CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

PHARMACOLOGY REVIEW(S)

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HFD-590

Sponsor: Advanced Care Products, Personal Products Company,
Division of McNeil-PPC, Inc.
691 Highway 1
P.O. Box 6024
North Brunswick New Jersey 08902-0724

Manufacturer: Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Drug: Monistat®3, miconazole nitrate cream (4%)
Chemical name: 1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-mononitrate
Molecular weight: 479.15
Molecular formula: $C_{18}H_{14}Cl_4N_2HNO_3$

Formulation: Monistat®3 contains 4.0 % miconazole nitrate in addition to [redacted] % isopropyl myristate, NF, [redacted] % polysorbate 60, NF, [redacted] % stearyl alcohol, NF, [redacted] % cetyl alcohol, NF, [redacted] propylene glycol, USP, [redacted] potassium hydroxide, NF, [redacted] % benzoic acid, USP, [redacted] % purified water, USP.

Related IND's, NDA's and DMF's: [redacted]

Indication: Over the counter use in the treatment of vaginal yeast infections

Introduction:

Miconazole nitrate has been available for the treatment of vaginal candidiasis since 1974. Miconazole inhibits ergosterol biosysnthesis in the cell membrane of susceptible organisms and it is thought that the accumulation of ergosterol precursors and toxic peroxides results in cytolysis.

The current product, Monistat®3, is a new preparation of miconazole nitrate and is used to treat vaginal yeast infections in 3 days. The overall dose of 600 mg of miconazole nitrate (200 mg/dose x 3 applications) is the same total dose of miconazole nitrate administered with the currently approved Monistat 3 vaginal suppositories (which are also administered for 3 days). This new base cream is designed to maintain its viscosity at body temperature, thereby producing less mess. Systemic absorption of miconazole from the vaginal wall is low (on the order of 1%).

Toxicology Studies Summary

The following preclinical toxicology studies were submitted to the agency to support the approval of Monistat®3 cream.

1. Acute (Single dose) oral toxicity of M3/Nf in male and female rats
2. Ten day vaginal irritation study of M3/NF in rabbits
3. Vaginal irritation study in rabbits
4. Primary eye irritation study of M3/NF in rabbits
5. Primary skin irritation study of M3NF in rabbits
6. Acute penile mucosal irritation study of M3/NF in rabbits
7. Delayed contact hypersensitivity study of M3/NF in guinea pigs

Toxicology Studies Review

1. **Acute (Single dose) oral toxicity of M3/NF in male and female rats**

Test material (miconazole (4 %) or the approved (2 %) cream) was administered orally by gavage to groups of Sprague Dawley rats (5 animals/sex) at 5000 mg/kg after which animals were observed for 14 days. Records were kept of mortality, clinical signs, body weights, and gross necropsy findings.

There was no mortality during this study. Treated animals gained weight in a fashion similar to animals treated with the 2 % product and showed no clinical signs. There were no remarkable macroscopic postmortem observations.

Conclusions

No mortality resulted from the dosing of rats with a 5000 mg/kg oral dose of miconazole (4 %). This dose is equivalent to a human dose of 795 mg/kg. Each prefilled applicator of the drug product contains 5000 mg of cream, resulting in a daily dose of 83 mg/kg for a 60 kg patient. As such, the safety margin for this product seems adequate.

2. **Ten day vaginal irritation study of M3/NF in rabbits**

Groups of three female albino rabbits (New Zealand White, Hra (NZW)SPF) each were treated with 4 % miconazole nitrate cream intravaginally for ten consecutive days. Other groups of (3) animals were (a) untreated, (b) sham treated (c) vehicle treated, and (d) treated with the approved 2 % miconazole cream. Records were kept of mortality, clinical signs, body weights, macroscopic findings and microscopic evaluation of the vagina.

All animals survived to the end of the study and were euthanized with intravenous pentobarbital. There were no drug related changes in body weight. One of three animals treated with 4 % miconazole showed a mild discoloration in the vagina (as did one of the three animals treated with the 2 % product). When microscopic findings were assessed, the animals treated with 4 % miconazole were no more irritated than sham treated animals and were less irritated than those treated with the 2 % product. Test substance was judged to be minimally irritating to the vaginal wall.

3. **10-day Vaginal irritation study in rabbits with miconazole nitrate (4 %) vaginal cream**

Test material was administered intravaginally to rabbits (New Zealand White , Hra (NZW)SPF) once daily for 10 consecutive days. Rabbits received a 1 ml dose administered using a 5 ml syringe attached to a K-Y jelly lubricated French catheter which was inserted to a depth of 15 cm and withdrawn as its contents were discharged. There were 4 groups of animals: (1) The untreated control group which consisted of 6 rabbits (2) the sham control group , which consisted of 6 animals which received saline (3) the test group which consisted of 10 animals which received 4 % miconazole nitrate and (4) the vehicle control group which consisted of 10 animals which received vehicle cream. Records were kept of mortality, clinical signs, vaginal changes, body weights. On study day 11, animals were sacrificed and the vagina dissected out for histological examination. The condition of the epithelium as well as the presence of vascular congestion, leukocyte infiltration, and edema were noted.

Treatment did not result in any mortality or significant changes in mean body weights across groups. Discharge was observed from the vagina of animals treated with cream or cream vehicle during the treatment period. No discharge was observed in the sham or untreated animals.

White colored viscous/gelatinous substance was observed in the vagina in 5/10 animals treated with 4 % miconazole. Red striations were also observed in the upper vagina in 2/10 animals in this group. Animals treated with vehicle showed the following findings: Small thin vagina (1/10 animals), white or yellow viscous gelatinous substance in the vagina (3/10 animals) red striations in the upper vaginal tract (1/10 animals) , slight brown discoloration around the tail (1/10 animals)

Irritation was scored using the following criteria:

Epithelium: Intact (0), Cell degeneration or flattening (1), metaplasia (2), focal erosion (3), generalized erosion or ulceration (4).
Vascular congestion: Absent (0), minimal (1), mild (2), moderate (3), marked, with disruption of vessels (4).
Leukocyte infiltration (per high power field): Absent(0), minimal, less than 25 (1), mild, 26-50 (2), moderate 51-100(3) marked, greater than 100 (4).
Edema: absent (0), minimal (1), mild (2), moderate (3), marked (4).

A total score of 1-4 was judged to be minimal irritation, while a score of 5-8 was judged to be mild irritation. A score between 0 and 8 was judged acceptable. A score between 9 and 11 was moderate irritation and 12 to 16 was seen as marked irritation. A total score between 9 and 11 was borderline and a score above 12 was unacceptable

Composite average for the 4 groups were as follows:

	Untreated	Sham	M3/NF	2 % cream
Composite average	1.6	5.1	6.3	6.3
Degree of irritation	Minimal	Mild	Mild	Mild

Conclusion

Vaginal administration of 4 % miconazole nitrate cream for 10 days to rabbits produced mild irritation to the vaginal epithelium. The mean severity score of 6.3 produced a level of irritation that was judged acceptable for this type of product.

4 Primary eye irritation study of M3/NF in rabbits.

This study was designed to determine the potential of a single dose of 4 % miconazole cream to produce corneal irritation in the rabbit. Groups of albino rabbits (New Zealand White , Hra (NZW)SPF), 6 animals per dose group, were treated with either 4 % miconazole or the approved cream.

On the day before dosing, both eyes of each animal were examined under fluorescein dye to check for the presence of corneal ulceration. Eyes were again examined on the day of dosing but without the dye. Each test material was administered directly onto the cornea of the right eye of the rabbits in a volume of 0.1 milliliters after which the eye was held closed for one second to minimize test material loss. Eyes were then examined for ocular irritation at 1, 24, 48 and 72 hours after treatment and on day 7 or until no signs of irritation were seen. Sodium fluoroscein dye was used to confirm the presence or absence of corneal ulceration.

Both 4 % miconazole and the 2 % miconazole cream were mildly irritating to the eye of the rabbit. Ocular irritation in the animals treated with both products were similar and consisted of conjunctival redness, chemosis and discharge. No corneal or iridial changes were seen. Five of six animals were free of irritation by 72 hours and the remaining animal had recovered by day 7.

Conclusion

Both miconazole (4 %) and the 2 % product are mildly irritating to the eyes.

5. **Primary skin irritation study of M3/NF in rabbits.**

This study was designed to determine the irritation potential of 4% miconazole cream when administered to the skin of rabbits. This was compared with the irritation seen with the approved 2 % miconazole cream..

The hair of six (New Zealand White , Hra (NZW)SPF) rabbits (3/sex) were closely shaved to expose the back and six dosing sites were selected. Three of the sites were abraded and three were left intact. Each test material (0.5 ml) was applied to two 1 x 1 inch gauze patches and applied to one abraded and one intact section of skin. Two sites were left untreated to serve as controls. The sites were occluded for 24 hours. The occlusive covering was removed at the end of the 24 hour exposure period and the area was wiped free of residual test material. Sections of skin were observed 30 minutes, 24, 48 and 72 hours after the occlusive covering was removed and scored according to the company's Dermal Irritation Grading System. It is outlined as follows:

Erythema: No erythema (0), very slight erythema (1), well defined erythema (2), moderate to severe erythema (3), severe erythema to slight eschar formation (4).

Edema: No edema (0), very slight edema (1), slight edema (2) moderate edema (3), severe edema, raised more than 1 mm and extending beyond the area of exposure (4)

Mean scores (Primary Irritation Index) of 0.0 reflect a nonirritant, 0.01-2.00 are classified as slight irritant, 2.01 to 5.00 are moderate irritants and 5.01 to 8.00 are severe irritants.

Miconazole(4 %) produced mild to moderate irritation at both abraded and intact sites. Five of six animals showed slight erythema with no edema and one animal had severe erythema at the intact site. At the abraded sites, one animal showed necrosis and eschar. By 72 hours 2 of the six animals showed no irritation. The remaining animals continued to show irritation at both sites. Animals treated with the approved 2 % miconazole cream had a primary irritation score of 2.2. Both abraded and intact sites on control animals showed no dermal irritation throughout the study. Primary Irritation Scores are showed below:

Group	Primary irritation Score
Untreated Controls	0.0
M3/NF	1.2
M3	2.2

Conclusion:

The primary irritation score of 4 % miconazole cream is 1.2 which places it in the "slight irritant" category. The approved 2 % miconazole cream is classified as a "moderate irritant".

6 **Acute penile mucosal irritation study of M3/NF in rabbits.**

This study was designed to determine the irritation potential of M3/NF in rabbits when administered in a single dose to the penile mucosa of albino (New Zealand White) rabbits.

Twenty-four male rabbits (six/dose group) were used for the study. Groups consisted of (1) sham control (2) vehicle controls (3) 4 % miconazole-treated and (4) 2 % miconazole-treated animals. Each rabbit was inverted and the penis fully extruded, after which the test material (0.2 ml) was applied to the exposed mucosa so that the entire mucosal surface was in contact with the test material. Penile irritation was evaluated prior to dosing and 1, 24 and 48 hours post dose.

No edema or erythema was observed in any of the treated animals.

Conclusion

Under conditions of this study, 4 % miconazole did not demonstrate potential for producing penile irritation.

7. **Delayed contact hypersensitivity study of M3/NF in guinea pigs.**

This study was designed to determine the potential of 4 % miconazole cream to produce delayed contact sensitization when administered to the skin of guinea pigs.

Groups of Hartley albino guinea pigs (5 animals /sex) were clipped free of hair and exposed to 0.3 ml of test material using a [redacted] The chamber was left in place for six hours This was performed once a week for a total of three induction exposures. A positive control group was exposed to 1-chloro, 2,4-dinitrobenzene (DNCB). Challenge treatment followed the same administration procedure as the induction phase but at naïve test sites. In order to differentiate between dermal reactions produced by sensitization and that produced by irritation, ten previously untreated animals were subjected to the same challenge procedures. Records were kept of mortality, body weights, clinical signs, and dermal signs. Dermal signs were evaluated 24 and 48 hours after each induction and 24 and 48 hours after the challenge exposure.

The grading scheme for assessing the extent of dermal hypersensitivity was as follows: No reaction (0), Slight patchy erythema (0.5), Slight, confluent or moderate, patchy erythema (1), Moderate erythema (2), Severe erythema, with or without edema (3).

All ten animals treated with DNCB exhibited clear dermal responses at challenge (mean score, 1.4 at 24 hours and 2.2 at 48 hours) which were significantly greater than those seen with the irritation controls (mean scores 0.7 at 24 hours and 1.0 at 48 hours). All ten animals treated with 4 % miconazole cream were free of distinct dermal responses although one animals showed slight patchy erythema (overall score of 0.0 at 24 hours and 0.05 at 48 hours) No dermal response was seen with the vehicle control and all ten irritation animals were free of dermal responses (mean score of 0.0 at all time points).

Conclusion

The 4% miconazole cream produced no evidence of delayed contact sensitization when administered to the skin of the guinea pig.

Summary and Overall Conclusion

Sufficient information has been provided to support the approval of the NDA. The information provided in the label and educational material provided with this product are accurate.

This new preparation of miconazole cream (4 %) is minimally irritating to the vaginal wall of rabbits and is no more irritating than the already approved vaginal cream. It is mildly irritating to the eyes and a slight irritant to the skin. The animal studies provided no evidence for penile irritation or delayed contact sensitization with this product.

/S/

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Concurrences:

HFD-590/RAlbrecht
HFD-590/KHastings 3/26/98

Disk:

HFD-590/KHastings

cc:
HFD-590 Division File
HFD-590/ Micro/LGosey
HFD-340
HFD-590/MO/JWinfield
HFD-590/CSO/CChi
HFD-590Pharm/OMcMaster
HFD-590/Chem/DMateka