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APPLICATION NUMBER:

205223Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 205-223
Supporting document/s: 1
Applicant's letter date: May 24, 2013
CDER stamp date: May 25, 2013
Product: Metronidazole Vaginal Gel 1.3%
Indication: Treatment of bacterial vaginosis.
Related IND: 107,484
Applicant: Valeant Pharmaceuticals North America LLC
700 Route 202/206 North
Bridgewater, New Jersey 08807
Review Division: Division of Anti-infective Products
Reviewer: Owen McMaster, Ph.D.
Supervisor/Team Leader: Wendelyn Schmidt, Ph.D.
Division Director: Sumathi Nambiar, M.D.
Project Manager: Jane Dean

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-223 are owned by Valeant or are data for which Valeant has obtained a written right of reference. Any information or data necessary for approval of NDA 205-223 that Valeant does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Valeant does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 205-223.

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

There are no nonclinical pharmacology or toxicology data that preclude the approval of Metronidazole vaginal gel 1.3%.

1.1.2 Additional Non Clinical Recommendations

No additional nonclinical pharmacology or toxicology studies of Metronidazole vaginal gel 1.3% are being recommended at this time.

1.1.3 Labeling

The applicant has proposed to include the following statement in section 13. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis studies have not been conducted with Metronidazole vaginal gel 1.3%
(b) (4)

The agency proposes the following

Carcinogenesis studies have not been conducted with Metronidazole vaginal gel 1.3%.

1.2 Brief Discussion of Nonclinical Findings

This NDA is largely supported by the nonclinical Pharmacology and Toxicology studies conducted under NDA 20-208 for METROGEL-VAGINAL 0.75 %, which was approved in August 1992. The applicant for NDA 20-208 was Medicis Pharmaceutical Corporation, which was acquired in 2012 by Valeant Pharmaceuticals International, Inc., the holder of NDA 205-223.

The current formulation, Metronidazole Vaginal Gel 1.3% was evaluated in an intravaginal study in rabbits, entitled: *Metronidazole Gel: 10-Day Vaginal Irritation Study in Rabbits*. After 10 days, treated rabbits showed mild vaginal irritation, but this was similar to that seen with vehicle or with the marketed METROGEL-VAGINAL 0.75 %. Please see the 30 day safety review of IND 107,484, (Metronidazole vaginal gel 1.3%) dated 1/15/2010 for additional details.

The prescribing information also describes adverse events of special interest for metronidazole, which included mutagenicity, carcinogenicity and distribution to breast milk.

Metronidazole was positive in the Ames assay. When administered orally, pulmonary tumors and malignant lymphoma were reported in numerous mouse studies and mammary and liver tumors were found in rats. Although plasma levels after vaginal administration were about a third of that expected after a similar oral dose, Metronidazole Vaginal Gel 1.3% could have direct effects on the vaginal tissues. Carcinogenicity studies have not been conducted with Metronidazole Vaginal Gel 1.3%.

In nursing women treated with oral metronidazole, drug levels in breast milk were similar to concentrations in plasma, but plasma levels were lower in women treated with Metronidazole vaginal gel 1.3%. In one study, plasma AUC levels measured after Metronidazole vaginal gel 1.3% (which contains 65 mg of metronidazole) were only 4% of the levels obtained with a 500 mg dose of oral metronidazole. Since metronidazole is known to transfer into breast milk, nursing mothers are warned to exercise caution and should pump and discard breast milk for 24 hours after using Metronidazole vaginal gel 1.3%.

The components of Metronidazole vaginal gel 1.3% are shown on Table 1, below. This new formulation was used in the nonclinical study and the clinical trials. Components were all either USP or National Formulary. There are no impurity concerns. Please see Chemistry review by Dr. Lin Qi for additional details.

Table 1. Drug Product Components and Composition

Component	Function	Quality Standard	Quantity (% w/w)
Metronidazole	Active	USP	1.3
Polyethylene Glycol 400	 (b) (4)	NF	 (b) (4)
Propylene Glycol		USP	
Benzyl Alcohol		NF	
Methylparaben		NF	
Propylparaben		NF	
Polycarbophil		USP	
Purified Water		USP	

USP= United States Pharmacopeia

NF=National Formulary

Conclusion

The data presented show that the 1.3 % formulation showed an adverse event profile similar to the marketed product and was no more irritating than the approved METROGEL-VAGINAL 0.75 %. There are no nonclinical data that would preclude the approval of Metronidazole Vaginal Gel 1.3%.

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/s/

OWEN G MCMASTER
01/06/2014

WENDELYN J SCHMIDT
01/07/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 205223

Applicant: Valeant **Stamp Date:** 5/24/2013

Drug Name: Metronidazole Vaginal Gel 1.3 % **NDA Type:** Standard

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	√		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	√		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Owen G. McMaster	July 15, 2013
Reviewing Pharmacologist	Date

Wendelyn Schmidt	July 15, 2013
Team Leader/Supervisor	Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

OWEN G MCMASTER
07/15/2013

WENDELYN J SCHMIDT
07/16/2013