of these results is unclear.

Immediate Hypersensitivity:

A variety or regimens were used in an attempt to induct and elicit immediate hypersensitivity to Chlorhexidine Gluconate in guineas pigs, rabbits, rats and man. No evidence of immediate hypersensitivity was observed in any of the tests.

Impairment of Fertility:
No evidence of impaired fertility was observed in rats at doses up to 100mg/kg/day.

LIGNOCAINE
Reproduction toxicity:
In studies aiming at the embryonic and foetal development in which rabbits were treated with lignocaine, during the period of organogenesis, no teratogenic effects were found. Embryotoxicity was observed at maternal toxic doses in rabbits. In rat dams that were treated with maternally toxic doses of lignocaine during pregnancy and lactation, influencing the length of pregnancy, the survival rate of the offspring was diminished.
Genotoxicity and carcinogenic potential:
Investigations with regard to lidocaine genotoxicity were negative. However, in vitro genotoxicity studies with the metabolite 2,6-xylidine showed a genotoxic potential.
In a carcinogenic study in rats, tumors have been observed in the nasal cavity, the subskin and the liver. 2,6-xylidine was administered in utero and lifelong postnatal.

7. Description
White to off-white colour gel

8. Pharmaceutical particulars
8.1 Incompatibilities
NA.

8.2 Shelf Life
Refer Pack

8.3 Packaging Information
Refer Pack

8.4 Storage and handling instructions
Refer Pack

9. Patient Counseling Information
- Always apply FLAGYL GEL, as directed by your physician. On the affected area, apply a thin layer of this medicine.
- Tell your healthcare provider about all your medical conditions, allergies, and all medicines you use.
- Use this GEL for the full prescribed length of time, even if your symptoms quickly improve. Skipping doses can increase your risk of infection that is resistant to medication. If you miss the dose, apply the gel as soon as you remember. Do not overuse it to compensate for the missed dose.

- Keep out of reach of children and pets. Do not swallow. Keep the cap tightly closed after use.
- Wash your hands before and after using this medicine
- You may experience temporary staining of the teeth and tongue
- You may notice a temporary change of taste or a burning sensation after using this gel.
- Be careful while having any hot or cold foodstuff, as you can feel numbness in your mouth or tongue after applying FLAGYL gel.
- Avoid contact with the eyes, and nose and do not swallow it while applying it in the mouth.
- You should not eat or drink anything for 30 minutes after applying this medicine
- Store FLAGYL GEL protected from moisture, sunlight and heat.
- Discard the expired or gel that is no longer required properly
- Consult your doctor or dentist if your symptoms persist or get worse.

10. Details of manufacturer
Refer Pack for manufacturers details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.
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11. Details of permission or licence number with date
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For product complaints and queries please write to **webmasterindia@abbott.com**