CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-074

MEDICAL REVIEW

CLINICAL REVIEW OF NDA 21-074
Original Submission

Date of Submission: June 25, 1999

Date CDER Received: June 25, 1999

Date Assigned to Reviewer: July 1, 1999

Date Review Initiated: August 25, 1999

Date Review to Supervisor: November 23, 1999

Drug: Avagard™ – CHG Antiseptic Hand Preparation (1% chlorhexidine gluconate, 61% ethyl alcohol)

Applicant: 3M Healthcare
St. Paul, MN 55144

Related IND: [redacted]

Proposed Indications: "Avagard™ – CHG Antiseptic Hand Preparation with moisturizers is indicated for use as a surgical scrub, as a healthcare personnel hand wash, [redacted]

Proposed Dosage and Administration:

"Surgical Hand Scrub

Apply to clean, dry hands and nails. Dispense one pump (2 ml) of Avagard-CHG HandPrep lotion into the palm of one hand. Dip the fingertips of the opposite hand into the lotion and work it under the nails. Spread the remaining lotion over the hand and up the forearm. Dispense another pump of the lotion into the palm of the other hand. Dip the fingertips of the opposite hand into the lotion and work it under the nails. Spread the remaining lotion over the hand and up the forearm. Dispense a final pump of the lotion into the palm of either hand and reapply to both hands to the wrist. Allow to dry before donning gloves."

"Healthcare Personnel Hand Wash

Apply to clean, dry hands and nails. Dispense one pump (2 ml) into the palm of one hand. Apply the lotion evenly to cover both hands. Allow to dry without wiping."

[redacted]

Packaging: This product is to be supplied in plastic bottles in 500 mL, 473 mL and 10 mL sizes.

Formuation:

Ingredient	Component Wt%
Alcohol	
Water	
Beheneth – 10	
Behenyl Alcohol	
Diisopropyl Dimer Dilinoleate	
Squalane	
Chlorhexidine Gluconate Solution[1]	
Polyethylene Glycol	
Dimethicone	
Glycerin	
Polyethylene Glycol	
C20-40 Pareth-24	
Cetyl Palmitate	
Total Weight	**100.00**

[1]Chlorhexidine Gluconate Solution is adjusted based on assay to yield 1% in the final formulation. (example, Solution density=1.065 gm/mL, Assay=20.0% gm/mL).

The chemical structure of chlorhexidine gluconate (CHG):

Molecular formula of CHG: $C_{22}H_{30}C_{12}N_{10} \bullet 2\ C_6H_{12}O_7$
Molecular weight of CHG: 897.8

Molecular formula of ethanol: C_2H_5OH
Molecular weight of ethanol: 46.1

Background: This is one of a number of combination CHG and alcohol (either isopropyl alcohol or ethanol) products under development at this time. Some are intended as IV preps and catheter site maintenance products, and others (such as Avagard) as hand decontamination products [redacted] The following comments are relevant:

A. Since both active ingredients are expected to have antimicrobial effect, this application must contain a study which establishes the contribution of each active to the total effect of the product. It was agreed during pre-NDA meetings with the applicant that only one study which establishes the contribution of both products would be necessary, and that if two studies were done which established the efficacy of the product as a surgical hand scrub, only one study supporting the health care personnel handwash indication would be required.

B. Because ethanol is easily flammable, there is concern that it could be ignited if allowed to pool during use [redacted] However, since the product reviewed here is approvable only for use as a hand decontaminant [redacted] The labeling should still bear warnings about the flammability of the product.

C. The applicant has devoted a considerable amount of effort to develop a handwashing product which will not be irritating. Compliance with handwashing procedures among healthcare personnel has been reported in the literature to be suboptimal. One reason for this may be that most hand preparations intended for healthcare use are irritating with repeated use. The Avagard formulation contains about 7% emollients and moisturizers which are intended to address the irritation problem. Of note:

   i. The product is to be used as a surgical hand scrub alone (without an accompanying brush). If the product is effective without the necessity of using a brush which abrades the skin, compliance may be improved.

   ii. The applicant has performed a number of studies intended to establish that the product is less irritating than other antiseptic hand products, and has included language in the labeling based on these studies. Claims include "formulated for compatibility with the skin," "mild material, and gentle on the hands," and "helps maintain skin integrity". These types of claims are often thought of as cosmetic claims and are not part of the anti-infective NDA review process. The "cosmetic" studies and accompanying claims will be reviewed though there is no precedent for such labeling in

products of this type.

[redacted]

Material Reviewed: The applicant has submitted the following materials concerning testing in humans in support of the NDA [redacted]

A. Pivotal efficacy studies

1. Study No: 7838 [demonstration of effect of each active in the combination product]
   Indication: Surgical scrub
   Number of subjects: Avagard 34
   Vehicle 31
   Hibiclens [4% CHG] 20

2. Study No: 7957
   Indication: Surgical scrub
   Number of subjects: Avagard 27
   Hibiclens 25

3. Study No: 7939
   Indication: Health-care personnel handwash
   Number of subjects: Avagard 24
   Hibiclens 24

B. Skin irritation and sensitization studies

1. Study No: 7770
   Type: Sensitization
   Number of subjects: 217 each for Avagard,
   vehicle and ethyl alcohol

2. Study No: 7771
   Type: Irritation
   Number of subjects: 36 each for Avagard, vehicle, ethyl alcohol, Hibiclens, 0.9% saline,
   0.1% sodium lauryl sulfate, and Curel [a non-antiseptic moisturizer]

C. "Cosmetic" studies

1. Study No: 7772

Type: Comparative hand irritation
Number of hands: Avagard 18
Vehicle 18
Hibiclens 36

2. Study No: 7821
Type: Comparative hand irritation
Number of subjects: 40 each for Avagard and Hibiclens

D. Supportive studies

The following pilot studies were performed during the development of this NDA. They do not add meaningful information concerning the effectiveness of the drug, so they will be briefly described and the safety data reviewed:

1. Study No: 7588
Type: Surgical scrub
Number of subjects: 8 each for Avagard, vehicle and Hibiclens

2. Study No: 7938
Type: Health-care personnel handwash
Number of subjects: 3 each for Avagard, vehicle and Hibiclens

3. Study No: 7372
Type: Comparative hand irritation
Number of subjects: Avagard 10
Vehicle 10
Hibiclens 5
Curel 5

Reviewer's Comment: Meetings were held on the following dates during the IND phase for this drug: March 19, 1998, May 6, 1998, December 8, 1998, and March 8 and 16, 1999. The minutes for these meetings have been consulted during the writing of this review.

This review will consist of the following sections:

I. Review of Pivotal Efficacy Studies and Efficacy Summary

II. Review of Skin Irritation and Sensitization Studies

III. Review of "Cosmetic" Studies

IV. Review of Supportive Studies

V. [redacted]

VI. Safety Summary

VII. Labeling Review

VIII. Conclusions and Recommendations

Other Reviews: Reviews from other disciplines are not available at this time with the exception of the pharmacology/toxicology review, dated September 7, 1999 by Dr. Kenneth Seethaler. The recommendations in this review read as follows:

> 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.

I. Review of Pivotal Efficacy Studies and Efficacy Summary

A. Study Title: Pivotal Study to Assess the Antimicrobial Effectiveness of Surgical Hand Scrub Formulations (Study No. 7838).

Investigator: [redacted]

Study Dates: September 28-December 4, 1998

Study Objectives: The following is taken directly from volume 34, p. 8-874 of the NDA:

> **Primary**
> - To evaluate the effectiveness of the HPD-5a formulation as a Surgical Hand Scrub in meeting the Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for immediate and persistent reductions in the number of bacteria on the hands and to demonstrate superior efficacy of the combination test product (HPD-5a) compared to the vehicle control

without chlorhexidine gluconate (HPD-5b).

Secondary

- To comparatively evaluate bacterial reductions achieved within 1 minute and at 3 and 6 hours post-treatment, HPD-5a versus Hibiclens.
- To comparatively evaluate subjects' assessment of the skin condition of their hands, HPD-5a versus HPD-5b and Hibiclens.

Method:

1. Study design: This was a single-center, randomized, parallel group, partially blinded comparison of Avagard, the product vehicle and Hibiclens (4% CHG) in their ability to lower resident bacterial counts on the hands, and to demonstrate substantivity with repeated scrubs. A total of 85 test subjects were randomized into the study (34 Avagard, 31 vehicle, 20 Hibiclens). These numbers of subjects have been shown in the past to be sufficient to statistically demonstrate the effect of the products.

2. Inclusion criteria: The following is taken directly from volume 34, p. 8-897 of the NDA:

   Subjects included in the study were healthy volunteers, of either gender, who met the following criteria:

   - Subject was at least 18 years of age and not older than 65 years of age
   - Subject was cooperative and willing to sign an informed consent statement
   - Subject's hands were free from cuts, abrasions, and irritation
   - Subject was willing to follow Subject Instructions
   - Subjects had 1st and 2nd baseline culture counts $\geq 1.0 \times 10^5$ colony forming units (CFU) per hand

3. Exclusion criteria: The following is taken directly from volume 34, p. 8-897 of the NDA:

   - Subject exposed to topical or systemic antimicrobials, including, but not limited to antimicrobial antiperspirants, deodorants, shampoos, lotions, soaps, body powers, and materials such as solvents, acids, or alkalis
   - Subject bathed in chlorinated pools, spas, or hot tubs
   - Subject exhibited any form of dermatitis, open wounds or other skin disorders that may have affected the integrity of the study
   - Subject had a history of sensitivity to CHG or alcohol, or allergy to latex
   - Subject was pregnant or nursing, or of child-bearing potential and was not using adequate birth control
   - Subject with artificial nails or artificial nail tips

4. Dosage and duration of therapy: This study was performed according to the protocol for surgical scrubs suggested in the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products. Eleven scrubbing procedures were done: one on day 1, three on days 2, 3 and 4, and one on day 5. Bacterial samples were taken at baseline (prior to scrubbing) and then at one minute and at 3 and 6 hours after the day 1 scrub. Subsequent samples were taken after the first scrub on day 2 and after the day 5 scrub. Details

concerning this sampling procedure (Glove Juice Test) and analysis may be found in the Microbiology Review for this NDA.

The scrub procedures used were as follows:

i. For Avagard and vehicle:

1. For the first scrub of each day, clean under nails with a nail stick.
2. Dispense 2 mL of the material into the palm of one hand.
3. Dip the fingertips of the opposite hand into the material and work it under the nails. Spread the remaining material over the hand and up to just above the elbow.
4. Using another 2 mL of material, repeat steps 2 and 3 with the other hand.
5. Dispense another 2 mL of material into the hand and reapply to all aspects of both hands up to the wrists.
6. Allow the material to dry before placing subject's hands in gloves.

ii. For Hibiclens:

1. For the first scrub of each day, clean under fingernails with a nail cleaner. Wet hands and forearms under running water (38-42°C).
2. Dispense 5 mL of the material into the palms and distribute over hands and up to just above the elbow.
3. Scrub for 3 minutes with a sterile scrub brush, paying particular attention to the nails, cuticles and interdigital spaces.
4. Rinse both hands and arms to just above the elbows for 30 seconds.
5. Wash for an additional 3 minutes with 5 mL of the material.
6. Perform final rinse by rinsing each hand and arm to just above the elbow separately for one minute per hand and arm.
7. Dry thoroughly with a sterile towel before placing subject's hands in sterile protective gloves.

Since the scrub procedures were different, the study was not blinded to the test subjects and lab technicians. However, the microbiological analyses were performed in a blinded fashion.

5. Effectiveness parameters: The TFM standards for surgical scrubs are an immediate one log reduction of resident microbial flora on day 1, with the count remaining below baseline on day 1 for 6 hours, an immediate two log reduction on day 2, and an immediate 3 log reduction on day 5.

6. Safety evaluation: The incidence of adverse experiences was compared between the treatment groups. In addition, test subjects were asked to evaluate the condition of their hands using a questionnaire which has four subjective criteria: appearance, intactness, moisture content, and sensation. The possible scores ranged from 1 to 7, with 7 representing completely healthy skin. The questionnaires were completed prior to the first scrub on day 1 and after the last scrub on day 5.

Results: By prior agreement between the supervisory microbiologist/HFD-520 and the clinical review team, the critical analyses of the bacterial reduction results for topical antiseptics are to be performed by the microbiologist. Therefore, the following results are identical to those presented by the applicant.

1. Efficacy: The following table is taken from volume 34, p. 8-913 of the NDA. The values represent log reduction seen at the various time points. That is, the baseline log count minus the log count measured is shown.

Table 1. Log Reductions in Bacterial Counts (CFU/Hand) (HFD-5a=Avagard, HPD-5b=vehicle)

		Treatment Group	
Day/Time Point	**HPD-5a (N=34)**	**Hibiclens (N=20)**	**HPD-5b (N=31)**
Baseline Period Mean	**6.1**	**6.0**	**6.0**
Day 1 Log Reduction			
N	21	13	21
1 minute	2.6	1.6	1.1
95% CI	(1.9, 3.3)	(0.7, 2.5)	(0.4, 1.8)
N	23	14	21
3 hour	3.1	1.8	1.4
95% CI	(2.7, 3.6)	(1.2, 2.4)	(1.0, 1.8)
N	24	13	20
6 hour	2.8	1.4	0.5
95% CI	(2.3, 3.2)	(0.8, 1.9)	(0.2, 0.8)
Day 2 Log Reduction			
N	21	13	21
1 minute	3.2	2.4	2.0
95% CI	(2.9, 3.6)	(2.1, 2.8)	(1.6, 2.3)
N	21	14	21
3 hour	3.7	2.3	1.3
95% CI	(3.3, 4.0)	(1.7, 2.9)	(0.9, 1.8)
N	22	13	20
6 hour	3.6	2.3	0.5
95% CI	(3.2, 3.9)	(1.9, 2.7)	(0.1, 1.0)
Day 5 Log Reduction			
N	20	13	20
1 minute	3.5	3.6	1.5
95% CI	(3.1, 3.9)	(3.1, 4.1)	(1.1, 1.9)
N	21	13	20
3 hour	3.9	3.6	1.4
95% CI	(3.7, 4.2)	(3.2, 4.0)	(1.0, 1.8)
N	21	12	18
6 hour	3.5	3.0	0.5
95% CI	(3.2, 3.8)	(2.3, 3.7)	(0.1, 0.9)

Reviewer's Comment: These results indicate that all three test compounds meet the day 1 TFM requirements of an immediate (1 minute) one log reduction, with counts not exceeding baseline at 6 hours. All three test compounds also meet the day 2 requirement of an immediate two log reduction. However, the vehicle [HPD-5b] does not meet the day 5 requirement of an immediate three log reduction. Hibiclens and Avagard [HPD-5a] do meet this requirement.

The following table presents the p-values for the differences between Avagard and the vehicle at the TFM designated time intervals. The log reduction difference represents the difference seen between the log reductions achieved by Avagard and the reductions achieved by the vehicle at the indicated time interval. These differences are always in favor of Avagard (that is, Avagard always demonstrates a greater log reduction than vehicle).

Table 2. Between Groups Differences in Log Reductions From Baseline Bacterial Counts (CFU/Hand) (Avagard vs. Vehicle)

Day/Time Point	Log Reduction Difference	95% C.I.	p-value
Day 1, 1 minute	1.52	(0.54, 2.50)	0.0032
Day 1, 6 hour	2.29	(1.73, 2.85)	<0.0001
Day 2, 1 minute	1.28	(0.80, 1.75)	<0.0001
Day 5, 1 minute	2.00	(1.44, 2.55)	<0.0001

Reviewer's Comment: These results indicate that the combination (CHG plus alcohol) product is superior to the vehicle [redacted] product at all time points. Thus, the requirement for proof that the combination is more efficacious than the single ingredients is fulfilled. It is noted that attempts to formulate a 1% CHG product for testing without alcohol were unsuccessful, and the requirement to test CHG alone was waived in pre-NDA meetings with the applicant.

2. Safety: There were six adverse events reported in 5 subjects. Two subjects withdrew from the study due to adverse events unrelated to drug use (one upper respiratory tract infection, one cut hand in an industrial accident).

Two Hibiclens patients reported adverse events which were probably or possibly related to drug use (one erythematous rash, one allergic reaction which consisted of a burning sensation on the upper arm). One Avagard patient suffered conjunctivitis for 13 days and blurred vision for 2 days after he rubbed his eye following product application.

The hand condition self-assessment results indicate that Avagard and its vehicle both performed better than Hibiclens in the parameters observed (appearance, intactness, etc). Since these observations were made by untrained personnel (each test subject rated him/herself), they are not sufficiently rigorous to be meaningful. More objective assessments of skin quality were made in other studies which will be reviewed later.

Reviewer's Summary of Study No. 7838

This study meets its defined objectives in that Avagard meets the standards in the TFM for surgical hand scrubs and the complete Avagard formulation is superior to its vehicle in

activity. The control product, Hibiclens, displayed antimicrobial activity consistent with its performance in other studies of this type.

The only remarkable safety result is the conjunctivitis and blurred vision in the subject who rubbed his eye after using Avagard. The proposed labeling for the product has adequate warnings concerning possible contact of the eyes with this product, but an additional warning on the front label would be useful (see Labeling Review, below).

B. Study Title: Pivotal Study to Assess the Antimicrobial Effectiveness of Surgical Hand Scrub Formulations (Study No. 7957)

Investigator: [redacted]

Study Dates: August 20-October 23, 1998

Study Objectives: The following is taken directly from volume 36, p. 8-1666 of the NDA:

> **Objectives:**
> **Primary**
>
> - To evaluate the effectiveness of the HPD-5a formulation as a Surgical Hand Scrub in meeting the Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for immediate and persistent reductions in the number of bacteria on the hands
>
> **Secondary**
>
> - To comparatively evaluate bacterial reductions achieved within 1 minute and at 3 and 6 hours post-treatment, HPD-5a versus Hibiclens
> - To comparatively evaluate subjects' assessment of the skin condition of their hands, HPD-5a versus Hibiclens.

Method:

1. Study design: This was a single-center, randomized, parallel-group, partially blinded comparison of Avagard and Hibiclens. A total of 52 test subjects were randomized into the study (27 Avagard, 25 Hibiclens).

2. Inclusion criteria: These were the same as for Study 7838, above.

3. Exclusion criteria: These were the same as for Study 7838, above.

4. Dosage and duration of therapy: These were the same as for Study 7838, above.

5. Effectiveness parameters: These were the same as for Study 7838, above.

6. Safety evaluation: This was the same as for Study 7838, above.

Results: As above, the following results are identical to those presented by the applicant.

1. Efficacy: The following table is taken from volume 36, p. 8-1703 of the NDA. The values represent log reductions seen at the various time points. That is, the baseline log count minus the log count measured is shown.

Table 3. Log Reductions in Bacterial Counts (CFU/Hand) (HPD-5a=Avagard)

	Treatment Group	
Day/Time Point	**HPD-5a (N=27)**	**Hibiclens (N=25)**
Baseline Period Mean	**6.3**	**6.4**
Day 1 Log Reduction		
1 minute	2.5	1.8
95% CI	(2.1, 2.9)	(1.5, 2.1)
3 hour	2.6	1.8
95% CI	(2.1, 3.0)	(1.3, 2.2)
6 hour	2.2	1.9
95% CI	(1.6, 2.7)	(1.6, 2.3)
Day 2 Log Reduction		
1 minute	3.0	2.6
95% CI	(2.5, 3.5)	(2.2, 2.9)
3 hour	3.1	2.7
95% CI	(2.8, 3.5)	(2.3, 3.1)
6 hour	3.3	2.3
95% CI	(3.0, 3.6)	(1.9, 2.7)
Day 5 Log Reduction		
1 minute	3.7	3.7
95% CI	(3.3, 4.1)	(3.3, 4.1)
3 hour	3.6	3.7
95% CI	(3.2, 4.0)	(3.2, 4.1)
6 hour	3.8	3.5
95% CI	(3.5, 4.1)	(3.1, 4.0)

Reviewer's Comment: These results indicate that both products meet all TFM requirements for a surgical scrub.

2. Safety: There were three adverse events reported in 3 subjects. Two subjects withdrew from the study due to adverse events unrelated to drug use (one menorrhagia, one viral infection). One subject developed a maculopapular rash of 23 days duration while using Avagard. This reaction was probably related to drug use.

The hand condition self-assessment results indicate that Avagard subjects evaluated their hands as having more moisture content than Hibiclens subjects. The other parameters rated did not reveal differences between the test medications. Again, these observations are not felt to be sufficiently rigorous to be meaningful.

Reviewer's Summary of Study No. 7957

This study meets its defined objective in that Avagard meets the standards in the TFM for surgical hand scrubs. Hibiclens displayed antimicrobial activity consistent with its performance in other studies of this type.

Studies 7838 and 7957 provide adequate evidence of the effectiveness of Avagard as a surgical scrub. The log reductions achieved by the two test laboratories are consistent. Further, Study 7838 establishes that both active ingredients contribute to the total effect of the product.

C. Study Title: Pivotal Study to Assess the Antimicrobial Effectiveness of Healthcare Personnel Handwash Formulations (Study No. 7939).

Investigator: [redacted]

Study Dates: October 26-November 5, 1998

Study Objectives: The following is taken directly from volume 35, p. 8-1353 of the NDA:

> The objective of this study was to evaluate the antimicrobial effectiveness of an investigational Healthcare Personnel Handwash (HPD-5a) in producing an immediate and persistent reduction in transient bacteria on the hands as specified in the Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM); Proposed Rule and on American Society for Testing and Material (ASTM) 1174-94, Standard Test Method for Evaluation of Health Care Personnel Handwash Formulations. The TFM criteria for Health Care Antiseptic Drug Products are a 2 $\log_{10}$ reduction in colony forming unit (CFU)/hand within 5 minutes after Wash 1 and a 3 $\log_{10}$ reduction in CFU/hand within 5 minutes after Wash 10. Hibiclens Antiseptic/Antimicrobial Skin Cleanser (Hibiclens), a currently marketed product, was included as a reference control.

Method:

1. Study design: This was a single-center, randomized, parallel-group, partially blinded comparison of Avagard and Hibiclens in their abilities to lower the microbial count on hands which have been artificially contaminated with *Serratia marcescens*. A total of 48 subjects were randomized into the study (24 Avagard, 24 Hibiclens). These numbers of subjects have been shown in the past to be sufficient to statistically demonstrate the effect of the products.

2. Inclusion criteria: These were the same as for Study 7838 above, with the exception that no minimum level of resident bacteria on the hands was necessary to enter the study.

3. Exclusion criteria: The following is taken directly from volume 35, p. 8-1355 of the NDA:

- Subject exposed to topical or systemic antimicrobial agents, including, but not limited to, antimicrobial antiperspirants, deodorants, shampoos, lotions, soaps, body powders, and materials such as solvents, acids, or alkalis
- Subject bathed in chlorinated pools, spas, or hot tubs

- Subject exhibited any form of dermatitis, open wounds, or other skin disorders on the hands and forearms that could affect the integrity of the study
- Subject had history of sensitivity to chlorhexidine gluconate (CHG) or alcohol, or allergy to latex
- Subject was pregnant or nursing, or of child-bearing potential
- Subject had history of allergies to more than one antibiotic
- Subject receiving steroid-based anti-inflammatory or immunosuppressant drug therapy
- Subject with artificial nails or nail tips
- Subject wearing contact lenses

4. Dosage and duration of therapy: This study was performed according to the protocol for health care personnel handwashes suggested in the TFM. The two test products were compared by contaminating the hands of the test subjects with 1.5 mL of a culture of *Serratia marcescens* containing 10^8 organisms per mL. The hands were allowed to air dry for 30 seconds before applying another 1.5 mL of the culture. This procedure was repeated a third time, with a final air drying of 1 minute. Thus, a total of 4.5 mL of the culture was used.

A baseline sample was then taken, the subjects hands were washed with a bland soap and dried, and the hands recontaminated and washed with the appropriate test substance. The contamination/wash cycle was repeated 10 times. Bacterial samples were taken after the first, third, seventh and tenth washes by a standard glove juice technique. The time between washes was not specified, though the entire study was performed in one day. Details concerning the sampling procedure and analysis may be found in the Microbiological Review for this NDA.

The scrub procedures used were as follows:

A. For Avagard:

1. Two mL (two 1 mL pumps from the dispensing bottle) of material was dispensed into the palm of one hand.
2. Material was applied to both hands up to but not above the wrist paying particular attention to the interdigital spaces.
3. Material was allowed to dry.

B. For Hibiclens:

1. Hands were rinsed under tap water.
2. Five mL of material was dispensed into cupped hands.
3. Material was applied to both hands up to but not above the wrists, paying particular attention to the interdigital spaces.
4. Subjects washed hands in a vigorous manner for 15 seconds.
5. Hands were rinsed and dried thoroughly.

Since the scrub procedures were different, the study was not blinded to the test subjects and lab technicians. However, the microbiologists analyses were performed in a blinded fashion.

5.Effectiveness parameters: The TFM standards for health care personnel handwashes are a 2 log reduction in the artificially applied organism after the first wash, and a 3 log reduction after the tenth wash.

6.Safety evaluation: The incidence of adverse experiences was compared between the treatment groups.

Results: By prior agreement between the supervisory microbiologist/HFD-520 and the reviewers, the critical review of the bacterial reduction results for topical antiseptics are to be performed by the microbiologist. Therefore, the following results are identical to those presented by the applicant.

1. Efficacy: The following table is taken from volume 35, p. 8-1384 of the NDA. The values represent log reduction seen after the first and tenth washes. That is, the baseline log count minus the log count measured is shown.

Table 4 Log Transformed Bacterial Counts (CFU/Hand) After Wash 1 and Wash 10 (HPD-5a=Avagard)

Log Reduction	Statistic	HPD-5a N=24	Hibiclens N=24
Wash 1	Mean	2.1	2.6
	SD	0.55	0.45
	Range	[redacted]	
	95% C.I.	(1.9, 2.4)	(2.4, 2.8)
Wash 10	Mean	3.7	3.7
	SD	0.98	0.70
	Range	[redacted]	
	95% C.I.	(3.3, 4.2)	(3.4, 4.0)

Reviewer's Comment: These results indicate that both products meet the TFM requirements of a 2 log reduction after the first wash and a 3 log reduction after the tenth wash.

2. Safety: There were no adverse events reported during this study.

D. Efficacy Summary

The studies presented here contain adequate evidence to support the approval of Avagard as a surgical scrub and health care personnel handwash, pending satisfactory reviews from the microbiologist and statistician assigned to this NDA.

1. Surgical scrub

The following table presents the log reductions in bacterial counts found in the two pivotal surgical scrub studies at the time points stated in the TFM for measurement of this variable. Only values for Avagard (and its vehicle, in Study 7838) are given.

Table 5. Log Reductions in Bacterial Counts (CFU/Hand)			
	Study 7838		Study 7957
Day/Time Point	Avagard	Vehicle	Avagard
Day 1, 1 minute	2.6	1.1	2.5
Day 1, 6 hour	2.8	0.5	2.2
Day 2, 1 minute	3.2	2.0	3.0
Day 5, 1 minute	3.5	1.5	3.7

In study 7838, the difference in log reduction achieved by Avagard and its vehicle were determined in order to assure that FDA's policy of requiring that each active ingredient in a drug contribute to the total effect of the product was met.

The following table presents those results.

Table 6. Differences Between Avagard and Vehicle in Log Reductions in Bacterial Counts (CFU/Hand)		
	Log Reduction	
Day/Time Point	Difference	p-value
Day 1, 1 minute	1.52	0.0032
Day 1, 6 hour	2.29	<0.0001
Day 2, 1 minute	1.28	<0.0001
Day 5, 1 minute	2.00	<0.0001

In both studies, Avagard easily met the requirements for surgical scrubs as outlined in the TFM. Further, the combination product was superior to the vehicle at all time points evaluated. By prior agreement between the applicant and HFD-520, only one study was necessary to establish the contributions of both ingredients in the combinations.

2. Health care personnel handwash

In the health care personnel handwash study, Avagard reduced artificially elevated bacterial counts by 2.1 logs after the first wash (TFM standard = 2) and 3.7 logs after the tenth wash (TFM standard = 3). Thus, the requirements of the TFM were met.

By prior agreement with the applicant, only one study in health care personnel handwashing was necessary if two satisfactory surgical scrub studies were available.

II. Review of Skin Irritation and Sensitization Studies

A. Study Title: Human Repeat Insult Patch Test of 3M Hand Prep Surgical Hand Scrub (HPD-5a) and Vehicle (HPD-5b) in Healthy Human Subjects (Study No. 7770).

Investigator: [redacted]

Study Objectives: The following is taken directly from volume 39, p. 8-3169 of the NDA:

The objective of this study was to determine the potential for inducing a sensitization with Test Article A (HPD-5a). HPD-5b, the NON-CHG vehicle formulation for HPD-5a, and Ethyl Alcohol were included in the challenge to help differentiate the cause of any irritation or sensitization.

Method:

1. Study design: This was a paired comparison of Avagard [HPD-5a], vehicle [HPD-5b] and ethanol in which each test subject served as his or her own control. Two hundred fifty-five subjects began the study and two hundred seventeen completed it. The evaluator was blinded concerning the identity of the compounds tested.

2. Inclusion criteria: The following is taken directly from volume 39, p. 8-3190 of the NDA:

   a. Males or females, 18 years of age or older, with a maximum allowable upper limit of 20% of the study population over the age of 65.

   b. Subjects who are able to understand and willing to sign an informed consent.

   c. Subjects who are cooperative and willing to complete a demographic/medical questionnaire.

   d. If female, subject is neither pregnant nor lactating (Urine pregnancy test prior to the first application, beginning of week three, and after completion of patching).

   e. Subject is willing and able to participate in the study as on outpatient making frequent visits to the clinical unit and willing to comply with study requirements.

3. Exclusion criteria: The following is taken directly from volume 39, p. 8-3191 of the NDA:

   a. Insulin-dependent diabetes.

   b. Mastectomy for cancer involving removal of lymph nodes draining the test site.

   c. Active clinically significant skin diseases which may contraindicate participation, including psoriasis, eczema, and atopic dermatitis.

   d. Participation in any patch test for irritation or sensitization within the last four weeks.

   e. Use of any prescribed anti-inflammatory drug (e.g., aspirin, ibuprofen, corticosteroids), immunosuppressive drugs or antihistamine medication (steroid nose drops and/or eye drops are permitted). Any over-the-counter medication that is ingested in quantities exceeding label instructions.

   f. Severe asthma.

   g. Immunological disorders such as HIV positive, AIDS, and systemic lupus erythematosus.

h. No oral antibiotics or topical drugs used at patch site two weeks prior to and throughout the study.

i. Pregnant or lactating women (confirmed by urine pregnancy testing).

j. Individual who has a medical condition or is taking or has taken medication which, in the Investigator's judgment, makes the subject ineligible or places the subject at undue risk.

k. Individual who has damaged skin in or around test site which includes sunburn, uneven skin tones, tattoos, scars, or other disfiguration of the test site.

l. Allergic to tape or any other study material(s). e.g. CHG.

4. Dosage and duration of therapy: The testing took place in 3 phases, as follows:

a. Induction phase: Approximately 0.1 mL of Avagard was applied to 2x2 cm test sites on the upper arm. The protocol is not clear concerning whether the vehicle and alcohol were tested during the induction phase. In a telephone conversation on December 6, 1999 with Ms. Teresa Skog of 3M, it was determined that only Avagard was applied during this phase. The substance was applied directly to the skin and allowed to dry for 15 minutes. The test site was then covered with an occlusive patch. The patch was left in place for 48 hours (72 hours over a weekend). This sequence took place over 3 weeks, for a total of 9 new patch applications. The site was graded for inflammatory response about 30 minutes after patch removal and prior to application of the new patch.

b. Rest period: Following the last induction application, a 10 to 17 day rest period took place during which no patches were applied.

c. Challenge phase: After the rest period, the subjects were challenged with a 48 hour patch of each test substance [including alcohol and vehicle] at a new, previously untested skin site. The test sites were graded for sensitization upon patch removal and 48 hours after removal.

5. Scoring scales: The responses were graded on the following scale:

0 No visible reaction
± Slight, confluent or patchy erythema
1 Mild erythema (pink)
2 Moderate erythema (definite redness)
3 Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade:

E = Edema – swelling, spongy feeling when palpated
P = Papule – red, solid, pinpoint elevation

V = Vesicle – small elevation containing fluid
B = Bulla reaction – fluid-filled lesion (blister)
S = Spreading – evidence of the reaction beyond the Webril pad area
W = Weeping – result of a vesicular or bulla reaction – serous exudate
I = Induration – solid, elevated, hardened, thickened skin
* = Residual reaction to earlier application after absence
~ = Response occurs on ≤ 25% of test site

Results:

1. Withdrawals: The following table, which is taken from volume 39, p. 8-3171 of the NDA, lists those patients who failed to complete the study and the reasons.

Table 7. Subjects Who Did Not Complete Study

Subject Number	Reason
010, 014, 018, 019, 020, 028, 040, 058, 059, 061, 066, 078, 091, 095, 101, 140, 178, 182, 183, 184, 185, 189, 191, 236	Withdrew Consent
029, 033, 067, 119, 132, 150, 160, 211	Exclusionary Medications
050, 056, 076	Participated on previous 3M study
221	No transportation
161	Out of town

Reviewer's Comment: The reasons for withdrawing consent (24 subjects) were not given. The applicant was asked to determine whether any of these withdrawals were due to adverse events. In a fax dated December 13, 1999, the applicant stated that 4 of these subjects did report adverse events, which are included in the tabulations under 4., below. None of the subjects discontinued due to an adverse event.

2. Irritation: Irritation results are not presented in a tabular fashion (this study was not intended as a formal irritation study). However, analysis of the line listings for Avagard reveals that 32/217 (15%) of the test subjects displayed a reaction of 1 or more on the 0 to 3 erythema rating scale shown under 5, Scoring scales, above during the induction phase of the study. Three of these 32 displayed reactions of 3 (moderate erythema). Many of these subjects also developed papules. Unfortunately, there are no data for the alcohol and vehicle to provide a perspective for these results.

3. Sensitization: The test laboratory states that there is no evidence to suggest that Avagard is a sensitizer. Review of the line listings does not reveal a sensitization reaction in any subject.

4. Adverse reactions: There were a number of events during the course of the study which were not related to drug utilization (arthritis, cold symptoms, sinus congestion, toothaches, etc).

A number of adverse events were considered to be possibly or probably related to drug therapy. For the vehicle, there were 4 reports of itching at the study site (1 mild, 3 moderate).

For alcohol, there were 3 reports of itching (1 mild, 2 moderate). For Avagard, the following table, which is taken from volume 39, p. 8-3176 of the NDA, presents the adverse events:

Table 8. Possibly Related Adverse Events [Avagard]

ADVERSE EVENT	NUMBER OF SUBJECTS	MILD	MODERATE	SEVERE	NUMBER OF OCCURRENCES
Itching	34	30	10	2	42
Burning	2	2	0	0	2
Rash on Back	1	1	0	0	1

Reviewer's Summary of Study No. 7770: This study was performed with a standard protocol and establishes that Avagard does not have unusual potential to cause sensitization reactions. Because chlorhexidine gluconate products have been associated with life-threatening hypersensitivity reactions, the standard warnings for products of this type should remain in the labeling.

Thirty-two patients displayed erythema during the induction phase of the study and 34 reported itching (the same patients may have been reporting both reactions, though the collation of patient numbers has not been performed). However, without a vehicle or alcohol comparator, the significance of these reactions is not clear.

It is also noted that Avagard was applied to the test sites and allowed to dry for 15 minutes prior to patch application, which would be expected to minimize irritation reactions. In addition, there were many more adverse events reported in the Avagard group, though this is probably because there was much more exposure to Avagard than to the other test products.

In summary, this is a successful sensitization study for Avagard, though it does raise some concerns, as outlined above.

B. Study Title: A 21-Day Evaluation of the Cumulative Skin Irritation Potential of Hand Prep Surgical Scrub and Various Control Articles in Healthy Human Subjects (Study No. 7771).

Investigator: [redacted]

Study Dates: April 14-May 5, 1998.

Study Objectives: The following is taken directly from volume 40, p. 8-8291 of the NDA:

> The objective of this study was to determine the relative skin irritation potential of Hand Prep HPD-5a and HPD-5b (vehicle) under occlusion and semi-occluded conditions when applied daily to healthy human subjects. Sodium lauryl sulfate (SLS) and saline were used as a positive and a negative control, respectively. Also included as controls, for comparison were ethyl alcohol (61%) and the commercial products Hibiclens® and Curel™.

Method:

1. Study design: This was a paired comparison study in which each test subject received all test medications and served as his or her own control. Thirty-nine patients began the study and 36 completed it. The evaluator was blinded concerning the identity of the compounds tested. The products tested were: Avagard, vehicle, ethyl alcohol, Hibiclens, sodium lauryl sulfate (positive control), 0.9% saline (negative control) and Curel (a moisturizing hand preparation).

2. Inclusion criteria: These are the same as for Study 7770, above, with the exception that female subjects must have been using an effective method of contraception as judged by the investigator.

3. Exclusion criteria: These are the same as for Study 7770, above.

4. Dosage and duration of therapy: Approximately 0.1 mL of each test material was applied to designated 2x2 cm test sites on the paraspinal region of the back. For Avagard and vehicle [non-CHG], the substances were applied directly to the skin and allowed to dry for 15 minutes. The test sites were then covered with occlusive patches (2 sites) or semi-occlusive patches (2 separate sites). Thus, both Avagard and vehicle were tested with occlusive and semi-occlusive covering.

For ethyl alcohol, Hibiclens, sodium lauryl sulfate and 0.9% saline, the materials were placed directly on the patch and the patches were then applied to the back and covered with occlusive tape. Curel was applied to a 2x2 cm test site and allowed to dry for 15 minutes [similar to Avagard]. The patches were left in place for 24 hours. Irritation readings were made upon patch removal and the patches were replaced. This sequence was repeated 21 times over 21 days.

5. Scoring scales: The responses were graded on the following scale:

0 No evidence of irritation
1 Minimal erythema, barely perceptible
2 Definite erythema, readily visible; or minimal edema; or minimal papular response
3 Erythema and papules
4 Definite edema
5 Erythema, edema and papules
6 Vesicular eruption
7 Strong reaction spreading beyond test site

Definition of letter grades appended to a numerical grade:

A Slight glazed appearance
B Marked glazing
C Glazing with peeling and cracking
F Glazing with fissures
G Film of dried serous exudate covering all or portion of the patch site
H Small petechial erosions and/or scabs

Results:

1. Withdrawals: Three of the 39 subjects who entered the study withdrew prior to its completion. Two of these were personal situations not connected to drug application. One subject exhibited hypersensitivity to all products tested and was removed from the study by the investigator.

2. Irritation: The simplest means of presenting the irritation scores is to sum the results for all subjects at all readings. The following table presents this data to the base 10. The table is taken from volume 40, p. 8-3305 of the NDA. HPD-5a is Avagard and HPD-5b is the vehicle.

Table 9 – Total Irritation Scores

Treatment (Code)	Total Group Score (Base 10)	Classification
HPD-5a, Occluded (A)	11.4	Mild material-No experimental irritation
HPD-5b, Occluded (B)	6.0	Mild material-No experimental irritation
HPD-5a, Semi-Occluded (C)	1.8	Mild material-No experimental irritation
HPD-5b, Semi-Occluded (D)	4.0	Mild material-No experimental irritation
Curel™ (E)	29.8	Mild material-No experimental irritation
Ethyl alcohol (F)	93.4	Probably mild in normal use
Hibiclens® (G)	51.0	Probably mild in normal use
Physiological Saline (Negative Control) (H)	45.6	Mild material-No experimental irritation
Sodium Lauryl Sulfate (Positive Control) (I)	439.1	Possibly mild in normal use

3. Adverse reactions: There were a number of events during the course of the study which were not related to drug utilization (headache, cold symptoms, etc.).

A number of adverse events were felt to be probably related to therapy (there were no possibly related events). The following table presents these events by compound.

Table 10-Probably Related Adverse Events

ADVERSE EVENTS	NUMBER OF SUBJECTS	MILD	MODERATE	SEVERE	NUMBER OF OCCURRENCES
Avagard occluded					
Itching	8	6	4	3	13
Burning	1	0	1	0	1
Pain	1	1	1	0	2
Stinging	1	0	1	0	1
Avagard semi-occluded					
Itching	7	2	6	4	12
Vehicle occluded					
Itching	6	3	5	3	11
Pain	2	1	2	0	3
Vehicle semi-occluded					
Itching	5	1	4	3	8

Curel					
Itching	9	6	4	2	12
Burning	1	0	1	0	1
Pain	2	1	2	0	3
Ethyl alcohol					
Itching	14	6	9	5	20
Burning	3	1	2	0	3
Pain	2	1	2	0	3
Hibiclens					
Itching	10	6	6	5	17
Burning	4	1	3	0	5
Pain	2	1	1	1	3
0.9% Saline					
Itching	13	6	5	7	18
Burning	2	1	1	0	2
Pain	2	1	2	0	3
Sodium lauryl sulfate					
Itching	9	7	3	4	16
Burning	1	2	1	0	3
Pain	2	1	2	0	3
Stinging	1	0	1	0	1

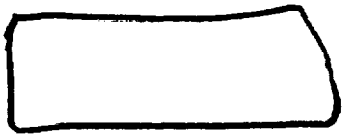
Reviewer's Summary of Study No. 7771: This study was performed with a standard protocol and establishes that Avagard does not have unusual potential to cause irritation reactions. It is interesting that even Hibiclens, a known irritant, scored lower than 0.9% saline in this study. This may have been due to the practice of applying the test products to the patch and then to the skin. Adverse events were roughly comparable between groups [even 0.9% saline and sodium lauryl sulfate did not display much difference].

It is also noted that Avagard and vehicle were applied to the skin and left to dry for 15 minutes. This may have influenced the relative irritancy scores for these products. It is commonly observed that products which are applied to the skin and covered with an occlusive patch without allowing a period for drying produce higher irritation scores than if drying is permitted.

In summary, this study, like the previous one, is acceptable although the protocol as performed would probably underestimate irritation in that the products were allowed to dry. The "cosmetic" studies that follow contain descriptions of repetitive use of Avagard which provide evidence that the results of the safety studies just reviewed can be accepted.

III. Review of "Cosmetic" Studies

A. Study Title: Bilateral Evaluation of the Skin Condition Effects of Pre-Surgical Scrubs HPD-5a and HPD-5b Versus Hibiclens in Healthy Human Subjects (Study No. 7772).

Investigator: 

Study Dates: April 17-May 1, 1998.

Study Objectives: The following is taken directly from volume 37, p. 8-2054 of the NDA:

> The primary objective of this study was to assess hand skin condition after multiple applications of either HPD-5a, as a Pre-Surgical Hand Scrub, or its vehicle control formulation, HPD-5b, in comparison with hand skin condition after multiple applications of a marketed reference product, Hibiclens.

Method:

1. Study design: This was a single-center, randomized, partially blinded, paired-comparison study in which each subject served as his or her own control. Avagard, the product vehicle and Hibiclens were applied bilaterally to 36 subjects: that is, each of the 36 subjects received Hibiclens on one hand, with 18 of these subjects receiving Avagard on the other hand, and the other 18 receiving vehicle. The condition of the skin on the hands was then compared.

2. Inclusion criteria: The following is taken directly from volume 37, p. 8-2055 of the NDA (the VSS rating is described in section 5., below):

> Subjects included in the study were healthy volunteers of either gender, who met the following criteria:
>
> - Subject VSS rating was 0 to 3 at baseline before treatment on Treatment Day 1
> - Subject was $\geq$ 18 years of age and $\leq$ 65 years of age, with no more than 20% of the population over the age of 55
> - Subject agreed not to use any hand products other than those provided for use before and during the study
> - Subject had read and signed an Informed Consent Form

3. Exclusion criteria: The following is taken directly from volume 37, p. 8-2055 of the NDA:

- Subject had history of psoriasis or has cracked, irritated, or broken skin on the hands
- Subject VSS score was Grade 4 (Very Scaly) or greater, at baseline Treatment Day 1 assessment
- Subject was allergic to any study material(s), e.g., chlorhexidine, or the latex in the gloves
- Subject was pregnant or lactating

4. Dosage and duration of therapy: This study ran for 5 days, with the study materials applied six times daily. Thus, there was a total of 30 scrubbing procedures performed. The scrub procedures used were as follows:

A. For Avagard and vehicle:

1. Prior to application hands should be clean and thoroughly dry. If dirt is present under the finger nails this should be cleaned out with a nail cleaner.
2. The technician will dispense 2 mL of the lotion into the palm of one gloved hand.
3. The subject will dip the fingertips of the appropriate hand into the lotion and the

technician will work the lotion under the nails and spread the remaining lotion over the hand and up the lower two thirds of the subjects forearms.

4. Dispense another 1 mL of lotion into the hand and reapply to all aspects of the hand up to the wrist.

B. For Hibiclens:

1. Wet hand and forearm under running water (38-42^0 C). Clean under fingernails with a nail cleaner.
2. The technician will dispense 2.5 mL of Treatment G into the sponge and distribute over the hand and lower two-thirds of forearm of the subject.
3. Scrub for 1.5 minutes with the scrub brush, paying particular attention to the nails, cuticles and interdigital spaces (the brush side will be used for the nails and the sponge side for the rest of the hand and forearm).
4. Rise thoroughly.
5. Wash for an additional 1.5 minutes with another 2.5 mL of Treatment G.
6. Perform final rinse by rinsing under running water.
7. Dry thoroughly.

Since the scrub procedures were different, the study was not blinded to the test subjects and lab technicians. However, the personnel who evaluated skin condition were blinded concerning the identity of the test products.

Reviewer's Note: Because the primary objective of this study was to assess skin condition after multiple uses of Avagard and Hibiclens, the use of a scrub brush with Hibiclens is problematic. It is true that use of a scrub brush is part of the standard scrubbing procedure for Hibiclens. However, use of the brush causes irritation and skin insult whether an antiseptic is also used or not. Thus, when skin condition is evaluated, the scorer sees damage from both Hibiclens and the brush. It is misleading to evaluate Avagard as superior to Hibiclens in skin maintenance under these circumstances. Since efficacy was not a consideration in the protocol, it would have been preferable to omit use of the scrub brush, even though it is true that in practice, the fact that Avagard does not require a scrub brush is an advantage in maintaining skin integrity.

5. Scoring scales: The Visual Scoring of Skin (VSS) condition was the primary outcome variable in this study. Each hand was assessed separately using the following scale:

0 = Normal
No observable scale or irritation of any kind.

1 = Very slightly scaly
Occasional scale that is not necessarily uniformly distributed.

2 = Slightly scaly
Scale in sulci and on plateaus. More visible scale that is more uniformly distributed, but no wide-spread uplifting.

3 = Scaly
Visible scale giving the overall appearance of the skin surface a whitish

appearance. Definite uplifting of edges or scale-sections. Hand is rough to the touch.

4 = Scaly to very scaly
More scale and pronounced separation of scale edges from skin, although they may still be lying flat on the skin surface. Some evidence of cracking in sulci and on plateaus. Also, skin may appear irritated with some reddening.

5 = Very Scaly
Extensive cracking of skin surface. In some cases, scales are very large but some individual never develop large scales. The skin may appear to be very irritated with wide-spread reddening and/or occasional bleeding.

This assessment was made prior to initiation of the study and at the beginning and end of each study day (total of eleven evaluations).

Other parameters measured were:

a. Erythema
Each hand was graded for erythema at the same time as the VSS, using the following scale:

0 = No Erythema
1 = Mild, Diffuse, Limited to Small Area
2 = Moderate Pinkness, More Extensive
3 = Marked, May Include Areas of Deeper Erythema/Slight Edema
4 = Severe Deep Erythema > 25% Hand/Edema

b. Expert grader hand assessment:
Both the professional evaluator and the test subjects were asked to fill out a Hand Skin Assessment (HAS) questionnaire which evaluated 4 criteria: appearance, intactness, moisture content and sensation. The possible scores ranged from 1 to 7, with 7 representing completely healthy skin. The professional evaluator could not evaluate sensation. These questionnaires were filled out prior to the beginning of the study and at the end of the study.

Reviewer's Comment: It is felt that the grades of the professional evaluator would be more meaningful than those of the test subjects. Therefore, only the results from the professional evaluator will be presented.

c. Conductance
This was a measurement of the effect of moisturizers on the skin using the change in electrical conductivity of the stratum corneum. A skin surface hydrometer was used to measure the change in conductivity at baseline and after the last wash cycle on the first test day.

d. Transepidermal Water Loss
This is another variable which uses an instrument (termed an evaporimeter). In this case, the amount of water lost through the skin in grams per square

meter per hour is measured at baseline and after the last wash cycle on the fifth day.

Results:

1. Withdrawals: Only one subject left the study. This subject was excluded due to lack of compliance with the protocol, and was in the group of 18 who received the vehicle on one hand.

2. Indicators of skin condition:
   a. Visual scoring of skin
   For this variable, a lower score represents healthier skin than a higher score. The following table represents the changes in this variable from baseline to after the last wash on day 5.

Table 11 – VSS Mean Scores

	Avagard vs. Hibiclens			Vehicle vs. Hibiclens		
Time Point	**Avagard**	**Hibiclens**	**p-value**	**Vehicle**	**Hibiclens**	**p-value**
Day 1 baseline	1.0	1.1	0.37	1.1	1.1	1.0
End of day 5	0.8	2.3		0.9	2.6	
Change at day 5	-0.2	1.2	0.0002	-0.2	1.5	<0.0001

   b. Erythema
   For this variable, a lower score represents healthier skin than a higher score. The following table represents the changes in this variable from baseline to after the last wash on day 5.

Table 12 – Erythema Mean Scores

	Avagard vs. Hibiclens			Vehicle vs. Hibiclens		
Time Point	**Avagard**	**Hibiclens**	**p-value**	**Vehicle**	**Hibiclens**	**p-value**
Day 1 baseline	0.4	0.4	1.0	0.6	0.6	1.0
End of day 5	0.8	1.4		1.0	1.4	
Change at day 5	0.4	1.0	0.004	0.4	0.8	0.007

   c. Expert grader hand assessment
   For this variable, a higher score represents healthier skin than a lower score. The following table, which is taken from volume 37, p. 8-2097 of the NDA, represents the change in the three variables assessed by the expert grader from baseline to the end of the study. (HPD-5a=Avagard, HPD-5b=vehicle).

Table 13 Hand Skin Assessments Performed by the Expert Grader (Mean Scores)						
	Series A			Series B		
Time Point	HPD-5a	Hibiclens	p-Value	HPD-5b	Hibiclens	p-Value
Appearance Baseline	6.6	6.5	1.000	6.2	6.2	1.000
End of Study	6.1	5.1	--	5.7	5.1	--
Change from Baseline to End of Study	-0.4	-1.4	0.0056	-0.6	-1.2	0.0391
Intactness Baseline	7.0	7.0	--	7.0	7.0	--
End of Study	6.8	6.2	--	6.9	6.0	--
Change from Baseline to End of Study	-0.2	-0.8	0.0469	-0.1	-0.1	0.0020
Moisture Content Baseline	5.9	5.7	0.3750	5.6	5.6	1.000
End of Study	5.8	3.9	--	5.8	3.3	--
Change from Baseline to End of Study	-0.1	-1.8	0.0032	0.1	-2.4	<0.0001
Total Baseline	19.4	19.2	0.4063	18.8	18.8	0.6973
End of Study	18.7	15.2	--	18.4	14.4	--
Change from Baseline to End of Study	-0.7	-4.0	0.0023	-0.5	-4.5	0.0001

d. Conductance
For this variable, a higher score represents more moist skin than a lower score. The following table represents the changes in this variable from baseline to after the last wash on day 1. The table is taken from volume 37, p. 8-2101 of the NDA (HPD-5a=Avagard, HPD-5b=vehicle).

Table 14 Skin Conductance Assessments (Mean Scores) (Units micro ohms)						
	Series A			Series B		
Time Point	HPD-5a	Hibiclens	p-Value	HPD-5b	Hibiclens	p-Value
Day 1 Baseline	104.7	103.5	0.6563	106.4	101.2	0.3347
End of Day 1	163.2	115.1	--	153.0	118.9	--
Change from Baseline To End of Day 1	58.5	11.6	0.0006	46.6	17.7	0.0157

e. Transepidermal water loss
For this variable a lower score represents better skin condition than a higher score. The following table represents the changes in this variable from baseline to the end of the fifth day. The table is taken from volume 37, p. 8-2102 of the NDA.

Table 15 Transepidermal Water Loss (TEWL) Assessments (Mean Scores) (HPD-5a=Avagard, HPD-5b=vehicle) (Units g/m^2/hr)						
	Series A			Series B		
Time Point	HPD-5a	Hibiclens	p-Value	HPD-5b	Hibiclens	p-Value
Day 1 Baseline	6.5	6.5	0.9697	6.2	5.9	0.0176
Day 5 End of Day	10.6	11.5	--	8.3	9.3	--
Change from Baseline To End of Day 5	4.1	5.0	0.1971	2.1	3.4	0.0002

3. Adverse reactions: There was only one adverse event reported during this study. On day 4, a patient experienced irritation on the hand treated with Hibiclens. This reaction was probably related to drug treatment. The hand was discontinued from the study, but the other hand (Avagard) completed the study.

Reviewer's Summary of Study No. 7772

As noted above, the results for Hibiclens in this study must be interpreted in the light of the concomitant use of a scrub brush with this preparation. Although Hibiclens generally fared less well in the parameters evaluated here than Avagard, the difference may have been due to use of the brush, which abrades and roughens the skin, rather than to additional harshness in the Hibiclens formulation. It is recognized that use of a scrub sponge is recommended when Hibiclens is used as a surgical scrub.

Further, the reviewers are not familiar with the conductance and transepidermal water loss variables as they are presented here. That is, the clinical relevance of these measures as they relate to skin condition has not been provided in the application.

However, the remainder of the data indicates that Avagard and its vehicle are able to maintain a baseline healthy skin condition through 30 scrubs over a 5 day period. The VSS variable is concerned with scaliness of skin, as opposed to the erythema variable, which indicates increased skin distress through redness. For both of these variables, Avagard and its vehicle were efficient at preventing scaliness and redness. The expert grader hand skin assessments were less exactly defined, and the variables listed (appearance, intactness, moisture) probably overlap scaliness and erythema to some extent. These hand skin assessments also indicate that Avagard was able to maintain skin quality under the conditions of the study.

It should be noted that in this study and the one that follows, technicians assisted in the scrub procedure to enhance reproducibility of scrub technique. This has the drawback of not duplicating the way the product will be used in practice, but is justified by the likelihood that the test preparations themselves, rather than scrub technique, are being compared.

In summary, this study indicates that Avagard may be associated with less scaliness and erythema, as well as better moisture retention after repeated use than has previously been seen with products of this type.

B. Study Title: Bilateral Evaluation of Skin Condition with Frequent Washings of Hand Prep (HPD-5a) vs. Hibiclens as a Health Care Personnel Handwash in Healthy Human Subjects (Study No. 7821).

Investigator: [redacted]

Study Dates: December 7-18, 1998.

Study Objectives: The following is taken directly from volume 38, p. 8-2618 of the NDA:

> The primary objective of this study was to assess the skin condition of the hands after multiple applications of HPD-5a, as a Health Care Personnel Hand Wash, compared with a marketed reference product, Hibiclens, over a 5-day period.

Method:

1. Study design: This was a single-center, randomized, partially blinded, paired-comparison study in which each subject served as his or her own control. Avagard and Hibiclens were applied bilaterally to 40 subjects. The condition of the skin was then compared.

2. Inclusion criteria: These were the same as for Study 7771, above.

3. Exclusion criteria: These were the same as for Study 7771, above with the exception that pregnancy and lactation were not exclusion criteria.

4. Dosage and duration of therapy: This study ran for 5 days, with the study materials applied 24 times daily (18 times on Day 4). Thus, there were 114 washing procedures performed. The washing procedures used were as follows:

A. For Avagard
Prior to application, the hands were cleaned and dried thoroughly. The technician then dispensed 1 mL of the lotion in the palm of his gloved hand. The subject then dipped the fingertips of the appropriate hand into the lotion and the technician worked the lotion under the nails and spread the remaining lotion over the hand, paying particular attention to the interdigital spaces. The hands were then allowed to dry.

B. For Hibiclens
The technician wet the subject's hands and forearm under running water (38-42°C). The technician then dispensed 2.5mL of Hibiclens into the palm of his gloved hand. The subject then dipped the fingertips of the appropriate hand into Hibiclens and the technician washed the subjects' hand with water for 14 seconds being careful not to use excessive pressure to produce additional lather. Hands were rinsed with water (15 seconds or until lather is removed). Hands were then dried thoroughly.

Since the wash procedures were different, the study was not blinded to the test subjects and lab technicians. However, the personnel who evaluated skin condition were blinded concerning the identity of the test products.

5. Scoring scales: These were the same as for Study 7771, above, with the addition of an evaluation of tactile roughness by the professional evaluator. The following scale was used:

0 = Normal, No Observable Roughness
1 = Slight Roughness
2 = Moderate Roughness
3 = Severe Roughness
4 = Extreme Roughness

Results:

1. Withdrawals: There were no withdrawals from this study.

2. Indicators of skin condition:
   a. Visual scoring of skin
   For this variable, a lower score represents healthier skin than a higher score. The following table represents the changes in the variable from baseline to after the last wash on day 5.

Table 16. VSS Mean Scores	[redacted]		
Time Point	**Avagard**	**Hibiclens**	**p-value**
Day 1 Baseline	1.3	1.3	0.68
End of Day 5	0.6	3.0	
Change at Day 5	-0.8	1.7	<0.0001

   b. Erythema
   For this variable, a lower score represents healthier skin than a higher score. The following table represents the changes in this variable from baseline to after the last wash on day 5.

Table 17. Erythema Mean Scores	[redacted]		
Time Point	**Avagard**	**Hibiclens**	**p-value**
Day 1 Baseline	0.3	0.3	0.42
End of Day 5	0.9	1.5	
Change at Day 5	0.6	1.2	<0.0001

   c. Tactile roughness
   For this variable, a lower score represents healthier skin than a higher score. The following table represents the changes in this variable from baseline to after the last wash on day 5.

Table 18. Tactile Roughness Mean Scores			
Time Point	**Avagard**	**Hibiclens**	**p-value**
Day 1 Baseline	1.1	1.1	0.61
End of Day 5	1.2	2.2	
Change at Day 5	0.1	1.1	<0.0001

d. Expert grader hand assessment
For this variable, a higher score represents healthier skin than a lower score. The following table, which is taken from volume 38, p. 8-2657 of the NDA, represents the changes in the three variables assessed by the expert grader from baseline to the end of the study (HPD-5a=Avagard).

Table 19 Hand Skin Assessments Performed by the Expert Grader (Mean Scores)			
Time Point	**HPD-5a**	**Hibiclens**	**p-Value**
Appearance Baseline	6.7	6.7	0.7744
End of Study	6.1	5.3	0.0004
Change from Baseline to End of Study	-0.6	-1.4	0.0001
Intactness Baseline	7.0	7.0	---
End of Study	7.0	6.3	0.0001
Change from Baseline to End of Study	0.0	-0.7	0.0001
Moisture Content Baseline	5.4	5.5	0.4545
End of Study	6.5	2.9	<0.0001
Change from Baseline to End of Study	1.1	-2.6	<0.0001
Total Baseline	19.1	19.1	0.8613
End of Study	19.6	14.5	<0.0001
Change from Baseline to End of Study	0.5	<4.6	<0.0001

e. Conductance
For this variable, a higher score represents more moist skin than a lower score. The following table represents the changes in this variable from baseline to after the last wash on day 1. The table is taken from volume 38, p. 8-2660 of the NDA (HPD-5a=Avagard).

Table 20. Skin Conductance Assessments (Mean Scores) (Units micro ohms)			
Time Point	**HPD-5a**	**Hibiclens**	**p-value**
Day 1 Baseline	130.4	129.3	0.4499
Day 1 End of Day	140.9	123.7	0.0035
Change from Baseline to End of Day 1	10.5	-5.6	0.0025

f. Transepidermal water loss
For this variable, a lower score represents better skin condition than a higher score. The following table represents the changes in this variable from baseline to the end of the fifth day. The table is taken from volume 38, p. 8-2660 of the NDA (HPD-5a=Avagard).

Table 21. Transepidermal Water Loss (TEWL) Assessments (Mean Scores) (Units g/m²/hr.)

Time Point	HPD-5a	Hibiclens	p-value
Day 1 Baseline	7.7	7.6	0.2984
Day 5 End of Day	10.5	11.7	0.0046
Change from Baseline to End of Day 5	2.7	4.0	0.0017

2. Adverse reactions: There was one adverse event reported during this study. At the end of the fifth day, a patient displayed mild exfoliative dermatitis on the hand treated with Hibiclens. This reaction was probably related to drug treatment.

Reviewer's Summary of Study No. 7821:

As noted above for Study No. 7772, the reviewers are not familiar with the conductance and transepidermal water loss variables as they are presented in these studies. That is, the statements from the applicant that these variables reflect skin condition cannot be verified from our experience.

However, the remainder of the data submitted indicate that Avagard is able to maintain a baseline healthy skin condition through 114 washes over a 5 day period. For the variable visual scoring of skin (scaliness), erythema and tactile roughness, the Avagard hands improved on baseline scaliness, maintained baseline tactile roughness, and displayed slightly more erythema than at baseline. In all cases, the Avagard hands ended the study in better condition than the Hibiclens hands. The expert hand grader assessments also indicate that Avagard maintained skin quality, while the skin quality of the Hibiclens hands was not as good as at baseline.

IV. Review of Supportive Studies

A. Study Title: Pilot Study to Assess the Antimicrobial Effectiveness of Surgical Scrub Hand Formulations (Study No. 7588).

Investigator:

Study Dates: August 27, 1997-July 17, 1998.

Study Summary: This was a surgical scrubbing study performed under the protocol recommended in the TFM and described under Study No. 7838, above. Avagard, vehicle and Hibiclens were tested, with 8 test subjects in each group (total 24).

Results:

1. Efficacy: The following table presents the mean log reductions found at the time points specified in the TFM.

Table 22. Log Reductions in Bacterial Counts (CFU/Hand)			
Day/Time Period	**Avagard**	**Vehicle**	**Hibiclens**
Day 1, 1 minute	3.0	0.7	1.5
Day 1, 6 hour	3.1	0.0	1.6
Day 2, 1 minute	3.4	1.0	2.1
Day 5, 1 minute	3.4	1.0	2.9

2. Safety: No adverse events were reported during this study.

B. Study Title: Pilot Study to Assess the Antimicrobial Effectiveness of Hand Prep as a Health Care Personnel Hand Wash (Study No. 7938).

Investigator: [redacted]

Study Dates: June 9-July 9, 1998.

Study Summary: This was a health care personnel handwash study performed under the protocol recommended in the TFM and described under Study No. 7939, above. Avagard, vehicle and Hibiclens were tested, with 3 test subjects in each group (total 9).

Results:

1. Efficacy: The following table presents the mean log reduction found at the time points specified in the TFM.

Table 23. Log Reductions in Bacterial Counts (CFU/Hand)			
	Avagard	**Vehicle**	**Hibiclens**
Wash 1	2.67	2.47	4.25
Wash 10	7.10	0.62	6.69

2. Safety: No adverse events were reported during this study.

C. Study Title: Multiple Skin Washing Protocol (Study No. 7372).

Investigator: [redacted]

Study Dates: December 16-20, 1996.

Study Summary: This was a study in 30 subjects in which two similar 3M CHG hand prep products were compared to Hibiclens or Curel lotion in their potential to cause (or relieve) skin irritation. The test products were applied 8 times daily to the hands of the subjects, who were split into parallel groups, with the 3M CHG prep groups having 10 each and the Hibiclens and Curel groups 5 each.

Prior to the application of each product, the hands were washed with Hibiclens. Thus, the Hibiclens group washed with Hibiclens 16 times daily, with the other groups washing with Hibiclens 8 times daily and the other test product 8 times daily. The study continued for 5 days.

Results: Results indicated that the subjects who alternated Hibiclens with either of the two 3M CHG hand prep products had better skin condition than did those who used Hibiclens alone. The group who used Curel alternated with Hibiclens had significantly better skin condition than any of the other groups. A total of 5 subjects in the 3M CHG hand prep groups and 1 subject in the Hibiclens only group dropped out of the study due to dry skin.

Reviewer's Summary of Supportive Studies:

The only remarkable result of the supportive studies concerns No. 7372 (skin irritation study). This study suggests that after skin has been irritated (with repetitive use of Hibiclens), Avagard does not repair the skin as well as Curel does. This opinion is based on the number of dropouts in the Avagard groups (5 of 20). One subject in the Hibiclens only group dropped out, but none in the Curel group did. It is also noted that in the pilot health care personnel handwash study, both Avagard and Hibiclens performed much better than they did in the pivotal study.

[redacted]

8 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

VI. Safety Summary

The safety data presented in support of this NDA establish that Avagard is safe for its intended uses. The following comments are pertinent.

1. In study 7838, one subject suffered conjunctivitis for 13 days and blurred vision for 2 days after he rubbed his eye while Avagard was on his hands. While the proposed back panel container label for the product bears adequate warnings about eye toxicity, this product is unusual in that it will be reapplied regularly, and it is reasonable to assume that this drug-to-eye occurrence will be fairly common. Therefore, it is recommended that an additional warning be placed on the front of the container labeling. (see Labeling Review, below).

2. Similarly, this product is flammable. While the back panel of the label for the container has adequate warnings concerning this, the flammability statement should also be on the front panel label (see Labeling Review, below).

3. In study 7957, one Avagard subject developed a maculopapular rash of 23 days duration. This reaction, as well as the eye toxicity described above, should be included in the proposed package insert for the drug. (see Labeling Review, below).

4. Study 7770 (sensitization test) did not reveal any propensity of Avagard to cause

sensitization reactions. However, there were many more itching and erythema reactions to Avagard than vehicle or ethyl alcohol during the induction portion of the study.

5. Study 7771 (cumulative irritation) was performed in an unusual manner in that Avagard and its vehicle were allowed to dry on the skin for 15 minutes prior to application of occlusive patches. This may have influenced the relative irritancy scores for these products. None of the products in the test with the exception of the positive control (sodium lauryl sulfate) displayed irritancy potential.

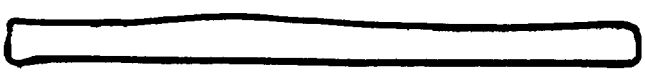
6. The "cosmetic" study 7772 suggests that when used as directed as a surgical scrub for 5 consecutive days of 6 times daily application, Avagard was able to maintain a baseline healthy skin condition. Comparisons to Hibiclens in this study are not useful because the Hibiclens group used a scrub brush, which abrades the skin (in addition to any possible irritation caused by Hibiclens).

7. The "cosmetic" study 7821 suggests that when used as directed as a health care personnel handwash for 5 consecutive days, with a total of 114 applications, Avagard was able to maintain a baseline healthy skin condition, while the condition of the skin of the Hibiclens patients was not as good at the end of the test as at the beginning.

In summary, the pivotal efficacy studies revealed toxicities [eye, skin] frequently associated with CHG products. Because risk of contact with the eye is greater since the product remains on the skin, additional labeling warnings are necessary. The predictive skin tests [irritation, sensitization] had unusual protocol provisions which make their results somewhat difficult to interpret. However, the "cosmetic" studies were sufficiently rigorous in terms of frequency of use to provide adequate evidence of relative safety for these products when used repeatedly.

VII. Labeling Review

The applicant has submitted both a proposed container label (front and back), and a package insert. Since products such as Avagard are intended for use by healthcare personnel without the supervision of a physician, and because the users are for the most part healthy, package inserts for topical OTC antiseptics are not usually required. The insert here is proposed by the applicant as a platform for advertising claims (3M has been straightforward about their intent in this regard). The container label and package insert will be reviewed separately.



5 page(s) of revised draft labeling has been redacted from this portion of the review.

[redacted]

VIII. Conclusions and Recommendations

Avagard-CHG Antiseptic Hand Preparation is recommended for approval as a [redacted]

[redacted] The product meets the standards set in the TFM, and information has been submitted which establishes the utility of both CHG and alcohol as active ingredients (please see the Efficacy Summary for details).

The product is safe for its intended use, though the fact that it is not rinsed off between uses makes injurious contact with the eye more likely, as the health care worker will always have a sufficient amount of CHG on the hands to cause eye discomfort and perhaps damage. Labeling revisions are necessary to make the user aware of this possibility.

[redacted]

The rationale for extrapolating safety and efficacy data in adults as to pediatric labeling of the drug is not adequate because no information is provided regarding potential absorption of CHG, particularly in young children. It also fails to account for the increased difficulty of preventing eye contact with the drug in the pediatric population.

The following are necessary prior to final approval of this product:

1. Revised labeling as specified in the Labeling Review, above.
2. Satisfactory reviews from the microbiologist, statistician and chemist assigned to this application.

It is also noted that the required Certification concerning financial interests of investigators has been reviewed and it is satisfactory.

David Bostwick

Alexander Rakowsky, M. D.

Amendent to Clinical Review of NDA 21-074

Date of Correspondence: February 14, 2000

Date Review Initiated: April 5, 2000

Drug: Avagard™ - CGA (formerly Avagard-CHG) Antiseptic Hand Preparation (1% chlorhexidine gluconate, 61% ethyl alcohol).

Applicant: 3M Healthcare
St. Paul, MN 55144

Indications: Surgical hand preparation and healthcare personnel handwash.

Packaging: This product is to be supplied in sizes of 500, [redacted] and 10 mL.

Background: Please see the previous clinical review of this NDA dated August 25, 1999. This review contained a number of labeling revision recommendations. As part of the process for approval of OTC drugs, the Division of OTC Drugs also performed a labeling review for this NDA. A draft version of this review (by Stephanie Mason, Debbie Lumpkins and Daiva Shetty, M.D.) is now available. There are some elements of the two labeling reviews which are not in exact agreement. The purpose of this review is to reconcile the disparities between the labeling comments in the August 25, 1999 clinical review and the Division of OTC Drugs review.

In addition, a consultative review concerning the proposed trade name of the product by the Office of Post-Marketing Drug Risk Assessment (OPDRA) dated December 13, 1999 objected to the "CHG" portion of the originally proposed trade name. This information was transmitted to the sponsor, who filed a written reply on February 14, 2000. OPDRA has reviewed the sponsor's correspondence and generated a second review on the subject dated March 23, 2000.

This review will consist of the following sections:

1. Reconciliation of HFD-520 and Division of OTC Drugs Labeling Comments
2. Discussion of Proposed Trade Name
3. Conclusions and Recommendations

1. Reconciliation of HFD-520 and Division of OTC Drugs Labeling Comments

There are three different labeling configurations for the three package sizes. These will be reviewed separately, as will the package insert.

A. 500 mL size.

This is a wedge-shaped bottle manufactured as a dispenser to be connected to a foot pump. Because the bottle is to be placed in a plastic holder which obscures its back, only the front label will be visible to the user. Therefore, it is necessary that all information essential to the safe use of the drug be placed on the front label. It is recognized that the usual format for products of this type is a "front" (or PDP-principal display panel) which bears the trade name, etc. and a"back" label which bears the "Drug Facts" required by the OTC labeling format. By necessity, the "front" label must be more detailed than is normal. The "front"label for the 500 mL size should read as follows:

3M Health Care

Avagard™ [redacted] NDC 17518-051-01

Chlorhexidine Gluconate 1% Solution and Ethyl Alcohol 61% w/w

surgical [redacted] and health-care personnel hand [redacted]

(The following statements should be in capital letters and in a contrasting color from the rest of the label. Red print is preferred).

WARNING: FLAMMABLE. [redacted]

Do not use

- if you are allergic to chlorhexidine gluconate or any other ingredients in this preparation

- routinely if you have wounds which involve more than the superficial layers of the skin

Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.

Directions

Surgical hand antiseptic

- apply to clean, dry hands and nails. For the first scrub of each day, clean under nails with a nail stick.
- dispense one pump (2mL) [redacted] into the palm of one hand
- dip the fingertips of the opposite hand into the lotion and work it under the nails
- spread the remaining lotion over the hand and up to just above the elbow

- using another 2 mL of lotion, repeat with the other hand
- dispense another 2 mL of lotion into either hand and reapply to all aspects of both hands up to the wrist
- allow to dry before donning gloves

Healthcare personnel hand antiseptic

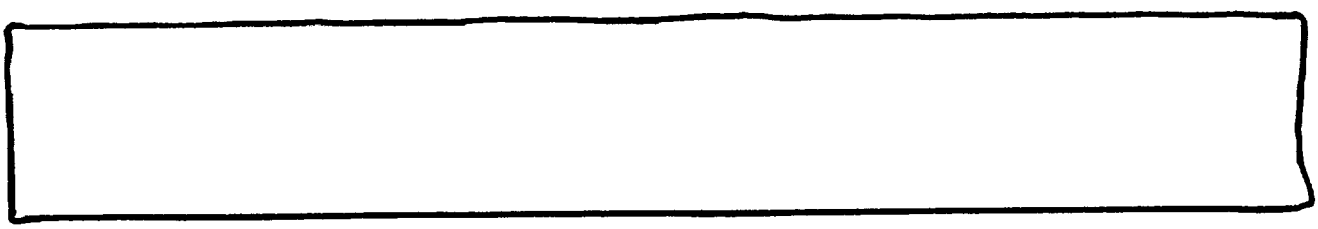
- apply to clean, dry hands and nails
- dispense one pump (2 mL) into the palm of one hand
- paying particular attention to the spaces between the fingers and under the fingernails, apply the lotion evenly to cover both hands up to the wrists
- allow to dry without wiping

Reviewer's Comment: It is recognized that this is a lot of information to be fit onto one relatively small label. It may be necessary to enlarge the size of the present label (there is approximately one half inch space between the bottle edge and the edge of the present label) and/or better utilize the space available.

The "back" label, containing "Drug Facts" should be the same as is recommended by the Division of OTC Drugs, with the following revisions [the Division of OTC Drugs label is appended to this review]:

i. In the "Directions" subsection, change the first "the" to "either" in the sixth direction for use as a surgical scrub.

ii. Delete the phrase "and lasts for more than 72 hours" from the "Stop use" subsection. Sensitization and/or allergic reactions should be treated immediately.



C. 10 mL size
This is a sample size in which the "front" label is affixed to the immediate container, and the "back" label is printed on a card which is attached to the container but is removed prior to use. Again, the label recommended by the Division of OTC Drugs is satisfactory (with the same changes as recommended in A. above for the back label), and is appended to this review. The "front" label for this size is designated as "Oval Labeling" in the OTC review.

D. Package insert

ADVERSE REACTIONS

There were two adverse events probably or possibly related to Avagard- use in the 85 subjects who used this product in pivotal clinical trials. One subject suffered conjunctivitis and blurred vision after he rubbed his eye with a hand which has been treated with Avagard- The other subject developed a maculopapular rash.

DIRECTIONS FOR USE

Surgical Hand Antiseptic

1. Apply to clean, dry hands and nails. For the first use of each day, clean under nails with a nail stick.
2. Dispense one pump (2 mL) of lotion into the palm of the hand.
3. Dip the fingertips of the opposite hand into the lotion and work it under the nails. Spread the remaining lotion over the hand and up to just above the elbow.
4. Using another 2 mL of lotion, repeat steps with the other hand.
5. Dispense another 2 mL of lotion into either hand and reapply to all aspects of both hands up to the wrists.
6. Allow to dry before donning gloves.

Healthcare Personnel Hand Antiseptic

1. Apply to clean, dry hands and nails.
2. Dispense 2 mL of the lotion into the palm of one hand.
3. Paying particular attention to the spaces between the fingers and under the fingernails, apply the lotion evenly to cover both hands up to the wrists.

Allow to dry without wiping.

CLINICAL STUDIES

Surgical Hand Antiseptic Studies: The procedure used was the FDA specified test method for surgical scrub products[5]. In two studies, the immediate bactericidal effect of Avagard after

a single application resulted in a 2.5 log reduction from a 6 log baseline (99.68%) in resident bacterial flora, with a continued 3.5 log reduction (99.96%) after the final (eleventh) scrub. Reductions on surgically gloved hands were maintained over the six hour test period.

(The graph included in the draft labeling may be included here, if desired).

Health Care Personnel Antiseptic Study: The procedure used was the FDA specified test method for health care personnel handwash products[5]. After one application, Avagard [redacted] demonstrated a 2.1 log reduction from a 7 log baseline (99.2%) of bacteria on artificially contaminated hands. After the final (tenth) application, the reduction increased to 3.7 logs (99.98%)

(The graph included in the draft labeling may be included here, if desired).

INFORMATION FOR THE USER

Two independent 5-day handwashing studies were performed in a total of 58 subjects who washed with Avagard [redacted] In these studies, use of Avagard [redacted] was associated with little change in moisture, scaliness, erythema, or tactile roughness after repeated use, when compared to baseline condition.

REFERENCES

This section should read as follows:

1. National Committee for Clinical Laboratory Standards, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically", Document M7-A2, Vol. 5, No. 22.
2. Jordan WP, King SE. Delayed hypersensitivity in females. The development of allergic contact dermatitis in females during comparison of two predictive patch tests. Contact Dermatitis 3, 19-23, 1977.
3. Jordan WP, 24-, 48-, and 48/48 hour patch tests. Contact Dermatitis 6, 151-152, 1980.
4. Lanman BM, Elvers EB, and Howard CJ. The role of human patch testing in a product development program. Joint Conference on Cosmetic Sciences. The Toilets Goods Association (Currently The Cosmetic, Toiletry, and Fragrance Association), Washington, D.C., April 21-23, 1968.
5. Tentative Final Monograph for Health Care Antiseptic Drug Products; Federal Register; Vol. 59, No. 116, Friday June 17, 1994.

HOW SUPPLIED

500 mL (16.9 fl oz) filled plastic bottle with wall-bracket dispenser assembly (NDC#17518-051-01); [redacted] and 10 mL (0.34 fl oz) filled plastic bottle (NDC #17518-051-10)

Store at 20-25°C (68-77°F)

[redacted]
Made in U.S.A. for

3M Health Care
St. Paul, MN 55144-1000
(U.S.A.) 1-800-228-3957

34-xxxx-xxxx-x

2. **Discussion of Proposed Trade Name**

The submission by the sponsor concerning the trade name proposed Avagard™- [redacted] as the trade name [redacted] In their March 23, 2000 review, OPDRA did not object to Avagard [redacted] HFD-520 also accepts the new trade name.

3. **Conclusions and recommendations**

This product is recommended for approval with the above labeling changes. Satisfactory microbiology and chemistry reviews are still necessary.

Original NDA
HFD-520/Div. File
HFD-340
HFD-520/Clin/Bostwick
HFD-520/TClin/Rakowsky
HFD-520/Dillon-Parker
HFD-520/Micro/Sheldon
HFD-520/Chem/Sloan
HFD-560/Mason
HFD-560/Shetty
HFD-560/Lumpkins
Attachment

David Bostwick

Alexander Rakowsky, M.D.

Concurrence: Chikami/DivDir/HFD520

Clinical Review of Package Insert and Promotional Material
NDA 21-074

Date of Submission: January 10, 2001

Date Assigned to Reviewer: January 24, 2001

Date Review Initiated: February 7, 2001

Date Review to Supervisor: February 16, 2001

Drug: Avagard™ (chlorhexidine gluconate 1% and ethyl alcohol 61%, w/w) Surgical and Healthcare Personnel Hand Antiseptic

Applicant: 3M Health Care
St. Paul, MN 55144

Indication: This product is indicated as a surgical hand antiseptic and healthcare personnel hand antiseptic.

Packaging: The product is to be available in 500 mL dispenser bottles. A 10 mL sample bottle will also be made.

Background: This NDA was made not approvable on June 23, 2000 due to inadequate manufacturing facilities. However, the clinical review was satisfactory for the two indications noted above, so draft labeling was included with the not approvable letter. A telephone conversation was held on July 20, 2000 (copy of minutes are attached) to discuss 3M's comments on the FDA label. 3M submitted final printed container labels on August 24, 2000, which were found to be satisfactory in a clinical review dated September 14, 2000.

Material Reviewed: The draft labeling sent with the not approvable letter and the minutes of the July 20, 2000 telecon were reviewed in conjunction with the package insert submitted on January 10, 2001. The submission also contains copies of the introductory promotional materials for the product. These were also reviewed, although as noted in the July 20, 2000 telecon, the Federal Trade Commission regulates advertising for OTC drug products such as this one.

Review: The agreements made in the July 20, 2000 telecon have been met and the submitted package insert is satisfactory. The promotional material submitted is in general reasonably satisfactory. The following comments are offered:

1. Each statement in the promotional material concerning *in vitro* antimicrobial data (these statements include the phrase "more than 99% microbial kill in 15 seconds," or a paraphrase of this statement) should end as follows:

   "...*in vitro*. The clinical significance of *in vitro* microbiology is unknown."

2. Refer to p. 4 of the multipage promotional brochure which includes a chart headed "Assessment of the Antimicrobial Effectiveness of Surgical Hand Scrub Formulations Against Normal Skin Flora," The chart presents comparative results for Avagard vs. Betadine and Hibiclens using the method in the Tentative Final Monograph (TFM) for Health Care Drug Products for testing surgical scrubs. This chart portrays Hibiclens as failing to meet the TFM standards for surgical scrubs. While a study may exist in which Hibiclens failed to meet these standards, both studies presented in the NDA for surgical scrubbing resulted in Hibiclens meeting the TFM standards. If the sponsor chooses to present results for surgical scrubbing, those reported in the NDA should be used, rather than results from another study which has not been subjected to FDA review.

3. Similarly, on p. 6 of the multipage brochure, a chart is presented which is headed "Assessment of the Antimicrobial Effectiveness of 3M Avagard Antiseptic Hand Prep as a Healthcare Personnel Handwash." This chart presents results for Avagard only, presumably because Hibiclens performed better in the healthcare personnel handwash study presented in the NDA than did Avagard. If comparative results are presented for the surgical scrub indication (vs. Hibiclens), they should also be presented for the healthcare personnel handwash indication.

4. On p. 2 of the multipage brochure, last paragraph, the phrase "protect and maintain skin barrier integrity" should be deleted. This is a meaningless concept, at least in terms of studies which were submitted in support of the NDA, and should be deleted wherever it appears in the advertising.

5. On pp. 8-10 of the brochure, there are presentations of skin condition assessed by using Avagard, Hibiclens and Betadine as surgical scrubs and healthcare personnel handwashes. As noted in the clinical review of the NDA, Hibiclens (and presumably Betadine) scrubbing was accomplished with use of a scrub brush (per instructions), while no brush was used with Avagard. Use of the brush causes irritation and skin insult whether an antiseptic is used or not. Thus, when skin condition is evaluated, the scorer sees damage from both Hibiclens (for example) and the brush. It is misleading to evaluate Avagard as superior to Hibiclens in skin maintenance under these conditions. Since efficacy was not a consideration in the skin condition protocol, it would have been preferable to omit use of the scrub brush, even though it is true that in practice, the fact that Avagard does not require a scrub brush is an advantage in maintaining skin integrity.

   Therefore, the tables comparing Avagard to Hibiclens and Betadine as surgical scrubs should be deleted. The tables comparing Avagard to Hibiclens as a healthcare personnel handwash may remain.

6. The information concerning the 21-day cumulative study on p .11 of the brochure should also be deleted. As noted in the clinical review, Avagard was applied to the skin and allowed to dry for 15 minutes prior to application of the occlusive patches used in the test. The other test materials (Hibiclens, ethyl alcohol) were placed directly on the patch and then placed on the skin while still wet. This procedure may have influenced the relative irritancy scores for these products.

Conclusions and Recommendations: The final printed package insert is satisfactory. The above comments are offered on the advertising materials. Since OTC advertising is under the supervision of the Federal Trade Commission, it is not clear to the reviewers whether these comments may be forwarded to the sponsor.

/S/
David Bostwick

/S/ 4/5/2001
Mamodikoe Makhene, MD

ATTACHMENT
Original NDA
HFD-520/file
HFD-340
HFD-520/clin/Bostwick
HFD-520/TL/Makhene
HFD-520/PMDillonParker

Concurrence Only:
HFD-520/Acting Divdir/Soreth /S/ 5/25/01