

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-806

PHARMACOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-806
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	07/26/04
PRODUCT:	Metronidazole Vaginal Gel. 0.75%
INTENDED CLINICAL POPULATION:	Non-pregnant women with bacterial vaginosis
SPONSOR:	Teva Pharmaceuticals USA 1090 Horsham Road, PO Box 1090 North Wales, PA 19454-1090
REVIEW DIVISION:	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
PHARM/TOX REVIEWER:	Dr Owen McMaster
PHARM/TOX SUPERVISOR:	Dr Robert Osterberg
DIVISION DIRECTOR:	Dr Renata Albrecht
PROJECT MANAGER:	Dr Yon Yu

Date of review submission to Division File System (DFS): July 19, 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

There are no preclinical data that would preclude the approval of metronidazole vaginal gel for the treatment of bacterial vaginosis.

B. Recommendation for nonclinical studies:

No preclinical studies are being recommended at this time.

C. Recommendations on labeling:

The sections labeled "Nursing Mothers", "Pregnancy" and "Carcinogenesis, Mutagenesis, Impairment of Fertility" will read as follows:

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity after chronic oral administration in mice and rats. Pulmonary tumors and lymphomas were reported in several oral mouse studies in which mice were dosed at 75 mg/kg and above (about 5 times the clinical human dose based on body surface area comparison). Malignant liver tumors were reported in male mice dosed at doses equivalent to a human dose of 41 mg/kg/day (33 times the recommended clinical dose based on body surface area comparisons). Chronic oral dosing of metronidazole in rats at doses above 150 mg/kg (about 120 times the clinical human dose based on body surface area comparison) has resulted in mammary and hepatic tumors. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative. No life-time studies were performed to evaluate the carcinogenic potential of metronidazole vaginal gel, 0.75%.

Metronidazole has shown mutagenic activity in a number of *in vitro* assay systems. In addition, a dose dependent increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosome aberrations has been reported in one study of patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1 to 24 months. However in a second study no increase in chromosome aberrations was reported in patients with Crohn's disease who were treated with metronidazole for 8 months.

Fertility studies have been performed in mice up to six times the recommended human oral dose (based on mg/m²) and have revealed no evidence of impaired fertility.

PREGNANCY

TERATOGENIC EFFECTS

PREGNANCY CATEGORY B

There are no data available regarding the use of Metronidazole Vaginal Gel, ~~—~~ in pregnant women and therefore, no adequate and well-controlled studies in pregnant women. Oral reproductive toxicology studies have been performed in mice at doses up to six times the recommended human dose based on body surface area comparisons have revealed no evidence of impaired fertility or harm to the fetus. However, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed.

Animal studies have shown that metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Because animal reproduction studies are not always predictive of human response, and because metronidazole crosses the placental barrier and is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole.

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No preclinical toxicology studies were performed in support of this NDA. The preclinical toxicology data that has been included in the label for Metronidazole Vaginal gel can be found in the label of other metronidazole drug products.

The oral LD₅₀ values were 1 to 5 g/kg in rats and mice. Metronidazole administration at very high doses has been associated with testicular dystrophy and prostatic atrophy, ataxia, muscular atrophy and tremors. At 500 mg/kg, pulmonary tumors were recorded in mice.

PHARMACOLOGY/TOXICOLOGY REVIEW

INTRODUCTION AND DRUG HISTORY

NDA number: 21806

Date of submission: July 19, 2004

Information to sponsor: Yes

Sponsor:

TEVA Pharmaceuticals USA.
1090 Horsham Road,
PO Box 1090 North Wales, PA 19454-1090

Manufacturer for drug substance:



Reviewer name: Dr Owen McMaster

Division name: Division of Special Pathogen and Immunologic Drug Products

HFD-590

Review completion date: May 5, 2005

Drug: Metronidazole vaginal gel.

Trade name: Metronidazole Vaginal Gel, 0.75 %

Generic name: metronidazole

Code names: Bayer-5630, NSC-50364, RP-8823, SC-10295

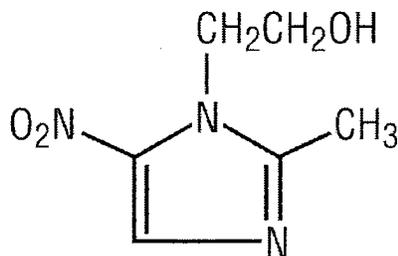
CAS number: 443-48-1

Chemical name: 2-methyl-5-nitro-1 *H*-imidazole-1-ethanol

Molecular formula: C₆H₉N₃O₃

Molecular weight: 171.16

Structure:



Relevant INDs: _____

Relevant NDAs: 19122, 19348, 21789, 70295, 70432, 73560

Relevant DMF: _____

Drug class: Imidazole

Intended clinical population: Non pregnant women with bacterial vaginosis

Clinical formulation: Metronidazole Vaginal gel is almost identical to the 3M product Metrogel-Vaginal[®], 0.75%. The comparison of the components of the two products is shown below: Metronidazole Vaginal gel contains hypromellose whereas the Metrogel-Vaginal[®], 0.75%. contains Carbomer 934, NF.

TEVA Product		3M Product (Metrogel-Vaginal [®] , 0.75%)	
Metronidazole	0.75	Metronidazole	0.75
Hypromellose		Carbomer 934, NF	
Edentate disodium		Edentate disodium	
Methylparaben		Methylparaben	
Propylene glycol		Propylene glycol	
Propyl paraben		Propyl paraben	
Sodium hydroxide		Sodium hydroxide	

Route of administration: Intravaginal

OVERALL CONCLUSION

Metronidazole is a member of the imidazole class of antibacterial agents and is classified as an antiprotozoan and antibacterial agent. Metronidazole is known to be active against *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*. Metronidazole is the active ingredient in a number of approved prescription products and TEVA (sponsor of Metronidazole Vaginal Gel, 0.75 %) has submitted a 505(b)(2) application with Metrogel-Vaginal[®], 0.75% as the reference product.

Metronidazole Vaginal Gel, 0.75 % is almost identical to a registered product Metrogel-Vaginal[®], 0.75%. There are no preclinical data that would preclude the approval of Metronidazole Vaginal Gel, 0.75 % for use in women for the treatment of bacterial vaginosis. The potential carcinogenic effects of metronidazole are reference in the label.

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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/s/

Owen McMaster
5/16/05 03:40:10 PM
PHARMACOLOGIST

Robert Osterberg
5/16/05 04:01:28 PM
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Steven Gitterman
5/17/05 09:18:24 PM
MEDICAL OFFICER