Research in Pharmacy and Health Sciences.2022,8(4):197-204. • https://doi.org/10.32463/RPHS.2022.v09i04.02 e-ISSN: 2455-5258

REVIEW ARTICLE OPEN ACCESS

Metronidazole: An Overview of the Disease

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Received: 22 August, 2022
Accepted: 12 October, 2022

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Published by: OZZIE Publishers
Web: www.ozziepublishers.com

Abstract
Metronidazole is an antibiotic that is commonly used in various medical conditions, including trichoniasis, amoebiasis and giardiasis. In 1950, Metronidazole was first used to treat Trichomonas vaginalis infection, and novel clinical features were subsequently identified. Metronidazole is currently used to treat Bacteroides, Fusibacterial and Clostridian infections, rosacea, oral and dental disorders, bone and joint infections, gynecological illness, endocarditis, septicemia and inflammation of the respiratory tract. This may also be used during surgical procedures to treat Crohn's disease, or also as prophylaxis. Metronidazole has been well tolerated with mild to severe side effects, including nausea, stomach pain and diarrhea. Nevertheless, in rare cases severe neurotoxicity, optic neuropathy, peripheral neuropathy and encephalopathy have been recorded. Metronidazole has been known to be a cost-effective drug, regardless of its low quality, strong efficacy against pathogenic anaerobic bacteria, beneficial pharmacokinetic & pharmacodynamic features, and mild adverse effects.

KEY WORDS: metronidazole, adverse effects, clinical features, anaerobic bacteria, anti-infective.

1. INTRODUCTION

Metronidazole is a type of nitroimidazole drug that is widely used to inhibit trichomonade and amoeba protozoa, with a good anti-anaerobic action[1,2] However, the medications nitroimidazole and its derivatives can be potentially carcinogenic, mutagenic and genetic toxic to animals[3]. It is a commonly used product owing to its tolerability, high oral bioavail¬ability, and ability to penetrate deep into tissues, including the central nervous system. Metronidazole is an imidazole used to treat antibacterial and antiprotozoal infections such as bacterial vaginosis and related antibiotic colitis. Successful regulation of Metronidazole in pharmaceutical products and the exclusion of Metronidazole residues in foods and beverages are a primary focus of research interest[4-8]. Metronidazole can be treated in many different ways such as activated carbon adsorption, acidic catalytic degradation, UV degradation, microscopic degradation, etc. It is difficult to remove entirely, like Metronidazole wastewater as an industrial wastewater specializing in pharmaceutical products with complex structure and restricted biodegradability. Adsorption of wastewater is widely used for the disposal of hazardous organic compounds. The adsorption process moves only contaminants from the water to the solid phase and does not deteriorate completely[9]. For the diagnosis of Trichomonas vaginalis, Metronidazole has become the first drug to use. In combination with Metronidazole, IgE mediated and non-IgE mediated reactions, including SJS, TEN, serum disease and fixed-drug eruptions, were identified[20]. Biotechnology is a popular approach for the treatment of antibiotic waste water, but it typically takes some time[10], and it doesn't have a strong removal effect. Flocking and centrifugation physical methods also cause secondary emissions. Oxidation is a very powerful procedure, but during the degradation cycle the chemical produced may be more harmful[11]. Figure 1 shows the chemical structure of Metronidazole.

1. METRONIDAZOLE

IUPAC Name: 2-(2-Methyl-5-nitro-1H-imidazol-1-yl) ethanol

Chemical Formula: $C_6H_9N_3O_3$

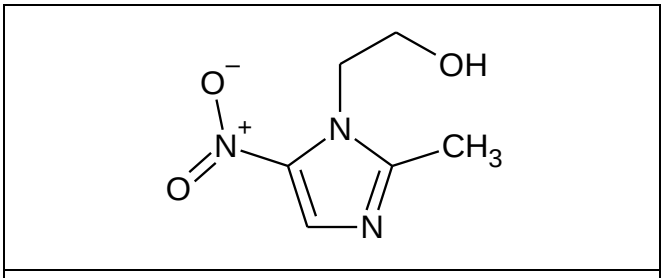

Figure 1. *Chemical structure of Metronidazole*

Molecular Weight: 171.154
Melting point: 160º C
Predicted water solubility: 5.92 g / L
Description: Metronidazole is a derivative of nitroimidazole used to treat amoebiasis, vaginitis, giardiasis, trichomonas infection.
Categories: Anti-Infective, Antiprotozoal agents and Radiation-sensitizing

Indication: It is effective in preventing bacterial and protozoal infections. This drug was used to cure anaerobic infections and prophylactically in colonic surgery[12,13] *Entamoeba histolytic*a was often used successfully. In 2015 WHO was added to the official list of pharmaceutical products. In the process of diagnosis with anaerobic and combined diseases, surgical anaerobic prophylaxis, Clostridium difficile-associated diarrhea and colitis, Helicobacter pylori infection and duodenal ulcer disease, Bacterial vaginosis, Giardialamblia gastro-enteritis, amoebiasis caused by Entamoeba histolytica, acne rosacea (topical treatment) and Trichomonas infections[14].

HISTORY

In the 1950s, Metronidazole was first synthesized as an effective antitrichomonal medication in the treatment of vaginal trichomoniasis was investigated by pharmaceutical firm Rhône-Poulenc.

Initially, a crude extract was found to destroy Tricho- vaginalis from Streptomyces bacterium and the active portion, which was previously characterized by nitroimidazole antibiotic, has been known as azomycin. Metronidazole was a synthetic azomycin derivative and was much more potent against T. vaginalis and less toxic. The first 8823 R.P. was identified. This result quickly led to successful use of trichomoniasis during human clinical trials[15].

MECHANISM OF ACTION

Metronidazole and other nitroimidazole (e.g., nimorazole, Ornidazole, ronidazole, secindazole, tinidazole) are inactive and are determined by their ability to activate drugs as they are actively diffused into the cell. Their bactericidal and parasite actions are fast and proportionate to the concentration in the target cell of the activated drugs[16]. The mechanism of action of Metronidazole defines the other nitroimidazoles. Figure 2 shows the Mechanism of action of Metronidazole[17]. The nitroimidazoles have a heterocyclic form composed of a NO_2 imidazole dependent nucleus. The mechanism of action of Metronidazole involves four main steps which lead to the intracellular formation of essential redox intermediate metabolites[18]. In the first two phases, the compound is passed into cells by means of passive diffusion, and an electron is passed to the Metronidazole nitro group, leading to a short life nitroso free radical, cytotoxic, which can interrelate with cellular DNA[19]. This activation process produces a concentration gradient which increases the organism's increased intake of the drug, further enhancing its antimicrobial activity. The third phase in the action of Metronidazole involves the cytotoxic effect of the reduced drug, as the active compound of Metronidazole can prevent synthesis of DNA and cause DNA damage by oxidation, resulting in splits of single and double strand[19]. This causes DNA degradation with Metronidazole and death of the cells. Finally, the inactive end products of the drug have been released[20].

The microbial selectively of Metronidazole indicates that aerobic bacteria are unable to activate the medication because they lack sufficiently negative redox potential with the required electron transport proteins[19]. However, the redox potential of the electron transport chain is sufficiently negative in susceptible anaerobic bacteria to reduce the nitro Metronidazole group.

In anaerobic bacteria, the drug is activated by receiving an electron of ferredoxins or flavodoxins, which are depleted by iron-sulphide proteins called pyruvate: ferredoxin oxidoreductase (PFOR)[21]. Depending on the organism, a certain donor of electron active in the reduction of nitroimidazole. For example, a different mechanism for Metronidazole susceptibility, which requires a 2-electron transfer step mediated by an oxygen- nitro reductases, occur in the micro aerophilous *Helicobacter pylori*. Many microaerophilic protists (*Giardia lamblia, Entamoeba histolytica* and *T. vaginalis*) have Metronidazole activated bacterium-like enzymes (nitro reductase)[22].

SPECTRUM OF ACTIVITY

Metronidazole and associated nitroimidazoles are found in two distinct anaerobic microbes, microaerophilic microbes and protozoa. Resistance has been found more and more in certain species as discussed later, but it cannot be readily identified, since the anaerobic susceptibility tests are not carried out systematically. However, the resistance emergence suggests that current surveillance is important[19].

Many gram negative anaerobes have a Metronidazole-susceptiblity[23,24]. In general, members of the Bacteroides and Parapacteroides genera are metronidazole susceptible with tolerance normally seen in less than 5% of isolate[25- 28]. In South Africa the Bacteroides Isolates have demonstrated higher resistance levels[29]. Desulfovibrio species, as is extremely susceptible[30]. Fusobacterium, Porphyromonas, Prevotella, and genera Bilophila are typically susceptible to clinical significance[23,31]. However, unsusceptible strains of Prevotella were identified[23]. In oral isolates of *Porphyromonas gingivalis*[32], metronidazole resistance has

been recently identified. Reduced sensitivity was also observed in Sutterella isolates and Veillonella gram-coccus[24,33]. Mobiluncus bacteria are typically not susceptible to Metronidazole due to bacteria infected with Vaginitis[34, 35].

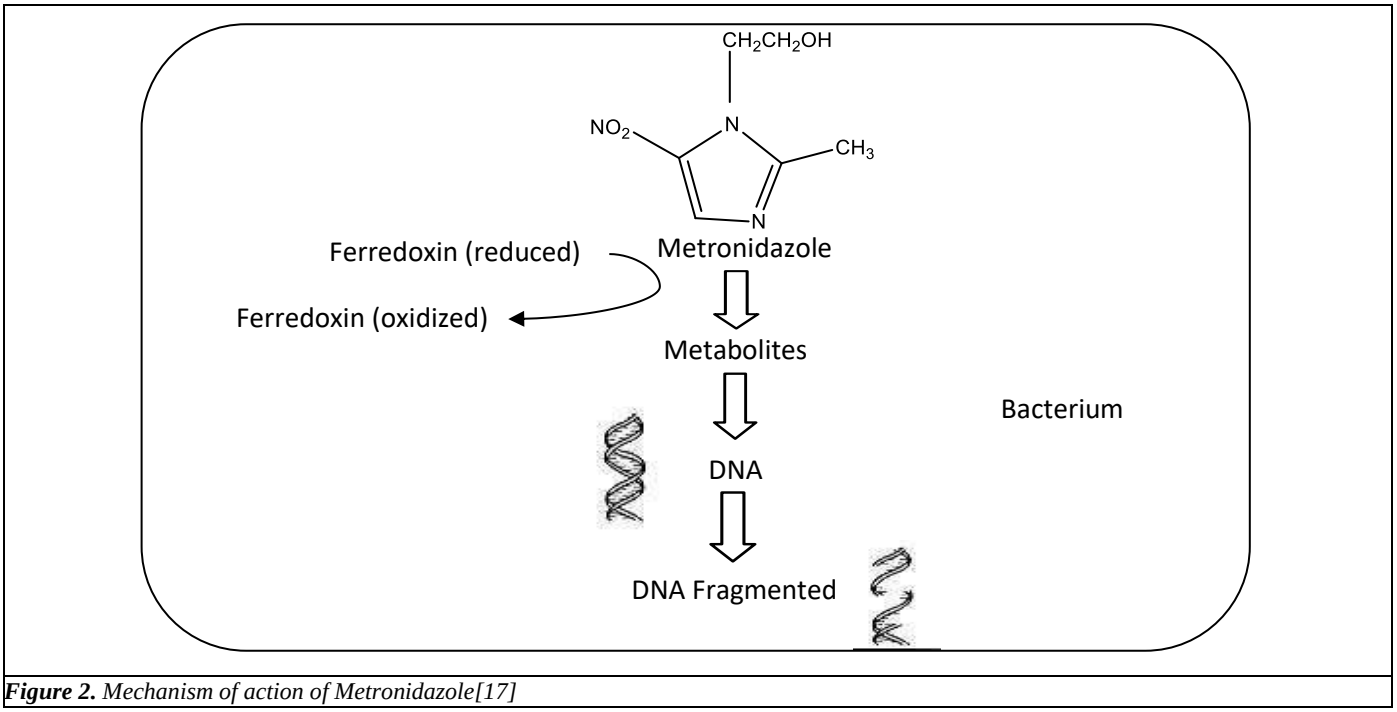

Figure 2. *Mechanism of action of Metronidazole[17]*

PHARMACOLOGY

Metronidazole is sold commercially in different ways, including: oral capsules and tablets, (immediate and extended release); intravenous fluid, creams, lotions, topical gels and vaginal gels[16,36].

Although no commercial oral Metronidazole suspension is available, it is frequently compounded in the pharmacy by the crush of immediate releases tablets and by the combining of the aqueous suspension solution and buffered oral syrup at a ratio of 1:1[37]. Table 1 illustrate that the dosage and duration of Metronidazole depends on the particular product and indication. The package insert suggests an IV loading dose of 15 mg / kg, followed by 7.5 mg / kg every 6 to 8 hours, with a maximum daily dose limit of 4 g[16]. The key substance is above normal Bacteroid MICs at the fixed dose of 500 mg IV every 8 hours and is effective in treating intra-abdominal infections[38-40]. It is generally recommended that the infusion time be 1 hour, but 20 to 30 minutes have been used.[41] Due to the long half-life, depending upon concentration and high-dose Metronidazole administered as 1 to 1.5 g every 24 hours can be a safe, effective alternative at 500 mg every 6 to 8 hours[42,43]. Depending on patient condition and indication, the standard duration of oral or intravenous Metronidazole courses vary from 1 to 10 days. Longer durations can be prescribed but due to an increased risk of peripheral neuropathy or adverse effects on the central nervous system, cautions should be taken for durations exceeding 1 month[44-46].

Oral Metronidazole is absorbed rapidly and almost completely with 100% bioavailability[16,36]. Metronidazole is also well absorbed with recorded bioavailability of 59% to 94% when rectally administration; topical and vaginal Metronidazole achieve systemic measurable concentrations with 2%to 25% bioavailability[16,36,47]. Oral Metronidazole administration in food is recommended to reduce the adverse effects of gastric intestines and does not affect bioavailability but can delay the time to peak serum concentrations. Peak serum concentrations range from 12 to 40 µg/mL and occur 1 to 2 hours after oral administration and about 3 hours after rectal administration[16,36]. Table 2 shows that Metronidazole is a lipophilic molecule with low protein binding and moderate to large distribution volume that allows widespread distribution in different tissues[16,36]. It is excellent to penetrate into inflamed cerebrospinal fluid, epithelial lining fluid, saliva and bile and serum concentrations are identical[16,36,48]. Patients with non-inflamed meninges often reach therapeutic concentrations at around 43% of serum[49]. In addition, there is very high penetration into abscesses, appendix tissue, peritoneal fluid, and pancreatic tissue, varying from 2.3to7.2µg/mL[16,36,50]. However, the amount of drug detected in the bile is negligible for patients with obstructive cholecystitis[16,36]. Metronidazole crosses the placental membrane and enters breast milk, which may be teratogenic in the first trimester (see "Precautions")[51]. Concentrations of stools during C. difficile colitis at the start of infection are highest and taper as inflammation subsides and stools are produced, but concentrations typically remain well above recoreded MICs[52]. The effect of higher stool concentrations is also observed during Crohn's disease outbreaks when diarrhea is present[53].

Product	Dosage form	Strengths	Indications	Dose & Administration
Metronidazole Tablet (Flagyl) Metronidazole Capsule (Flagyl)	Tablet Capsule	250 mg 500 mg 375 mg	Symptomatic trichomoniasis asymptomatic trichomoniasis, treatment of asymptomatic consorts, amebiasis, anaerobic bacterial infections, intra-abdominal infections, skin and skin suture infections, gynecologic infections, bacterial septicemia, bone and joint infections, CNS infections, lower respiratory tract infections, endocarditis	**Adults** **Acute intestinal amebiasis:** 750 mg tid for 5-10 days **Amebic liver abscess:** 500 or 750 mg tid for 5-10 days **Anaerobic bacteria:** 7.5 mg/kg every 6 hr for 7-10 days (may be longer) **Trichomoniasis:** 250 mg tid daily for 7 days 375 mg (capsule) bid for 7 days 2 g single dose or 1 g bid for 1 day **Children:** 35-50 mg/kg daily divided into 3 doses for 10 days
Metronidazole extended-release tablet (Flagyl ER)	Extended-release tablet	750 mg	Bacterial vaginosis	**Adults:** 750 mg once daily for 7 days
Metronidazole intravenous solution (Metro)	Intravenous solution	500mg/100 mL (0.74% NaCl) 5mg/mL (0.74% NaCl)	Anaerobic infections, intra-abdominal infections, skin and skin structure infections, gynecologic infections, bacterial septicemia, bone and joint infections, CNS infections, lower respiratory tract infections, endocarditis, prophylaxis	**Adults:** **Anaerobic infections:** Loading dose of 15 mg/kg IV over 1 hr Maintenance dose: 7.5 mg/kg IV over 1 hr every 6 hr. Usual duration 7-10 days. **Colorectal surgery prophylaxis:** Initial: 15 mg/kg IV over 30-60 min about 1 hr before surgery Maintenance: 7.5 mg/kg IV over 20-60 min at 6 and 12 hr after initial dose
Metronidazole gel (MetroGel Vaginal, Vandazole)	Vaginal gel	0.75%	Bacterial vaginosis	**Adults:** Bacterial vaginosis: 1 applicatorful (≈5 g containing metronidazole 37.5 mg) intravaginally once or or twice daily for 5 days. For once-a-day dosing, administer at bedtime.
Metronidazole cream (MetroCream), Rosadan-0.75% Noritate-1.0%	Cream	0.75% 1.0%	Rosacea	**Adults:** 1% strength: apply a thin film once daily 0.75% strength: apply a thin film twice daily
Metronidazole gel (Metrogel-1.0%) (Rosadan-0.75%)	Gel	0.75% 1.0%	Rosacea	**Adults:** 1% strength: apply a thin film once daily 0.75% strength: apply a thin film twice daily
Metronidazole lotion (MetroLotion)	Lotion	0.75%	Rosacea	**Adults:** 0.75% strength: apply a thin film twice daily
Metronidazole Kit (Rosadan)	Kit	Metronidazole 0.75% cream + wash	Rosacea	**Adults:** 0.75% strength: apply a thin film twice daily

Table 1. *Major Preparations and Indications for Metronidazole: Administration and Dosage[16]*

Pharmacologic/Pharmacokinetic Factor	Result	Comments
Absorption Oral Rectal Vaginal cream Vaginal gel Topical	 98%-100% 59%-94% 20% 56% 2%	
Time to Peak Oral Rectal Topical	 1-2 hrs 3 hrs 8-12 hrs	
Peak Serum Concentrations		

Intravenous	25 and 18 µg/mL	After 15 mg/kg load and 7.5 mg/kg every 6 hr
Oral	6, 12, 21.4, and 40 µg/mL	After single dose of 250 mg, 500 mg, 750 mg, and 2000 mg
Rectal	18.5 µg/mL	After 500-mg dose
Topical	27.5 µg/mL	After application of 1% cream
Volume of Distribution		
Adults	0.55 L/kg	
Neonates	0.54-0.81 L/kg	
Tissue and Fluid Penetration		
CSF (inflamed meninges)	Approximates serum concentration	
CSF (noninflamed meninges)	45% of serum concentration	
Bile	Approximates serum concentration	
Epithelial lining fluid	Approximates serum concentration	
Saliva	Approximates serum concentration	
Abscess	Variable, but high concentration	
Peritoneal fluid	High concentrations: 7.2-14.2 µg/mL	
Pancreatic tissue	High concentration: 5.1-8.5 µg/mL	
Metabolism		
Oxidation	Primary mechanism of elimination	
Glucuronidation	Secondary mechanism of elimination	
Cytochrome P450	Secondary mechanism of elimination	
Excretion		
Unchanged drug	6%-18%	
Metabolites	60%-80%	
Haemodialysis	Removes 25%-45% over 4 hr	
Peritoneal dialysis	Removes 10% over 7.5 hr	
Protein binding	<20%	
Pregnancy	Avoid in first trimester Category B	
Lactation	Avoid	Significant penetration into breast milk

Table 2. *Pharmacokinetic and Pharmacologic Properties of Metronidazole[16,36]*

ADVERSE EFFECTS AND PRECAUTIONS

ADVERSE EFFECTS

Metronidazole is commonly well tolerated. Dose dependent, mild and reversible are the most common adverse effects. In 2% to 10% of patients, nausea, diarrhea, dry throat, metallic taste, candidal vaginitis, and stomatitis occur[16,36]. Severe adverse effects of central nervous system (ataxia, encephalopathy, dysarthria, epilepsy, aseptic meningitis, and peripheral neuropathy) have been more frequently reported but are reversible during prolonged treatments[51,54]. Caution should be taken in patients with history of epilepsy when administering Metronidazole. Certain moderate symptoms in central nervous systems, such as dizziness, headache, confusion, vertigo, and insomnia have been identified. In Addition, Stevens-Johnson syndrome, pancreatitis, ophthalmologic toxicity (myopia and blurry vision), ototoxicity, and hemolytic uremic syndrome are unusual and severe adverse effects of Metronidazole treatment[16,36].

PRECAUTIONS

Patients can prohibit the use of Metronidazole, where the history of hypersensitivity has been present with Metronidazole, parabens or nitroimidazole agents, alcohol consumption within 3 days of therapy, and/or disulfiram concomitant intake within 2 weeks of Metronidazole therapy. Disulfiram-like alcohol reactions can occur along all routes of administration, including topical and vaginal administration[16,36]. Caution should be done in patients with peripheral neuropathy, liver disorder, epilepsy history or diagnosis of vaginal candidiasis due to antibiotics, while prescribing Metronidazole[16,36]. In Addition, patients currently undergoing Metronidazole with aseptic meningitis, conjunctivitis, edema, seizure, superficial skin abnormalities, and peripheral neuropathy will discontinue treatment before severe drug-related adverse effects are excluded[16,36].

CLINICAL USES

PARASITIC INFECTIONS

Metronidazole has been developed as an antitrichomonal agent for its use. The nitroimidazoles are the most effective pharmaceutical class for these diseases, in this regard, tinidazole appears to be similar or superior to Metronidazole[55]. For the use in pregnant women with T. *vaginalis* infections, Metronidazole appears to be safe. Nitroimidazole drugs such as Metronidazole are mainly used for *Giardia* infections[55].

ANAEROBIC INFECTIONS

In view of its potent bactericidal action of Metronidazole against anaerobes and its beneficial pharmacodynamics profile (distribution across the body, including the central nervous system and into abscess cavities), it is effective in treating a myriad of anaerobic infections[16,19]. Metronidazole is widely used to treat gastrointestinal anaerobic diseases, central nervous system (including meningitis and brain abscess), gynecologic diseases, bacteremia, endocarditis, infections of bones and joints, respiratory tract infections, infections of the skin and skin-systems, oral and dental infections, and tetanus[16,19,56].

OTHER NITROIMIDAZOLE ANTIMICROBIALS

Certain members of the 5-nitroimidazole class include Tinidazole, Secnidazole and Orn

idazole. In 2004, Tinidazole was commonly prescribed and approved for use in the United States, both in Europe and in developing countries. The mechanism of action, spectrum of activity, toxicity and adverse effects of all agents of the class are identical[57]. However, the characteristic feature of agents is half-life and less frequent dosage compared to Metronidazole is required[57]. Half-life for tinidazole, secnidazole, and ornidazole is 10 to 15 hours, 17 to 28.8 hours, and 11 to 14 hours, respectively, for once daily dose. As a single-dose alternative for the treatment of intestinal amebiasis, giardiasis, and bacterial vaginosis, these agents provide a possible benefit over metronidazole. However, Metronidazole is considered the drug of choice for life-threatening anaerobic infections, while the efficacy and safety of other nitroimidazole agents was tested on restricted basis[58,59].

MARKETED AND COMBINATION PRODUCTS OF METRONIDAZOLE

Marketed Products of Metronidazole and Combination product of Metronidazole are summarized in **Table 3** and **Table 4** respectively.

Brand Name	Dosage form	Manufacturer
Aldezole®	Tablets 200 mg and 400 mg; Suspension 200 mg; Injection 500 mg	Albert David
Antamebin®	Tablets 200 mg; Suspension 200 mg	Raptakos
Aristogyl®	Tablets 200 mg and 400 mg; Suspension 100mg	Aristo
Flagyl®	Tablets 200 mg and 400 mg; Suspension 200mg	NPIL
Metrogyl®	Tablets 200 mg and 400 mg; Suspension 200 mg; Injection 500 mg; Dental and Vaginal gel 1%	J B Chemicals
Metron®	Tablets 200 mg and 400 mg; Suspension 100mg	Alkem
Metgyl®	Tablets 200 mg and 400 mg	Jagsonpal
Met®	Tablets 400 mg	Ind-Swift
Unimezol®	Tablets 200 mg and 400 mg; Suspension 200mg	Unichem

Table 3. *Marketed Products of Metronidazole*

Brand Name	Combination and Dosage Form	Manufacturer
Abdogyl-N®	200 mg Metronidazole + 300 mg Nalidixic acid tablets and suspensions	Glaxo SmithklineBeechem
Amibex®	300 mg Metronidazole + 100 mg Furazolidine tablets	Ind-Swift
Aristogyl-F®	400 mg Metronidazole + 100 mg Furazolidine+ 50 mg Simethicone tablets	Aristo
Metrohex®	1% Metronidazole + 0.25% Chlorhexidine gel	Dr. Reddy's laboratory
Metrokind-P®	1% Metronidazole + 5% Povidone iodine gel	Mankind
Stedmox-M®	200 mg Metronidazole + 250 mg Amoxicillincapsules	Stedman
Dyrade-M®	200 mg Metronidazole + 250 mg Diloxanidetablets and suspensions	Cipla
Gramogyl®	100 mg Metronidazole +100 mg Norfloxacin suspension	Ranbaxy
Fenigyl®	200 mg Metronidazole + 200 mg Norfloxacintablets and suspensions	Finecure

Table 4. *Combination Products of Metronidazole*

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