Metronidazole:

Class: Amebicide; Antibiotic,Antiprotozoal.

Indications:

Treatment of susceptible anaerobic bacterial and protozoal infections in the following conditions: Amebiasis, symptomatic and asymptomatic trichomoniasis; skin and skin structure infections, bone and joint infections, CNS infections, endocarditis, gynecologic infections, intra-abdominal infections (as part of combination regimen), respiratory tract infections (lower), systemic anaerobic infections; treatment of antibiotic-associated pseudomembranous colitis (AAPC); as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; surgical prophylaxis (colorectal); useful as single agent or in combination with amoxicillin, amoxicillin/clavulanic acid, or ciprofloxacin in the treatment of periodontitis associated with the presence of *Actinobacillus actinomycetemcomitans* (AA).

Available dosage form in the hospital: 500MG/100 I.V. INFUSION VIAL, 125MG/5ML SUSP, 250MG TAB, 500MG TAB.

Trade Names:

Dosage:

-Anaerobic infections (diverticulitis, intra-abdominal, peritonitis, cholangitis, or abscess): Oral, I.V.: 500 mg every 6-8 hours, not to exceed 4 g/day; Note: Initial: 1 g I.V. loading dose may be administered

-Amebiasis: Oral: 500-750 mg every 8 hours for 5-10 days

-Antibiotic-associated pseudomembranous colitis: IDSA Guidelines (Cohen, 2010):

-Mild-to-moderate infection: Oral: 500 mg 3 times/day for 10-14 days

-Severe complicated infection: I.V.: 500 mg 3 times/day with oral vancomycin (recommended agent) for 10-14 days

-Note: Due to the emergence of a new strain of *C. difficile*, some clinicians recommend converting to oral vancomycin therapy if the patient does not show a clear clinical response after 2 days of metronidazole therapy.

-Crohn's disease (unlabeled use): I.V.: 10-20 mg/kg/day; long-term (eg, several months) safety has not been established (Lichtenstein, 2009). **Note:** Reserved for mild-to-moderate disease in patients not responsive to sulfasalazine and/or who have colonic involvement (eg ileocolitis and colitis) (Lichtenstein, 2009; Sutherland, 1991).

-Giardiasis: 500 mg twice daily for 5-7 days

-Intra-abdominal infection, complicated, community-acquired, mild-to-moderate (in combination with cephalosporin or fluoroquinolone): I.V.: 500 mg every 8-12 hours **or** 1.5 g every 24 hours for for 4-7 days (provided source controlled)

-Peptic ulcer disease: *Helicobacter pylori* eradication: Oral: 250-500 mg with meals and at bedtime for 14 days; requires combination therapy with at least one other antibiotic and an acid-suppressing agent (proton pump inhibitor or H_2 blocker)

-Bacterial vaginosis or vaginitis due to *Gardnerella*, *Mobiluncus*: Oral: 500 mg twice daily (regular release) or 750 mg once daily (extended release tablet) for 7 days

-Pelvic inflammatory disease (unlabeled use): Oral: 500 mg twice daily for 14 days (in combination with a cephalosporin and doxycycline) (CDC, 2010)

-Periodontitis treatment (monotherapy or combination) associated with presence of *Actinobacillus actinomycetemcomitans* (AA): Oral: 250-500 mg every 8 hours for 8-10 days used in addition to scaling and root planing (Varela, 2011)

-Surgical prophylaxis (colorectal): I.V. 15 mg/kg 1 hour prior to surgery; followed by 7.5 mg/kg 6 and 12 hours after initial dose

-Trichomoniasis: Oral: 250 mg every 8 hours for 7 days **or** 375 mg twice daily for 7 days **or** 2 g as a single dose **or** 1 g twice daily for 2 doses (on same day)

-Urethritis (unlabeled use): Oral: 2 g as a single dose with azithromycin (CDC, 2010)

<u>- Renal Impairment :</u>

-Cl_{cr} <10 mL/minute (not on dialysis): Recommendations vary: To reduce possible accumulation in patients receiving multiple doses, consider reduction to 50% of dose or administer normal dose every 12 hours; **Note:** Dosage reduction is unnecessary in short courses of therapy. Some references do not recommend reduction at any level of renal impairment (Lamp, 1999).

-Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Dialyzable (50% to 100%): 500 mg every 8-12 hours. **Note:** Dosing regimen highly dependent on clinical indication (trichomoniasis vs *C. difficile* colitis) (Heintz, 2009). **Note:** Dosing dependent on the assumption of thrice weekly, complete IHD sessions.

-Peritoneal dialysis (PD): Dose as for Cl_{cr} <10 mL/minute

-Continuous renal replacement therapy (CRRT) (Heintz, 2009; Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1-2 L/hour and minimal residual renal function) and should not supersede clinical judgment:

-CVVH/CVVHD/CVVHDF: 500 mg every 6-12 hours (or per clinical indication; dosage reduction generally not necessary)

Hepatic adjustement :

Manufacturer's recommendations:

Mild or moderate impairment (Child-Pugh A or B): No dosage adjustment is necessary; use with caution.

Severe impairment (Child-Pugh C):

Extended-release tablets: Use is not recommended.

Immediate-release capsules:

Amebiasis: 375 mg 3 times daily for 5-10 days

Trichomoniasis: 375 mg once daily for 7 days

Immediate-release tablets, injection: Reduce dose by 50%.

Alternative recommendations: The pharmacokinetics of a single oral 500 mg dose were not altered in patients with cirrhosis; initial dose reduction is therefore not necessary (Daneshmend, 1982). In one study of I.V. metronidazole, patients with alcoholic liver disease (with or without cirrhosis), demonstrated a prolonged elimination half-life (eg, ~18 hours). The authors recommended the dose be reduced accordingly (clearance was reduced by ~62%) and the frequency may be prolonged (eg, every 12 hours instead of every 6 hours) (Lau, 1987). In another single I.V. dose study using metronidazole metabolism to predict hepatic function, patients classified as Child-Pugh class C demonstrated a half-life of ~21.5 hours (Muscara, 1995).

Common side effect:

Cardiovascular: Flattening of the T-wave, flushing, syncope

Central nervous system: Aseptic meningitis, ataxia, confusion, coordination impaired, depression, dizziness, , fever, headache, insomnia, irritability, seizure, vertigo

Dermatologic: Erythematous rash, pruritus, Stevens-Johnson syndrome, urticaria

Endocrine & metabolic: Disulfiram-like reaction, dysmenorrhea

Gastrointestinal: Nausea, anorexia, abdominal cramping, constipation, diarrhea, epigastric distress, furry tongue, unusual/metallic taste, vomiting.

Genitourinary: darkened urine.

Pregnancy Risk Factor: B