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APPLICATION NUMBER:

21-074

PHARMACOLOGY REVIEW

M. Dillon-Parker

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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
Division of Anti-infective Drug Products, HFD-520

KEY WORDS: Avagard, CHG Hand Prep, chlorhexidine, ethanol, local lymph node assay

Reviewer Name: Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.

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Sponsor: 3M Health Care
3M Center
St. Paul, MN 55144

Contact person: Suzanne Danielson,
Regulatory Affairs Manager
Phone 651-737-9117

Relevant INDs: [redacted]

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INTRODUCTION

Avagard is an antimicrobial skin cleansing lotion, containing chlorhexidine gluconate, ethanol, and about a dozen inactive ingredients. At least 18 formulations of the product have been developed, that have differed slightly in the percentage composition of the various ingredients. The formulation that was selected for commercial development is designated HPD-5-a. The composition of this formulation is shown below.

Ingredient	Component Wt%
Alcohol	
Water	
Beheneth-10	
Behenyl Alcohol	
Diisopropyl Dimer Dilinoleate	
Squalane	
Chlorhexidine Gluconate Solution[2]	
Polyethylene Glycol	
Dimethicone	
Glycerin	
Polyethylene Glycol	
C20-40 Pareth-24	
Cetyl Palmitate	
Total Weight	100.00

TOXICOLOGY

The toxicology studies were GLP studies, that were conducted for the sponsor by . The numbers in parentheses refer to last four digits of the sponsor's study number.

Dermal Irritation and Sensitization Study in Mice

The irritation and sensitization potential of seven formulations (HPD-1-a, HPD-2-a, HPD-3-a, HPE-1-a, HPE-2-a, HPF-1-a, HPF-2-a) were tested in a single assay in female BALB/c mice (5/group). In this model, the test agent (50 microliters) was applied to both sides of one ear, once daily for four days, and the increase in ear thickness, as measured with a special micrometer caliper, was used as a measure of dermal irritation. On day 5, tritiated thymidine was injected intravenously, and five hours later the animals were sacrificed. Both superficial cervical lymph nodes were collected, and prepared for radioactivity counting. The incorporation of thymidine into lymph node cells was used as an indication of sensitization. Groups that received sodium lauryl sulfate (a known irritant), and 2,4-dinitrofluorobenzene (a known sensitizer and irritant), were carried through the assay as positive controls.

Ear swelling was observed in the positive control group, but there were no statistically significant increases in ear thickness in any of the other groups. In the local lymph node assay, in addition to the positive control, two of the test formulations (HPD-1-a and HPE-1-a) showed slight, but statistically significant increases in thymidine incorporation, and these two formulations were considered to be mild sensitizers.

Subchronic Dermal Toxicity Study in Rats [redacted]

Two formulations (HPD-5-a and HPD-5-b) were tested in a three-month dermal study in Sprague-Dawley rats (10/sex/group). The test materials were applied to the shaved, intact dorsal skin, three times daily with intervals of 2-4 hours between doses. During the first 24 days of the study, the doses were 0.03, 0.15, or 0.30 mL/application for HPD-5-a, and 0.30 mL for HPD-5-b. The control group received "0.9% Sterile Water for Injection" (sic). Dosing was suspended for five days because of dermal irritation and technical difficulties with the volume of liquid being administered three times daily. On day 30, dosing was resumed with the volumes cut in half. The application sites were occluded with plastic film, and each rat had a harness to prevent oral ingestion. Excess test material remaining at the application site, was wiped off prior to the next dose. Additional animals (5 male, 5 female) for a recovery period, were carried in the two high-dose groups.

In addition to evaluations for dermal irritation, measurements were also made for body weights, food consumption, ophthalmic effects, hematology, serum chemistry, urinalysis, gross observations, organ weights, and microscopic histopathology.

There were no deaths, or systemic signs of toxicity in the study. No dermal irritation was observed in the HPD-5-b group. Dose-related erythema was seen in the HPD-5-a groups, and was sometimes accompanied by sores and scabs. Females were affected to a greater extent than were males. The sores and scabs usually occurred in the areas where the harness had been in place. The dermal effects were reversible during the recovery phase.

Dermal Teratology Study in Rats [redacted]

The same two formulations (HPD-5-a and HPD-5-b) were tested in an embryo-fetal toxicity study in Sprague-Dawley rats (25 pregnant females/group). The test materials were applied to the shaved, intact dorsal skin, three times daily with intervals of 2-4 hours between doses. The group designations were as follows:

Group 1	Deionized water	0.3 mL	TID
Group 2	HPD-5-b	0.3 mL	TID
Group 3	HPD-5-a	0.15 mL	TID
Group 4	HPD-5-a	0.3 mL	TID

The doses were administered during days 6 through 17 of gestation. The application sites were occluded with plastic film, and each rat had a harness to prevent oral ingestion. Excess test material remaining at the application site, was wiped off prior to the next dose.

On gestation day 20, the animals were sacrificed and the ovaries and uteri were removed and opened. The numbers of corpora lutea, implantation sites, early and late resorptions, and live and dead fetuses were recorded. Fetuses were weighed, sexed, and examined for external abnormalities. About half of the fetuses were prepared for visceral examination [redacted] while the other half were prepared for skeletal examination [redacted]

There were no deaths in the study; dermal irritation was seen in the dams. There were no treatment-related effects on pregnancy rate, corpora lutea, implantation sites, early and late resorptions, or live and dead fetuses. Also, there were no external, visceral, or skeletal fetal abnormalities that could be attributed to treatment.

Dermal Sensitization Study in Guinea Pigs [redacted]

HPD-2-a was evaluated for the potential to induce contact sensitization in Hartley albino guinea pigs (10 males, 10 females), using the standard [redacted] experimental design. The test material (0.2 mL, undiluted) was placed in the special [redacted] chamber. Hair was removed using electric clippers. The chamber was applied to the skin on the left side of the body, and secured in place [redacted] Nine applications (induction phase) were made over a three-week period. For the challenge phase, the hair was again clipped, and the material was applied to the right side of the body. The assessment of sensitization potential was based on dermal responses such as erythema, edema, ulceration, desquammation, etc.

HPD-2-a did not induce sensitization. A positive control (DNCB) produced the expected sensitization reaction.

Primary Dermal Irritation Studies in Rabbits [redacted]

One day prior to test article administration, hair was clipped from the sides of six female New Zealand albino rabbits, and two test sites were selected on each rabbit lateral to the midline of the back. Making four epidermal incisions abraded one site, while the other site remained intact. The test article (HPD-2-a) was applied to each test site. The test sites were allowed to dry and were then wrapped with gauze and occlusive plastic. After a 24-hour exposure period, the wrapping was removed and the test sites were examined and scored for erythema and edema on a graded scale of 0-4.

In the repeat dose experiment with HPD-2-a, the test article was applied once daily for five consecutive days.

After the 24-hour exposure period, slight amounts of erythema and edema were seen at both the intact and abraded sites. The formulation was found to be mildly to moderately irritating at both sites (mean primary irritation scores averaged 2.1-2.9 out of a possible 8.0).

Repeat dosing was also classified as mildly irritating and this classification remained the same throughout the five days of dosing.

In another study using the same experimental design, six formulations (HPD-1-a, HPD-2-a, HPD-3-a, HPE-1-a, HPF-1-a, HPF-2-a) were tested. These formulations were also found to be mildly to moderately irritating.

Primary Ocular Irritation Study in Rabbits [redacted]

Two groups of six New Zealand albino rabbits, were used to evaluate the ocular irritation potential of HPD-5-a and HPD-5-b. Before dosing, the eyes were found to be free of irritation, based on macroscopic and fluorescein/ultraviolet examination. The test material (10 microliters) was instilled into the conjunctival sac of the right eye. The left eye was not treated, and served as a control. In three of the animals from each group, the treated eye was rinsed with water 30 seconds after instillation of the test material. In the other three rabbits in each group, the eye was not rinsed. At 1, 24, 48, and 72 hours after dosing, the eyes were evaluated using Draize scoring system to evaluate the cornea, iris, and conjunctiva.

Conjuntivitis occurred at one hour after dosing, in all 12 of the treated eyes; it had resolved by 72 hours. Iritis was seen in 3/6 eyes treated with HPD-5-a (2 rinsed, 1 unrinsed) at one hour after dosing, but not in any eyes treated with HPD-5-b. The iritis resolved within 24 hours. Sloughing of the corneal epithelium occurred in one animal (an unrinsed HPD-5-a-treated eye). Both formulations were classified as mild ocular irritants.

LITERATURE

The sponsor included brief summaries from the scientific literature that described dermal absorption (or lack of absorption). The following information has been excerpted from those summaries.

A group of five neonatal monkeys was bathed daily for 90 days with an antimicrobial skin cleanser containing 8% chlorhexidine gluconate. In blood samples collected two hours after washing, chlorhexidine levels were below the limit of detection (11 nanograms/mL). It was concluded that the percutaneous absorption of chlorhexidine gluconate was negligible.

The percutaneous absorption of Hibitane (5% chlorhexidine gluconate) was reported to be 0.01% through intact rat skin.

In rabbit studies, ethyl alcohol was reported to be "not absorbed through the skin in any appreciable amounts".

OVERALL SUMMARY AND EVALUATION

Ethyl alcohol and chlorhexidine have been used in topical antimicrobial preparations for many years.

This Avagard formulation (HPD-5-a) was shown to be only minimally irritating to rat and rabbit skin, and mildly irritating to the eyes of rabbits. A similar formulation was not a sensitizer in guinea pigs. Avagard was not teratogenic in rats; it has not been tested for mutagenicity or carcinogenicity.

RECOMMENDATIONS

Approval of this NDA is recommended based on the safety demonstrated in the animal dermal studies, the negligible percutaneous absorption, and the long history of human exposure to alcohol and chlorhexidine-containing skin products.

The following information should be added to the **SAFETY** section of the labeling:

Avagard produced mild ocular irritation when instilled into the eyes of albino rabbits. Avagard was not teratogenic when applied to the skin of rats. Avagard has not been tested for mutagenicity or carcinogenicity.

The sentence in the **SAFETY** section of the label referring to the safety assessment report on chlorhexidine gluconate in the Journal of the American College of Toxicology should be removed.

The sponsor should submit revised labeling to incorporate the safety information described above.

/S/

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original NDA 21-074
HFD-104
HFD-340
HFD-520
HFD-520/Pharm/K. Seethaler
HFD-520/MO/D.Bostwick
HFD-520/Micro/A.Sheldon
HFD-520/Chem/M.Sloan
[redacted]
HFD-520/Biopharm/F.Pelsor
HFD-520/Biostat/L.Dong

Concurrence only:

HFD-520/R. Osterberg /S/ 9/21/99

HFD-520/L. Gavrilovich /S/ 9/22/99