JUN 0 2 1997

Meeting Date: January 9, 1997 Time: 1000 Location: N225

IND : miconazole nitrate ointment

Sponsor: Johnson and Johnson

Pre-NDA

Meeting Chair: Jonathan K. Wilkin. M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross. Jr.. M.A., LCDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Denise Cook, M.D., Medical Officer, DDDDP, HFD-540
Susan Walker, M.D., Acting Dermatology Team Leader, DDDDP, HFD-540
Ping Gao, Ph.D., Biostatistician, DOBIV, HFD-725
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Bill Timmer, Ph.D., Chemist, DNDCIII, HFD-540
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, HFD-880
Frank H. Cross, Jr., M.A., LCDR, Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Geert Cauwenbergh, Ph.D., - Vice President, Skin Research Center
Rachel Grossman, M.D., - Medical Director
James Haviland - Regulatory Compliance Manager - Project Manager
Paul Manley - Director, Drug Regulatory Affairs
Matthew Nunes - Laboratory Services Manager
Donna Saligan - Regulatory Affairs Senior Associate - Scribe
Stanley Shapiro, Ph.D., Drug Development Director

Meeting Objectives:

To reach agreement on all points (as outlined below) relevant to the pre-NDA filing needs for this IND (also outlined below).

Discussion Points (see attached):

NONCLINICAL

1. The sponsor believes the proposed nonclinical data is sufficient. Is there general concurrence?

CLINICAL/STATISTICS

1. To gain acceptance that the additional ADME and Clinical work conducted since the 1986 non-approval letter are acceptable for filing.

2. To gain agency acceptance on our proposal for provision of electronic data sets.

CHEMISTRY, MANUFACTURING, and CONTROLS

1. The sponsor believes that the manufacturing methods used for the pivotal clinical trials are equivalent to the proposed methods for commercial production. The sponsor proposes that no clinical bioequivalence study is required.

2. The sponsor proposes to submit the application with three months stability in final package form.

ENVIRONMENTAL ASSESSMENT

1. Will the sponsor be granted an exclusion from preparing an Environmental Assessment?

Decisions (agreements) reached:

NONCLINICAL

The Agency advised the sponsor that the Non-Clinical development is acceptable. The sponsor will need to resubmit the old material or summarize it. The sponsor will also need to summarize and cross-reference other NDA's.

CLINICAL/STATISTICS

CLINICAL

1. The Agency asked if the sponsor is relying on the combination 10833 and 10844.A32. The sponsor said that it is not.

2. The Agency advised the sponsor that in terms of safety, that no additional systemic studies will be needed depending on the age of the child. Four weeks may be a problem. The age limit will probably have to be increased, probably at least three months, although it will depend on the age of the infants in the study. A six month time frame may be reasonable, because the dermatitis tends to be most prevalent in infants six months and older.

3. The Agency recommended to the sponsor that it will need to stratify the population for each part of its indications, diaper dermatitis without Candida and diaper dermatitis with Candida. The former would need to have a 3-arm study (active vs. the vehicle vs. an active control) in order to prove that the vehicle is not having a negative effect, thus giving a false impression of effectiveness of the active. The second part of the stratification would be concerning diaper dermatitis with Candida. The sponsor would need to demonstrate colonization vs. infection. Under infection, the sponsor would need to demonsurate Candida albicans vs. other Candida species, if indeed, the sponsor wants "Candida species." Secondly, if the sponsor wants the indication of diaper dermatitis without Candida infection, evidence would have to be forthcoming to demonstrate that using an anti-infective in the absence of infection would not give rise to resistant organisms.

4. The Agency advised the sponsor that at the present time there is no monograph for zinc oxide. It was recommended to the sponsor that, if there is a monograph at the time of filing, they will need to show zinc oxide's contribution to the formulation. It was also recommended to follow the combination policy, if the miconazole and the zinc oxide are both active. A general rule of thumb for the number of arms in a trial under combination policy is N + 2. The Agency said that it may be possible to do some bridging studies. The sponsor asked if they could amend their application during the review during Phase 4 for just Candida infection. The Agency said that the sponsor did not use this inclusion criterion in its studies, i.e., signs and symptoms of Candida albicans infection. The Agency said that it would need to see data to support having a labeling claim for diaper dermatitis due to Candida infection. A 4-arm study will also be needed for this area.

5. The Agency recommended to the sponsor that it needs to demonstrate an organism other than C. albicans in order to make the claim for Candida species.

6. The Agency cannot allow a prevention claim to go into the label.

7. The sponsor was advised that it needs to differentiate between colonization and infection.

8. Questions of microbial resistance need to be resolved.

STATISTICS

1. The electronic data sets need to be submitted in SAS Version 6.11. A code book should be submitted. The same nomenclature should be used across the studies.

   Several questions still need to be answered, i.e.,

   a. What was the rash score? How was it created or obtained? The sponsor said that this will be submitted to the NDA. It obtained the rash score by marking and evaluation for severity at each visit.

   c. In the analysis of clinical impression, what is the definition of evaluable infants with diaper dermatitis? The dropouts were not included in the final analysis. We only evaluated those patients that continued with the trial up to seven days. The Agency also advised the sponsor to conduct an LOCF analysis of those patients that dropped out in the middle of the study.

3. The Agency recommended to the sponsor that if all the studies are combined then the sponsor will need to make sure that they are adequately powered. If the sponsor decides to pursue only diaper dermatitis with Candida infection, the sponsor will need to make sure that the trials are adequately powered.

CHEMISTRY, MANUFACTURING, and CONTROLS

1. The Agency recommended to the sponsor that basic test results on each lot will need to be submitted, particularly content uniformity, before the Agency can comment on the proposal. Further, it was recommended that the sponsor consult the SUPAC-SS guidance, even though this guidance usually applies to Post-Approval changes. The sponsor said that it is using Janssen's manufacturing process. The sponsor will need to provide which formulations were used in the clinical studies. The sponsor may need to submit a post-approval supplement depending on how extensive the changes were from the original manufacturing process. The sponsor said that it intends to ask for a 36-month expiration on the product. The sponsor will submit all stability data. The Agency advised the sponsor to submit at least six months of stability data.

2. The Agency also recommended to the sponsor that more than three months of stability should be submitted. Also, a disagreement noted in the briefing package needs to be resolved. The sponsor said that all other stability data will be submitted, i.e., three years from Janssen, five years from and three months from the new batch sizes.

3. The Agency recommended that if the sponsor wants to promote zinc oxide then it will be necessary to discuss its contribution.

ENVIRONMENTAL ASSESSMENT

The Agency recommended to the sponsor that if they are going to file this NDA during the first quarter of 1997, then they will need to submit an Environmental Assessment. There is no basis for an exclusion at this point. The sponsor was encouraged to stay in touch with the Agency on this point.

It was recommended to the sponsor that they file a new IND so as to archive the data separately and thereby minimize confusion between the current formulation and indication for this drug that was previously filed to IND

Unresolved issues or issues requiring further discussion:

None.