



NDA 18-657/S-029

APPROVAL LETTER

Baxter Healthcare Corporation
Attention: Ms. Vicki Drews
Director, Global Regulatory Affairs
1620 Waukegan Rd. MPGR-AL
McGaw Park, IL 60085

Dear Ms. Drews:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flagyl[®] (metronidazole) I.V. Injection, 500 mg USP RTU[®] (in Viaflex[®] Plus Container).

We acknowledge receipt of your submission dated June 12, 2009.

This "Changes Being Effected in 30 days" supplemental new drug application provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert (PI).

The revisions to the package insert (PI) are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

1. The **WARNINGS** section was revised as follows:

Central And Peripheral Nervous System Effects-~~Convulsive Seizures and Peripheral Neuropathy~~

~~Convulsive Seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt evaluation of the benefit/risk ratio of a continuation of therapy.~~

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 metronidazole.

Aseptic 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.

2. The **ADVERSE REACTIONS** section was revised as follows:

The ~~most~~ ~~Two~~ serious adverse reactions reported in patients treated with ~~intravenous~~ metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged oral administration of metronidazole, patients should be observed carefully if neurologic symptoms occur and a prompt evaluation made of the benefit/risk ratio of the continuation of therapy.

The following reactions have also been reported during treatment with Metronidazole Injection, USP RTU®.

Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea and an unpleasant metallic taste.

Hematopoietic: Reversible neutropenia (leukopenia).

Dermatologic: Erythematous rash and pruritus.

Central Nervous System: Encephalopathy, aseptic meningitis, optic neuropathy, ~~h~~Headache, dizziness, syncope, ataxia, ~~and~~ confusion and dysarthria.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of the mouth (or vagina or vulva) and fever.

Local Reactions: Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling intravenous catheters.

Other: Fever. Instances of a darkened urine have also been reported, and this manifestation has been the subject of a special investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

The following adverse reactions have been reported during treatment with oral metronidazole:

Gastrointestinal: Nausea, sometimes accompanied by headache, anorexia and occasionally vomiting; diarrhea, epigastric distress, abdominal cramping and constipation.

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Encephalopathy, aseptic meningitis, cConvulsive seizures, optic neuropathy, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness and insomnia.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of the mouth (or vagina or vulva) and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure and darkened urine.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metronidazole Injection, USP RTU®.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Please submit revised content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, which is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert (PI)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
08/06/2009