CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

CORRESPONDENCE

Minutes of the Teleconference
Dermatologic and Dental Division - FDA and
Hyal Pharmaceutical Corporation

August 7, 1997

Present: FDA:	Dr. Wilkin Director of Dermatologic and Dental Division
	Dr. Ko - Medical Reviewer
	Dr. Roy Blay - Project Manager
Hyal:	Dr. M.Cohen Senior VP and Chief Medical Officer
	Mr. Mike Vanzieleghem - Director Clinical Services
	Mr. Al-Karim Rehemtula - Clinical Manager
	Ms. Patricia Anderson - Director Regulatory Affairs

The purpose of the teleconference was to discuss whether Hyal had sufficiently characterized sensitization potential of 3% diclofenac gel.

The following major points were discussed

Hyal has conducted three studies, one initial —— Study with 100 patients however occlusion was not utilized. On the recommendation of the Pilot Drug Group another study was completed with 100 patients with occluded patch however the patients were on oral NSAIDs. The final study was completed to satisfy the Canadian regulatory concerns.

Dr. Ko and Dr. Wilkin indicated that the study without oral NSAIDs was well done but unless Hyal's formulation was a frank irritant then complete occlusion is necessary. M. Vanzieleghem stated that in our irritancy study our formulation was shown to be a non- irritant, however in clinical studies a significant proportion of patients exhibited mild irritancy and localized dermal reactions.

Dr. Wilkin stated that he felt that he could not state from the data submitted the sensitization potential of our formulation. Patients using diclofenac or other like NSAIDs may develop specific tolerance to the NSAID thereby patients using an oral NSAID will not be good predictors for a dermal sensitization study. Dr. Wilkin referred to the 1960's work in minipigs and di:NO,chlorobenzene by Ed Lowny. Dr. Wilkin also pointed to the induced 'tolerance' or 'depressed severity of dermal reactions' to poison ivy/oak. Other references were also cited.

Ms. Anderson asked whether we could not utilize some of the patients on oral NSAIDs excluding patients receiving diclofenac and diclofenac related compounds as only 19 or 20 patients in the second —— study were on diclofenac and the lack cross-reactivity between families of NSAIDs has been shown.

Dr. Wilkin stated that it may be possible to cull out that group of patients.

Dr. Cohen asked Dr. Wilkin if he knew of any information indicating that there existed a sensitization concern with diclofenac or other NSAIDs. Dr. Wilkin stated that any information would be from specific formulations and that Hyals formulation being unique must be characterized.

M. Cohen concluded the meeting with an agreement to complete a new 200 patient sensitization study in naive patients (not on oral NSAIDs and/or having previously received the Hyal formulation) rather than complete a post-hoc analysis.

Dr. Wilkin stated that the protocol submitted by Hyal could be quickly reviewed. —— protocols are known to them and would be acceptable if they contained features like a fully occluded patch, 3 week induction, 2 week rest period and 72 hour challenge with 200 healthy volunteers.

Hyal thanked the division for its time and assistance.

APPEARS THIS WAY
ON ORIGINAL

SkyePharma

October 16, 2000

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

BL

Attention: Document Control Room

Desk Copy: Kevin Darryl White
Project Manager

Via Facsimile - (301) 827-2075

Dear Dr. Wilkin,

RE: Approval of NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%

SkyePharma Inc. acknowledges receipt of FDA's fax of October 16, 2000 of the Sponsor's label with FDA's revisions.

SkyePharma accepts the FDA's revisions as indicated in FDA's fax of October 16, 2000.

SkyePharma is submitting this information to the Agency via fax, with a hard copy being sent via Federal Express.

If you have further questions, please contact me at (858) 625-2424, ext. 3370.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical Research and Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

SkyePharma

October 3, 2000

Kevin Darryl White
Project Manager (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

NDA ORIG AMENDMENT

Via Facsimile - (301) 827-2075

Attention: Document Control Room

BM

Dear Mr. White,

RE: NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%
Amendment – Solaraze labeling

Reference is made to the FDA's fax dated September 15, 2000, in which the Agency provided SkyePharma Inc. with the recommended labeling for Solaraze. In response to the Agency's recommendations, SkyePharma Inc. hereby submits an amendment revising the package insert, patient information leaflet, and container labels for Solaraze. As discussed via telephone, SkyePharma is submitting this amendment to the Agency via fax on October 3, 2000, with hard copies being sent via Federal Express on the same date.

The following items are included in this amendment.

Appendix #	Item
1	SkyePharma's response to FDA's fax
2	Copy of FDA's fax dated 9/15/00
3	Redlined version of Package Insert
4	Clean copy of revised Package Insert
5	Redlined version of Patient Information Leaflet
6	Clean copy of revised Patient Information Leaflet
7	Electronic copy of labeling on diskette
8	Revised container (tube and carton) labels

If there are any question regarding this amendment, please contact me at (858) 625-2424, ext. 3231.

Sincerely,

Pearl T. Amos

Pearl T. Amos
Associate Director, Regulatory Affairs

DUPLICATE

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
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NDA ORIG AMENDMENT

SkyePharma

September 22, 2000

Jonathan K. Wilkin, M.D.
Director (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

BC

Desk Copy: Kevin Darryl White
Project Manager

Attention: Document Control Room

RE: NDA 21-005: Solaraze™ (diclofenac sodium) Gel, 3%
Amendment – Contract Manufacturer's Name Change

Dear Dr. Wilkin,

Reference is made to Solaraze™ NDA 21-005, originally submitted on October 20, 1998. The purpose of this amendment is to inform the Agency that the contract manufacturer responsible for _____ of Solaraze, as listed in the NDA, has been acquired by another company.

As of September 1, 2000, _____ is now operating as _____ The ownership change has not affected personnel and GMP operations at the faciiity where _____ is manufactured, nor has the location of the facility changed. The facility's address is:

_____
_____
_____
_____
_____

Should you have any questions or concerns regarding this amendment, please contact me at (858) 625-2424, ext. 3231 or by FAX at (858) 558-6617

Sincerely,

Pearl T. Amos
Associate Director, Regulatory Affairs

DUPLICATE

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Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

PCDOC #67456

SkyePharma

NDA ORIG AMENDMENT August 15, 2000

Johnathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. (HFD-540)
Rockville, Maryland 20857

BL

Attention: Document Control Room

RE: NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%
Labeling Amendment – Draft Labels of Immediate Container and Carton

Dear Dr. Wilkin,

Reference is made to FDA's approvable action letter dated July 19, 2000, and SkyePharma Inc.'s response dated July 28, 2000. The purpose of this amendment is to provide the Agency with draft labeling of the immediate container and carton labels for Solaraze™ (diclofenac sodium) gel, 3%. Proof copies of the 25g and 50g container and carton labels are included in **Appendices 1** and **2**, respectively. We understand that upon receipt of this amendment, a 45-day review period will commence.

With regard to safety information on Solaraze, no additional clinical studies have been conducted since the submission of the original NDA (i.e., no other dosage forms and/or dosage levels, and no new indication is being sought for the drug product). Therefore, no new safety data are available.

Should you have any questions or concerns regarding this amendment, please contact me by telephone at (858) 625-2414, ext. 3231 or by fax at (858) 558-6617.

Sincerely,

Pearl T. Amos
Associate Director, Regulatory Affairs

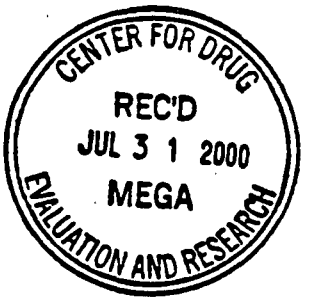
DUPLICATE

Desk Copy: Kevin Darryl White
Project Manager

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

SkyePharma

NEW CORRESP



July 28, 2000

N 2

Jonathan K. Wilkin. M.D.
Director (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville. Maryland 20857

Desk Copy: Kevin Darryl White
Project Manager

Attention: Document Control Room

Dear Dr. Wilkin.

RE: Approvable Action Letter to NDA 21-005, Solarase™ (diclofenac sodium) Gel, 3%

SkyePharma Inc. acknowledges receipt of FDA's approvable action letter dated July 19, 2000. (A fax copy of the action letter was received on July 19, 2000; original letter was received on July 24, 2000.) In accordance with 21 CFR 314.110(a)(1), this correspondence serves as notification to the Agency that SkyePharma Inc. intends to file a complete amendment to NDA 21-005, Solarase (diclofenac sodium) Gel. 3%. We also acknowledge that, per regulation, the filing of an amendment will extend FDA's review period for 45 days after receipt of the complete amendment. The amendment, expected to be submitted mid-August 2000, will contain the requested revised labeling including proof copies of the immediate container and carton labels.

The Agency also requested commitment on additional Phase 4 (post-approval) studies to be completed within 12 months of the NDA approval. SkyePharma Inc. intends to complete these post-approval commitments within the stated time frame. Please reference the telephone conversation on July 20. 2000. with the Division Project Manager in which SkyePharma acknowledged receipt of the action letter and requested a telephone conference with the Division Chemistry Reviewer for clarification on additional study to further investigate the possible ——— of diclofenac sodium. We will contact the Project Manager next week to confirm a date for the teleconference.

If there are any questions regarding this correspondence, please contact me at (858) 625-2424, ext. 3370.

Sincerely,

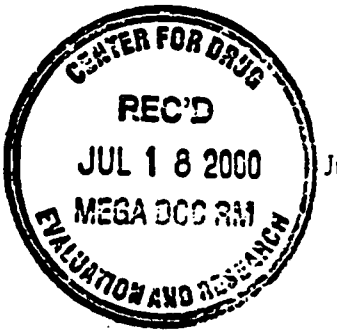
Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical Research & Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive. San Diego. California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly. London W1V 9FN

SkyePharma

NDA [illegible] AMENDMENT



July 17, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. (HFD-540)
Rockville, Maryland 20857

EL

Via facsimile – (301) 827-2075

Attention: Document Control Room

RE: NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%
Labeling Amendment – Product Insert

Dear Mr. White,

Reference is made to the labeling amendment submitted June 2, 2000 in which a copy of a revised product insert for Solaraze was submitted. We herewith submit an updated version of the product insert in response to your request that the *Geriatrics Use* section of the label be updated to address the requirements in the regulations (21 CFR § 201.57 (f)(10)(ii)(B)).

As requested, we have updated the *Precautions – Geriatric Use* section with data obtained from clinical trials to support the safety of Solaraze in the geriatric population. In addition, your division requested changing the trade name Solarase™ so that the name would not be confused with an enzyme product because of the "ase" ending. Therefore, we have changed the trade name Solarase™ to Solaraze™. We are in the process of obtaining a trademark for this name, but have used it in this labeling amendment to show true representation of our labeling.

Appendix 1 contains a copy of the revised product insert. **Appendix 2** contains copies of container labels (25 gram and 50 gram dose) that were revised to reflect the change in trade name from Solarase™ to Solaraze. An electronic copy of the revised container labels and product insert is also enclosed on diskette in MS Word format.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
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Registered no. 1175582 England. Registered office 105 Piccadilly, London W1V 9FN

SkyePharma Inc. • 10450 Science Center Drive. • San Diego California 92121, USA

Tel (858) 625 2424 • Fax (858) 625 2439 • www.skyepharma.com

Hard copies of this submission will be sent via Federal Express today. Should you have questions or other concerns regarding this NDA, please do not hesitate to contact me by telephone at (858) 625-2414, ext. 3231 or by fax at (858) 558-6617.

Sincerely,

Pearl T. Amos

Pearl T. Amos
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

SkyePharma

BEST POSSIBLE COPY

NDA ORIG AMENDMENT

June 27, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. (HFD-540)
Rockville, MD 20857

XR

Attention: Central Document Room

Subject: **NDA 21-005 Solarase™ (diclofenac sodium) Gel, 3%**
Amendments - New Patent Information and
Updated DMF letters of authorization

Dear Mr. White,

Reference is made to NDA 21-005 Solarase™ (diclofenac sodium) Gel, 3%, originally submitted October 20, 1998 and to the Agency's verbal request on April 28, 2000 for updated DMF letters of authorization for the NDA. Reference is also made to the June 23, 2000 transfer of ownership letter stating that effective October 28, 1999, the rights to NDA 21-005 has been transferred from Hyal Pharmaceutical Corporation, Mississauga, Ontario, Canada to SkyePharma Inc., San Diego, California.

In accordance with 21 CFR 314.53, an amended Section 13 of the original NDA, along with the required patent certification is enclosed in **Appendix 1**. United States Patent Number 5,985,850 entitled "Compositions Comprising Hyaluronic Acid and Drugs" was issued on November 16, 1999. SkyePharma Inc. is the official owner of Patent No. 5,985,850.

Copies of supplier DMF letters of authorization referencing SkyePharma Inc. are enclosed in **Appendix 2**.

Should you have questions regarding this submission or other matters relevant to this NDA, please contact me by telephone at (858) 625-2414 ext. 3231 or by FAX at (858) 558-6617.

Sincerely,

Pearl T. Amos
Associate Director, Regulatory Affairs

ORIGINAL

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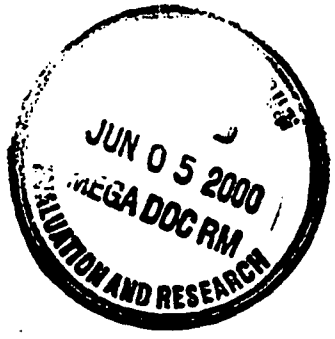
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered in England Registered office 105 Piccadilly London W1V 9FN

SkyePharma

NDA ORIG AMENDMENT



June 2, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857

BL

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005)
Labeling Amendment

Dear Mr. White,

This amendment to NDA 21-005 is submitted as a follow up to SkyePharma's May 18, 2000 labeling amendment. Data required to complete the second table included on page three of the insert labeling has now been added. No further revisions have been incorporated.

Each comment included in FDA's May 9, 2000 labeling comments has now been addressed. A hard copy of the revised insert labeling, as well as an electronic copy on diskette are included in this submission.

Should you have any questions regarding this amendment please contact me by telephone at 858/625-2414 ext. 3370 or FAX 858/558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President,
Clinical Research & Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
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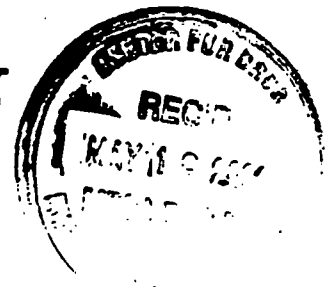
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

SkyePharma

NDA ORIG AMENDMENT



May 18, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857

BL

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005)
Response to Labeling Comments

Dear Mr. White,

Please find included in this amendment a complete and adequate response to the Agency's Labeling Comments FAX dated May 9, 2000. Three copies of the revised insert labeling incorporating each of FDA's recommendations, as well as an electronic version of the labeling is also included.

Please note that the information requested by the Agency to complete the table included in item (5) "*Under CLINICAL STUDIES . . .*" is not yet available. SkyePharma commits to forward these date to complete the table within the next week.

Finally, as noted in our response SkyePharma is not familiar with the "Information for the Consumer" leaflet commented on in Section B. SkyePharma requests that the Agency forward a copy of the document to us so that this section may be addressed.

Please feel free to contact me with an questions or further comments at TEL 858/625-2414 ext. 3370 or FAX 858/558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President,
Clinical Research & Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly. London W1V 9FN

SkyePharma

April 24, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857

NDA ORIG AMENDMENT

BL

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005)
Response to Teleconference (April 18, 2000)

Dear Mr. White,

This amendment to NDA 21-005 is submitted per your telephone request on April 18, 2000 for the following three items; (1) the proposed Solarase™ labeling, submitted on diskette, preferably in MS Word® format, (2) clinical investigator financial disclosure, and (3) a pediatric study waiver request. Please find included within this amendment a complete and adequate response to each individual request.

Should you have any questions regarding this amendment please contact me by telephone at 858/625-2414 ext. 3370 or FAX 858/558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President,
Clinical Research & Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England Registered office 105 Piccadilly, London W1V 9FN

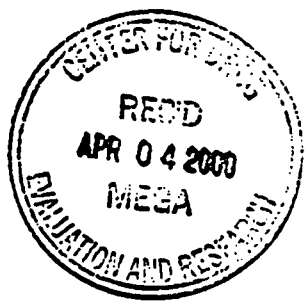
SkyePharma

BEST POSSIBLE COPY

NDA ORIG AMENDMENT

April 3, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857



Attention: Central Document Room

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005)
Amendment – Response to "not approvable" letter

Dear Mr. White:

Reference is made to our telephone conversation on April 3, 2000 and to the January 21, 2000 submission in which we responded to the not approvable letter for NDA 21-005. As stated in the cover letter of the January 21, 2000 submission, we did not provide updated safety information as requested on page 4 of the Agency's not approvable letter. All available safety data were reported in the NDA for this product, and there are no ongoing clinical trials from which patient data is available to report.

Solarase™ has been approved for marketing in six countries including Canada, United Kingdom, Sweden, Italy, Germany and France. Solarase has not yet been launched in these markets.

Should you have any questions regarding this meeting package please contact me by telephone at (858) 625-2414 ext. 3370, or by FAX at (858) 558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Sr. Vice President,
Clinical Research & Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 525 2439 www.skyepharma.com
SkyePharma PLC Registered Office 105 Piccadilly London W1V 9FN

SkyePharma

BC

January 21, 2000

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857

Attention: Central Document Room

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005)
Response to "not approvable" letter

Dear Dr. Wilkin,

Please accept this amendment as a complete response to items contained in the Agency's October 21, 1999 "not approvable" letter for Solarase Gel (NDA 21-005). Each item has been individually responded to with supporting documentation included in referenced attachments.

Per the December 22, 1999 "change of ownership" amendment to NDA 21-005, SkyePharma Inc. of San Diego, CA has assumed ownership and management of the Solarase NDA. In our effort to provide the Agency with complete responses to each of the items included in the "not approvable" letter, SkyePharma performed a thorough examination of all related documentation provided to us by the previous owner, Hyal Pharmaceutical Corporation. During this examination it became evident that confusion between Hyal and FDA had arisen over several issues. SkyePharma discovered that repeated requests by the Agency to resolve these areas of concern were inadequately addressed by Hyal. Finally, the unresolved issues were cited as deficiency items in the October 21, 1999 "not approvable" letter.

In a letter dated July 9, 1999, FDA requested, among other items, identification of the decomposition products generated when the drug substance is exposed to sunlight (Item 6 of the July 9 letter). A partial response to this specific item was provided to FDA on October 8, 1999. At that time, only preliminary results were available for ——— analysis of the major ——— observed, and only three compounds arising from sunlight exposure were identified. In the present submission, the remainder of the ——— analysis is provided from ——— and can be found in ATTACHMENT 2, pages 1, 3-11 and 18. This should complete the responses to item 6.

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England Registered office 105 Piccadilly, London W1V 9FN

DUPLICATE

SkyePharma Inc. • 10450 Science Center Drive. • San Diego, California 92121, USA

Tel (858) 625 2424 • Fax (858) 625 2439 • www.skyepharma.com

Regarding page four of the Agency's "not approvable" letter, the request for updated safety information, please note that no new safety data are available. The most recent data available were submitted in February, 1999

Finally, a copy of the cover letter from an [redacted] recent submission to FDA is included. This submission responded to deficiency items to [redacted] DMF [redacted] which is referenced in NDA 21-005.

Please contact the undersigned with any questions at 858/625-2414 ext. 3370 or FAX 858/558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President,
Clinical Research & Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HPC DUPLICATE DUPLICATE

Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

NEW CORRESP

NC

October 29 1999

Mr. K.D. White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel
Deficiency Issues

We acknowledge receipt of the non-approvable letter dated October 21, 1999. Our intention is to address all deficiencies outlined in the letter by November 30, 1999. To ensure the accuracy of our response, it would be beneficial to have a teleconference with the reviewing chemists at the earliest convenient time.

If there are any questions regarding this request, please contact me at (905) 625-8181.

Sincerely,

PAnderson

Patricia Anderson
Director, Regulatory Affairs

PA:jae

APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

October 8, 1999

ORIG AMENDMENT
BC

Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel - Chemistry and Manufacturing Review Question

Please find enclosed a response to Question 6 of the Chemistry and Manufacturing Review for 3% Diclofenac gel. The sodium diclofenac raw material was exposed to sunlight and assayed for degradation or decomposition products. Tests have been completed by ———— ———— The samples were further tested by ———— using ———— Preliminary results from ———— have been submitted. I have also enclosed a revised finished product specification with the correct HA assay.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

PAnderson

Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

October 20, 1998

Food and Drug Administration
Centre for Drugs and Biologics
Central Document Room
Park Building Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

Re: NDA 21.005 Solarase™(diclofenac sodium) Gel

Gentlemen:

In accordance with 21 CFR 314.50 Hyal Pharmaceutical Corporation is submitting NDA 21.005 for Solarase™ (sodium diclofenac) gel 30 mg/g.

Solarase™ offers a topical treatment for actinic keratoses. Clinical studies presented in this dossier have been conducted in the United States and abroad. All facilities connected with the manufacturing, packaging and testing of the drug substances and drug product are ready for inspection. These facilities are identified in the attached listing.

If there are any questions regarding this submission, please contact me at Hyal Pharmaceutical (905) 625-8181; Fax (905) 625-6113.

Appendices to this application include the following:

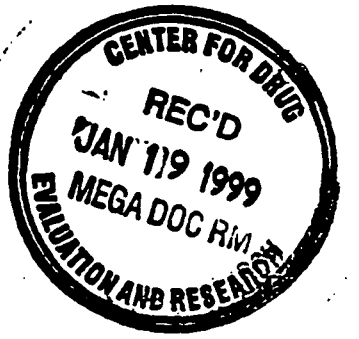
- Identification of manufacturing and testing facilities: Drug Substance and Drug Product
- A letter from the Office of the Commissioner granting exemption of payment for the application fee.
- A list of DMF's that are utilized in this submission.
- Minutes of meetings with the FDA regarding this file. These include an agreement that HA in the formulation will be considered an inactive excipient by the Dermatological Division and agreement in principal to the format of Section 11, CRFs.

HYAL PHARMACEUTICAL CORPORATION

Patricia Anderson
Director, Regulatory Affairs

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL



NDA ORIG AMENDMENT
BZ

January 18, 1999

Dr. J. Wilkin, Director
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

Dear Dr. Wilkin:

Re: Fax Dated December 18, 1998 Issues Regarding the NDA 21-005

We would like to address the issues raised in your fax regarding the NDA for Solarase:

Clinical issues:

1. We have completed a thorough indexing of the volumes in question and have attached this for the Reviewer. Section C was added incorrectly to the index.

2. The ISS has addressed the data in Volumes 47-50 but as stated by the reviewer may be confusing given the lack of indexing. We have attached a Reviewer's guide which displays the references and a table to aid the reviewer in locating references discussed in the ISS and supporting data in the appendices.

3. The adverse event data in this NDA is based on the evaluable population which consisted of all patients in whom safety data was collected. There was no safety data from two diclofenac treated patients. The reason for the exclusion of these two patients is provided below.

Patient #2010 - Study CT-1101-03 - Diclofenac treated - There was adequate evidence of study medication use as the study medication was returned to the clinic but no post randomization data were collected and the patient was lost to follow-up.

Patient #4016 - Study CT-1101-03 - Diclofenac treated - There was no indication that the patient took any study medication as no medication or diary was returned to the clinic at 30 days post treatment initiation and the patient, being very uncooperative, was thereafter lost to follow-up. Notably, the patient was reported by the investigator as having experienced no adverse events.

4. A safety update will be submitted at the 120 day timeframe.

tatistical issue

Diskettes with the SAS programs (versions 6.12), SAS datasets and Study Reports MS Word are enclosed as requested.

harmacology /Biopharmaceutics issues

1. We have obtained another copy of the SBA of Voltaren from FOI. This copy is not as clear as the one presented but we enclose the copy sent to us for your review. We would seek the advice of the agency on the best next step to handle this issue.
2. Bioresearch is preparing the PDR files for the Two Year Carcinogenicity Study and these will be sent as soon as they are available.
3. A statement has been attached regarding the acceptable state-of the-art protocols which were used in the preclinical investigations of this drug.

there are any questions or concerns regarding this information please contact me at Hyal.

incerely,

PA-Anderson

APPEARS THIS WAY
ON ORIGINAL

atricia Anderson
irector, Regulatory Affairs

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

February 8, 1999

NDA ORIG AMENDMENT
BS

Dr. Roy Blay
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

Dear Dr. Blay:

Re: NDA 21.005 Solarase Diclofenac Gel

As per your request, we have enclosed copies on diskette of the three studies, CT 1101-03, CT 1101-04 and CT 1101-07 for the reviewing statistician. Please note that the copy of CT 1101-07 has been converted from Wordperfect to Word so the pagination maybe different than the hard copy in our NDA due to this conversion. The diskettes provided have been virus checked.

We would also like to add new patent information to our file as attached.
Further, we would like to amend the letter of Authorization to Access the DMF for ——— as the original one submitted was given to us by ——— in error. The one submitted was for a ——— versus the ——— used in our formulation.

If there are any questions or queries regarding this, please contact us.

Yours sincerely

Patricia Anderson
Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

February 17, 1999

ORIGINAL

Dr. Roy Blay
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

NEW CORRESP
NC

Dear Dr. Blay:

Re: NDA 21.005 Solarase Diclofenac Gel Your fax requesting further information dated Feb. 3, 1999 and January 26, 1999

Please find attached responses to requests by Dr. Ko regarding further analysis of an efficacy endpoint, and severity and outcome of adverse events.

If there any questions regarding this submission, please contact me at Hyal.

Yours sincerely

PAnderson

APPEARS THIS WAY
ON ORIGINAL

Patricia Anderson
Director Regulatory Affairs

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

ORIG AMENDMENT

N(SU)
1

March 17, 1999

Dr. Roy Blay
Dermatologic and Dental Division
Food and Drug Administration
9201 Corporate Blvd - HFD 5401
Rockville, Maryland
20857

Dear Dr. Blay,

Re: NDA 21.005 Solarase Diclofenac Gel
Safety Update

Please find enclosed one original and 4 desk copies of the Safety Update for our NDA 21.005 Solarase diclofenac gel for the treatment of actinic keratosis.

If you have any questions, please contact us.

Sincerely,

Jennifer A. Ellis
Regulatory Affairs Associate

APPEARS THIS WAY
ON ORIGINAL

:jae
encl.

By Courier 301-827-2075

ORIGINAL

82

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

May 21, 1999

Mr.D.K.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

ORIG AMENDMENT

noted
6-10-99
/S/

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel
Your call May 19 requesting information regarding the HA used in preclinical studies

Please find enclosed a table reflecting the HA used in each preclinical and clinical study as requested and the Certificate of Analysis for each lot of HA used.

If there are any questions regarding, please contact me at Hyal.

Sincerely

P Anderson

APPEARS THIS WAY
ON ORIGINAL

Patricia Anderson
Director of Regulatory Affairs

HPC

Hyal Pharmaceutical Corporation

2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

BZ

ORIG AMENDMENT

July 7, 1999

Mr. K.D. White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel
Your letter dated June 22, 1999 requesting further information

Please find enclosed responses to Questions A and C of your letter dated June 22, 1999. We would like to request a teleconference to discuss question B prior to our submission addressing these concerns.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

P Anderson

APPEARS THIS WAY
ON ORIGINAL

Patricia Anderson
Director of Regulatory Affairs

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

August 5, 1999

fax: (301) 827-2075

Mr.D.K.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel - Letter dated June 22, 1999 Questions and Comments

Please find attached a response to comments and questions from the Pharmacology and Toxicology review. The FDA questions and comments have bolded followed by Hyals response.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

P Anderson

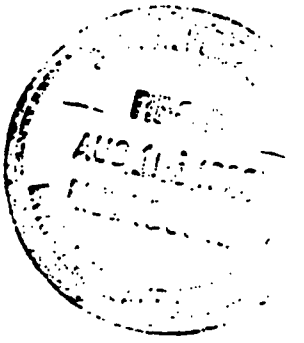
Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

AMENDMENT
BC

August 12, 1999



Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20857

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel - Letter dated Jul 9, 1999 Chemistry Review Questions and Comments

Please find attached a partial response to comments and questions from the Chemistry and Manufacturing review. Questions/comments from the FDA review are bolded with responses immediately after. In order to respond appropriately we would like to request a teleconference for clarification of question 6.

If there are any questions regarding, please contact me at Hyal.

Sincerely

PAnderson

APPEARS THIS WAY
ON ORIGINAL

Patricia Anderson
Director of Regulatory Affairs

ORIGINAL

ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1584

ORIG AMENDMENT
BP

August 19, 1999

fax: (301) 827-2075

Mr.K.D..White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel -Request for Additional Pharmacology/Toxicology Information, 1999 Questions and Comments

Please find attached a response to comments and questions from the Pharmacology and Toxicology review. The FDA questions and comments have bolded followed by Hyal's response.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

Patricia Anderson
Director of Regulatory Affairs

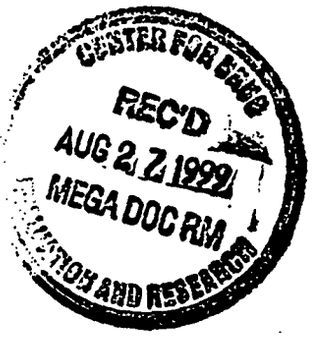
APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

COPY

August 19, 1999

fax: (301) 827-2075



Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

NDA ORIG AMENDMENT

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel

Please find attached new patent information that should be amended to our NDA.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

P Anderson

Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

ORIGINAL

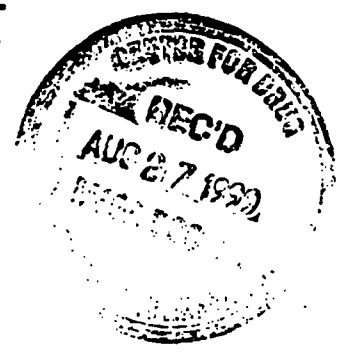
BM

August 25, 1999

fax: (301) 827-2075

Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

NDA ORIG AMENDMENT



Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel

Please find attached responses to clinical questions received on August 16, 1999. FDA questions have been bolded, with Hyal's response following immediately after.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax: (905) 625-1884

Amend
ORIG ~~NEW CORRES~~
NC BP

September 1, 1999

Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel -Pharm Tox Quetions

Please find enclosed pre-clinical reports from ———— involving — as promised. We have included the original reports in —— as well as the english version as translated by ————

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

PAnderson

Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

HPC
Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
(905) 625-8181 Fax. (905) 625-1884

ORIGINAL

ORIG AMENDMENT

BI

September 3, 1999

Mr.K.D.White
Dermatologic and Ophthalmic
Food and Drug Administration
9201 Corporate Blvd. Room HFD540
Rockville, Maryland
20850

Dear Mr. White:

Re: NDA 21.005 Solarase Diclofenac Gel - Microbiological Review Question

Please find enclosed stability summaries for lots of 3% Diclofenac gel where ——— efficacy tests have been completed and the associated reports from ——————— to support these summaries. Copies of the raw data from the contract lab for two of the lots (DT80 and DT81) available have been also submitted.

If there are any questions regarding this submission, please contact me at Hyal.

Sincerely

P Anderson

Patricia Anderson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 6 PAGE (S)

Draft

Labeling

SkyePharma

Rita L. Pendergrass
Sr. Administrative Assistant
Global Regulatory Affairs Group
858/625-2414, ext. 3214
858-625-0804/facsimile
rita_pendergrass@skyepharma.com/e-mail

facsimile

to: Kevin Darryl White

date: 10/16/00

company: FDA

number of pages to follow: 2

fax no: 301-827-2075

telephone no: 301-827-2020

subject: Solaraze

message:

Kevin Darryl,

As discussed, attached is our letter accepting FDA's changes to the PI.

Gordon

Gordon,

APPEARS THIS WAY
ON ORIGINAL

SkyePharma

October 16, 2000

Jonathan K. Wilkin, M.D.
Director (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

Desk Copy: Kevin Darryl White
Project Manager

Attention: Document Control Room

Via Facsimile - (301) 827-2075

Dear Dr. Wilkin,

RE: Approval of NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%

SkyePharma Inc. acknowledges receipt of FDA's fax of October 16, 2000 of the Sponsor's label with FDA's revisions.

SkyePharma accepts the FDA's revisions as indicated in FDA's fax of October 16, 2000.

SkyePharma is submitting this information to the Agency via fax, with a hard copy being sent via Federal Express.

If you have further questions, please contact me at (858) 625-2424, ext. 3370.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical Research and Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Rita L. Pendergrass
Sr. Administrative Assistant
Global Regulatory Affairs Group
858/625-2414, ext. 3214
858-625-0804/facsimile
rita_pendergrass@skyepharma.com/e-mail

facsimile

to: Kevin Darryl White

date: 10/17/00

company: FDA

number of pages to follow: 1

fax no: 301-827-2075

telephone no: 301-827-2020

subject: Solaraze Package Insert

message:

Kevin Darryl,

As discussed by telephone today, attached is the first page of the Solaraze package insert for your review of the drawing for Diclofenac Sodium. Please let me know if the chemist approves of this drawing.

Sincerely,

Rita Pendergrass

Rita Pendergrass
Sr. Administrative Assistant
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1 PAGE (S)

Draft

Labeling

SkyePharma

October 11, 2000

Kevin Darryl White
Project Manager (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

Via Facsimile - (301) 827-2075

Attention: Document Control Room

Dear Mr. White,

RE: NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%
Labeling Amendment – Package Insert

Reference is made to the package insert submitted to the above referenced NDA on October 3, 2000. Reference is also made to the subsequent discussions between the Agency and SkyePharma on October 6 and 10, 2000, in which inconsistencies were observed in the tables found in the package insert for Solaraze. Reference is also made to the information faxed to the Agency on October 10, 2000, in which the following were provided: (1) a description of COSTART codes with expanded terms for application site reactions were used to create the Integrated Summary of Safety (ISS) section of the NDA and Table 1 of the package insert, and (2) a revised Efficacy Table of the package insert.

The purpose of this amendment is to submit additional information to verify that the AEs listed in Table 1 of the package insert are correct. Background information and justification on AE reporting in the ISS and Table 1 of the Package Insert are provided in this amendment.

As discussed via telephone, SkyePharma is submitting this amendment to the Agency via fax, with hard copies being sent via Federal Express.

If there are any questions regarding this amendment, please contact me at (858) 625-2424, ext. 3231.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical Research and Regulatory Affairs

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

Background and Justification on AE Reporting in the Integrated Summary of Safety and Table 1 of Package Insert

In a pre-NDA meeting package (submitted November 21, 1997 by Hyal Pharmaceutical Corporation, former owner of NDA 21-005) that was discussed during the meeting held on December 15, 1997, the Sponsor proposed that adverse events (AEs) reported in the ISS would be based upon a modification of the COSTART terminology where Application Site Reactions (ASRs) are expanded into an additional layer of events, such as ASR-pruritus, ASR-rash, ASR-dry skin, etc. The AEs with expanded ASRs would be recorded separately from pruritus, rash and dryskin, etc. that were observed in areas outside the application site.

The study reports for each individual adequate and well-controlled Phase 3 trial were completed in 1996, prior to the pre-NDA meeting. The structure of the AE tables was different for each study report. Study CT-1101-03 presents AEs by COSTART major body system and commonly reported dermal AEs. Study CT-1101-07 presents AEs by COSTART major body system and application site reactions. Study CT-1101-04 presents AEs including 14 subclasses for skin and appendages, inclusive of an application site reaction category. The Sponsor's proposal at the pre-NDA meeting and description of COSTART terms with expanded ASRs in the ISS section of the NDA were made to standardize reporting of AEs for the three studies and provide specificity to application site reactions.

Based on the discussions from the pre-NDA meeting, the Integrated Summary of Safety (ISS) section of the NDA (Vol. 45, page 105), *Section 8.5.1.2 Recording and Classifying Adverse Events*, describes the COSTART terms with the expanded ASRs to give more detailed information on AEs occurring on the application site. *Table 8.5.2.3.1* of the ISS (NDA Vol. 45, page 111-117) lists all AEs obtained from the three adequate and well-controlled Phase 3 trials, in which AEs are reported with the expanded ASRs. (For reviewer convenience, referenced ISS pages are provided in **Attachment 1**.)

To verify the data contained in the ISS and Table 1 of the package insert, the COSTART terms with expanded ASRs were applied to each study report. The AEs for each study report (CT-1101-03: 90-day treatment, CT-1101-07: 90-day treatment, and CT-1101-04: 30/60-day treatment) using the COSTART terms with the expanded ASRs are provided in **Attachments 2, 3, and 5**, respectively. **Attachment 4** is a sum of the AEs from the two 90-day treatment trials, CT-1101-03 and CT-1101-07. Attachments 4 and 5 are the basis for Table 1 of the package insert. A summary of all AEs reported during the three studies (appearing in Attachments 2, 3, and 5) are provided in **Attachment 6**, which supports the data reported in the ISS of the NDA that is presented in Attachment 1. Attachments 1 – 6 report the number of patients with one or more AEs.

Provided in **Attachment 7** is a patient listing sorted by COSTART with the expanded ASR terms, as used to generate the AE tables for Attachments 2 – 6. The listing also includes a separate column for COSTART without the expanded ASR terms used in the original study reports.

The package insert has been revised to correct the errors in the Efficacy Table, as follows:

- Study 2 Back of Hand – Vehicle: had the correct percentage value, but had an incorrect numerator of – The correct numerator is 3.
- All Data Combined for Forehead – Solaraze: had the correct percentage value, but had an incorrect numerator of – The correct numerator is 43.
- Study 3 – denominators have been added

Data contained in Table 1 of the Package insert has not been changed from the previous version submitted on October 3, 2000. The "Other" category in Table 1 was moved to the bottom of the table, as requested by the Agency during the October 6, 2000 teleconference. A clean copy of the package insert is provided in **Attachment 8**.

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

NDA Volume 45, pages 105, 111-117 (ISS section)

APPEARS THIS WAY
ON ORIGINAL

8.5.1 Overview of the Integrated Summary of Safety

8.5.1.1 Definitions and Conventions Used for Safety Data

Definitions used for recording and classifying adverse events (AEs) and laboratory abnormalities considered to be adverse events have been taken from the ICH guidelines. COSTART terminology has been utilized for classification of AEs by body system.

8.5.1.2 Recording and Classifying Adverse Events

In these studies, adverse events were volunteered by subjects, observed by investigators and/or elicited with a question by the investigator. All adverse events (including abnormal laboratory values deemed AE's by the investigator) were recorded on appropriate case report forms (CRF) or adverse event forms. The investigator determined both the severity and the causality of the events on a blinded basis but had the ability to unblind by patient if he/she felt it necessary. The Hyal Director of Clinical Services reviewed the serious adverse events to determine agreement or disagreement with an investigator's assessment of causality in a blinded fashion. Only questions regarding an investigator's assessment of causality were taken to the Hyal Medical Director for final determination. This occurred in only one case and is discussed in the serious adverse event section.

COSTART terminology was used but did not lend itself to a dermal adverse event profile (e.g. numbing of the treated skin area was originally recorded as *paresthesia* under the Nervous System COSTART body system). Creation of a safety profile which made sense for a dermal product was undertaken based upon a review of the AE database in September 1997 after completion of all actinic keratosis (AK) clinical studies. A reclassification of COSTART terms referring to local dermal reactions with the new term 'Application Site Reaction' (ASR) under the heading Skin and Appendages was made. *Paresthesia* (eg. changes in skin sensation at treatment application sites), for example, was reclassified under Skin and Appendages as an ASR rather than under Nervous System provided the case report form was clear as to where the event occurred. Any event that could not be verified as being a localized, cutaneous reaction by reference to the CRF was left as originally coded. All studies except one (study #ST-5101-AUS-01) underwent this reclassification and the database was updated accordingly in the ongoing Hyal Safety Database of November 1997.

8.5.1.4 Presentation of Drug-related Adverse Events

A Safety Database has been developed from safety information of patients treated with 3% diclofenac gel, vehicle or comparator drug for indications that have been pursued. This database currently contains information from 2230 patients, 1209 treated with 3% diclofenac gel, 911 treated with vehicle gel and 110 treated with Voltaren Emulgel (Ciba Product - topical 1% diclofenac cream not approved in North America). The indications studied and the numbers of patients treated within each indication are: ——————— (684 active, 550 vehicle, 110 Voltaren topical cream). ——————————— (181 active, 62 vehicle), and *Treatment of Actinic Keratoses* (344 active, 299 vehicle). A table of studies completed for indications other than AK can be found in section 8.9, Table 8.9.1. This integrated Summary of Safety is based primarily upon adverse events included in the Safety Database as reported in the AK clinical studies which are presented in Table 8.5.2.

8.5.2.3 Adverse Events and Relationship to Study Medication:
All adverse events (AEs) experienced by patients participating in the three adequate and well controlled clinical trials (AWC studies; CT-1101-03, CT-1101-04, and CT-1101-07) at the dosing recommended in the proposed labeling are tabulated in **Table 8.5.2.3.1.**

Of the 423 patients evaluable for safety (any patient that used Solarase (Diclofenac, D) or Vehicle (V)), 211 were Diclofenac treated patients and 212 were Vehicle treated. Eighty-seven percent of the Diclofenac treated patients (183 patients) and 84%(178 patients) of the Vehicle treated patients experienced one or more AEs during the study, whether or not related to the medication. **Table 8.5.2.3** also displays event frequency and causality. Three categories are shown: **r**: all related AEs include *probable, possible, definite* and *yes;* **ur**: all unrelated AEs include *unlikely;* and **U**: all AEs for which causality is *unknown*. The bracketed percentages use as their denominator the total population within the treatment group.

Table 8.5.2.3.1: All Adverse Events by Treatment Group and by Relationship To Study Medication (no. of patients experiencing AE)

BODY SYSTEM	Diclofenac n=211		Vehicle n=212	
	no.(%)	Causality	no.(%)	Causality
Procedure	1 (0)	1 r	3 (1)	3 nr
BODY AS A WHOLE				
Abdominal pain	2 (1)	1 nr, 1 r	0	0
Accidental injury	5 (2)	4 nr, 1 r	2 (1)	2 nr
Allergic reaction	1 (0)	1 nr	3 (1)	3 nr
Asthenia	2 (1)	1 nr, 1 u	1 (0)	1 nr
Back pain	4 (2)	1 u, 3 nr	2 (1)	2 nr
Chills	0 (0)	0	1 (0)	1 nr
Chest pain	2 (1)	1 u, 1nr	0	0
Eye pain	0	0	1 (0)	1 r
Face edema	1 (0)	1 r	0	0
Fever	1 (0)	1 r	1 (0)	1 nr
Flu syndrome	6 (3)	1 u, 5 nr	8 (4)	8 nr
Headache	8 (4)	8 nr	12 (6)	10 nr, 2 r
HIV positive	0	0	1 (0)	1 nr
Infection	7 (3)	7 nr	10 (5)	2 u, 8 nr
Malaise	0	0	1 (0)	1 nr
Pain	3 (1)	3 nr	2 (1)	2 nr
Neck pain	3 (1)	1 u, 2 nr	0	0
Photosensitivity reaction	1 (0)	1 r	0	0
MUSCULOSKELETAL				
Arthalgia	1 (0)	1 nr	2 (1)	2 nr
Arthritis	0	0	1 (0)	1 nr
Arthrosis	1 (0)	1 nr	0	0
Myalgia	4 (2)	4 nr	1 (0)	1 nr

Table 8.5.2.3.1: All Adverse Events by Treatment Group and by Relationship To Study Medication (no. of patients experiencing AE)

BODY SYSTEM	Diclofenac n=211		Vehicle n=212	
	no.(%)	Causality	no.(%)	Causality
CARDIOVASCULAR				
Angina pectoris	0	0	1 (0)	1 u
Cardiomyopathy	1 (0)	1 nr	0	0
Coronary artery disorder	1 (0)	1 nr	0	0
Congestive heart failure	0	0	1 (0)	1 nr
Hypertension	3 (1)	3 nr	0	0
Migraine	1 (0)	1 nr	1 (0)	1 nr
Phlebitis	0	0	1 (0)	1 nr
METABOLIC AND NUTRITIONAL				
BUN increased	0	0	1 (0)	1 nr
Creatine phosphokinase >	4 (2)	4 nr	1 (0)	1 nr
Creatinine >	1 (0)	1 nr	2 (1)	2 nr
Edema	0	0	1 (0)	1 nr
γ-glutamyl transpeptidase >	1 (0)	1 nr	0	0
Hypercholesteremia	1 (0)	1 nr	1 (0)	1 u
Hyperglycemia	1 (0)	1 nr	1 (0)	1 nr
Lactic dehydrogenase >	1 (0)	1 nr	0	0
SGOT>	3 (1)	3 nr	0	0
SGPT>	2 (1)	2 nr	0	0
Weight loss	1 (0)	1 u	0	0
NERVOUS				
Anxiety	0	0	2 (1)	2 nr
Dizziness	0	0	5 (2)	5 nr
Hypokinesia	1 (0)	1 nr	0	0
Hypertonia	1 (0)	1 nr	0	0
Insomnia	0	0	1 (0)	1 r
Nervousness	0	0	1 (0)	1 nr
Somnolence	1 (0)	1 nr	0	0
Vertigo	1 (0)	1 nr	0	0
DIGESTIVE				
Colitis	1 (0)	1 nr	0	0
Constipation	0	0	2 (1)	2 nr
Diarrhea	3 (1)	2 nr, 1 r	4 (2)	4 nr
Dyspepsia	4 (2)	4 nr	4 (2)	1u, 3 nr
Nausea	2 (1)	1 nr, 1 r	1 (0)	1 nr
Rectal disorder	2 (1)	2 nr	1 (0)	1 nr
Ulcerative stomatitis	1 (0)	1 nr	0	0
Stomach ulcer	0	0	1 (0)	1 nr
Mouth ulcer	1 (0)	1 r	0	0
Vomiting	1 (0)	1 nr	1 (0)	1 nr

Table 8.5.2.3.1: All Adverse Events by Treatment Group and by Relationship To Study Medication (no. of patients experiencing AE)

BODY SYSTEM	Diclofenac n=211		Vehicle n=212	
	no.(%)	Causality	no.(%)	Causality
UROGENITAL				
Dysmenorrhea	0	0	1 (0)	1 nr
Epididymitis	0	0	1 (0)	1 nr
Hematuria	2 (1)	2 nr	2 (1)	2 nr
Nephritis	1 (0)	1 nr	0	0
Prostatic carcinoma	1 (0)	1 nr	0	0
Pyuria	0	0	1 (0)	1 nr
Urinary frequency	0	0	1 (0)	1 nr
Urinary tract infection	1 (0)	1 nr	1 (0)	1 nr
HEMIC AND LYMPHATICS				
Eosinophilia	1 (0)	1 nr	0	0
Leukocytosis	0	0	1 (0)	1 nr
Lymphadenopathy	0	0	1 (0)	1 r
RESPIRATORY				
Asthma	1 (0)	1 nr	0	0
Bronchitis	1 (0)	1 nr	3 (1)	1u, 2 nr
Cough Increased	1 (0)	1 nr	1 (0)	1 nr
Dyspnea	3 (1)	2 nr, 1 r	0	0
Pharyngitis	4 (2)	4 nr	9 (4)	9 nr
Pneumonia	1 (0)	1 nr	2 (1)	2 nr
Rhinitis	3 (1)	3 nr	3 (1)	3 nr
Sinusitis	2 (1)	1 nr, 1 r	0	0

Table 8.5.2.3.1: All Adverse Events by Treatment Group and by Relationship To Study Medication (no. of patients experiencing AE)

BODY SYSTEM	Diclofenac n=211		Vehicle n=212	
	no.(%)	Causality	no.(%)	Causality
SKIN AND APPENDAGES				
Acne	0	0	2 (1)	2 nr
Contact dermatitis	1 (0)	1 r	0	0
Herpes simplex	0	0	2 (1)	2 nr
Skin hypertrophy	1 (0)	1 nr	1 (0)	1 nr
Skin nodule	0	0	1 (0)	1 r
Skin carcinoma	2 (1)	2 nr	7 (3)	6 nr, 1 r
Pain	2 (1)	2 nr	2 (1)	2 r
Paresthesia	1 (0)	1 r	0	0
Pruritus	7 (3)	3 nr, 4 r	6 (3)	3 nr, 3 r
Rash	5 (2)	2 nr, 3 r	7 (3)	5 nr, 2 r
Maculopapular rash	0	0	1 (0)	1 r
Seborrhea	1 (0)	1 r	0	0
Dry skin	3 (1)	1 nr, 2 r	3 (1)	3 nr
Skin ulcer	2 (1)	2 r	0	0
Urticaria	1 (0)	1 nr	0	0
Application site reaction (ASR)				
Acne	1 (0)	1 r	2 (1)	2 r
Alopecia	2 (1)	2 r	1 (0)	1 r
Skin carcinoma	1 (0)	1 nr	0	0
Contact dermatitis	47 (23)	47 r	6 (3)	6 r
Dry skin	49 (23)	1 nr, 48 r	30 (14)	30 r
Exfoliation (scaling)	33 (16)	33 r	17 (8)	17 r
Edema	5 (2)	5 r	0	0
Hyperesthesia	3 (1)	3 r	1 (0)	1 r
Hypertonia	0	0	1 (0)	1 r
Skin hypertrophy	2 (1)	2 r	0	0
Lacrimation disorder	1 (0)	1 r	0	0
Pain	52 (25)	52 r	52 (25)	1 nr, 51 r
Paresthesia	35 (17)	35 r	32 (15)	1 nr, 31 r
Photosensitivity	3 (1)	1 nr, 2 r	1 (0)	1 r
Pruritus	93 (44)	1 nr, 92 r	105 (50)	105 r
Rash	83 (39)	2 nr, 81 r	39 (18)	39 r
Maculopapular rash	2 (1)	2 r	0	0
Purpuric rash	1 (0)	1 r	0	0

Table 8.5.2.3.1: All Adverse Events by Treatment Group and by Relationship To Study Medication (no. of patients experiencing AE)

BODY SYSTEM	Diclofenac n=211		Vehicle n=212	
	no.(%)	Causality	no.(%)	Causality
ASR-Vesiculobullous rash	4 (2)	4 r	1 (0)	1 r
Vasodilation	0	0	1 (0)	1 r
SPECIAL SENSES				
Conjunctivitis	5 (2)	1 nr, 4 r	1 (0)	1 nr
Ear pain	0	0	1 (0)	1 nr
Eye pain	2 (1)	2 r	0	0

Of the 211 patients treated with Diclofenac, 172 (82%) experienced AE's involving skin and the application site compared to 160 (75%) Vehicle treated patients. Thirteen Diclofenac treated patients (6%) experienced AE's classified as *unrelated* to treatment while 170 patients (81%) experienced AEs rated as *related*.
In the Vehicle treated group, there were 153 patients (73%) who experienced AEs rated as *related*, and 25 patients (12%) with AEs rated as *unrelated*.

Application site reactions (ASRs) were the most frequent related AEs in both Diclofenac and Vehicle treated groups. Of note, four reactions, *contact dermatitis*, *rash*, *dry skin* and *exfoliation* (scaling) were significantly more prevalent in the Diclofenac group than in Vehicle treated patients.

Several AEs were notable. In study CT-1101-03, patient #1017 (Diclofenac treated, D) intermittently experienced 'puffy eyes' of moderate intensity coded as *face edema*. The reaction began about two months after treatment had been initiated. This patient also was reported to have had an intermittent vesiculobullous rash with itching, redness, scabbing, erythematous papules, and burning, at the application site, which, along with the 'puffy eyes' event, caused treatment discontinuation. About a month after end of treatment, the patient was rechallenged in a Provocative Use Test (PUT) after the reactions had apparently subsided. After seven days exposure to the Diclofenac gel on the upper arm, mild erythema was seen along with a few vesicles, suggestive of a mild irritant reaction. However, a flare of dermatitis was described as having simultaneously occurred at the previously treated site (scalp), along with itchy eyes and nose, indicating possible allergy. Upon cessation of therapy all reactions were cleared. This patient's swollen eyelids likely represents a reaction to medication getting on the skin of the eyelids. The same patient six months later participated in a 48 hour patch test of the finished product and of diclofenac containing test items which was negative.

Several other patients experienced vesiculobullous rash. They were patients #3010 (study #CT-1101-03, Diclofenac treated, D), #3015 (study #CT-1101-03, D), # 053 (study #CT-1101-07, D) and #105 (study #CT-1101-07, Vehicle treated, V).

Patient #3010 experienced *tenderness*, localized *vesiculitis* (vesiculation), *pruritus*, *exfoliation*,

periodic *edema*, as well as excessive *lacrimation*, all of an intermittent nature, being mild in intensity, starting several days after intitiating treatment. The treatment site was the forehead. No action was taken. Prior to cessation of therapy complete resolution of these local AEs occurred. A PUT was not performed.

Patient #3015 reported intermittent *vesiculation*, *erythema*, *irritation*, *scaliness* (crusting) at the treatment site (right forehead), and *hives* (neck) reported by the patient over a four day period, which were rated as *unrelated* to study medication (possible insect bite). The local reactions started about six weeks after intitiating treatment and were mild to moderate in intensity, causing discontinuation of treatment but were completely resolved with cessation of treatment. A PUT was completed with negative findings.

Patient #053 reported *stinging*, *redness*, *blistering*, and *peeling* occurring intermittently on the left temple, of mild to moderate intensity, starting about three days after initiating the treatment. No action was taken. Just prior to cessation of therapy the reactions were cleared. A PUT was not performed.

The vesiculobullous reaction reported in patient #105 (Vehicle treated) was characterized by *stinging*, '*tightness*', and *blistering* at the application site (forearm). The reactions were mild in intensity. Resolution was complete prior to cessation of treatment. The blistering episode lasted only one day (a comment made in the diary "tops of cancers looks like a blister") having occurred about nine days after intitiating treatment. A PUT was not performed.

In summary, these patients demonstrate that vesiculobullous reactions may occur in response to Diclofenac or its gel vehicle. They tend to be limited to the treatment area, and resolve both during treatment continuation or after discontinuation. One of the reactions listed earlier (patient #1017) suggests the possibility of allergic contact dermaitis.

Certain events were coded as *photosensitivity reactions*; patient #1014 (study #CT-1101-03, Diclofenac treated, D) was coded under Body as a Whole and patients #1005 (study #CT-1101-03, D), #053 (study #CT-1101-07, D), #1014 (study #CT-1101-07, D) in the Diclofenac treated group and patient #4019 (study #CT-1101-04, Vehicle treated, V) were coded with local ASRs.

Patient #1014 from study #CT-1101-03 reported "*working in the sun for 2 hours got slightly sunburned*". The event, on the face, was mild in intensity, and resolved in two days with no action being taken. Patient #1005 reported a *sunburned forehead* (the application site) over a three day period, of mild intensity, which cleared with no action taken. In patient #053, the solar reaction occurred on the forehead (the application site) over one day, was mild and no action was taken. Patient #1014 from study CT-1101-07 reported having a "*more sensitive feeling to the sun in this area*" (on the forehead, the application site) for the duration of treatment exposure (58 days). It was rated as mild and cleared upon cessation of treatment. No action was taken in response to this event. Vehicle treated patient #4019 from study CT-1101-04 reported "*skin sensitive in sun*" for four weeks of the treatment period, an event of mild intensity with no action having been taken, the outcome complete recovery upon cessation of therapy.

Two types of possibly sun-related events occurred. One was a localized sun burn of mild clinical

consequence and the other was a sensation of the skin being sensitive to the sun without any clinical manifestations.

One patient was coded with a severe, purpuric rash (patient #3005 in study #CT-1101-03, D treated) at two of the three treatment application sites (on left and right hands but not on the central face). It was coded as such because the individual events (*dermatitis and pruritus, fissures, erythema, hemorrhage, exfoliation*) suggested the term according to COSTART. However, the term is misleading. The patient did not have severe purpura but superficial bleeding from a fissure secondary to eczema. The patient was reported to have used chemical cleansers and solvents which apparently triggered the eczematous type reaction which, in turn, resulted in discontinuation of treatment.

ATTACHMENT 2

Clinical Study CT-1101-03 (90-day treatment)

using

COSTART terms with expanded ASRs

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All Adverse events reported during CT-1101-03 trial

Body & Costart	CT-1101-03 * Gel Vehicle, N (% N=58	Solaraze, N (%) N = 58
OTHER	2 (3)	0 (0)
PROCEDURE	2 (3)	0 (0)
BODY AS A WHOLE	12 (20)	12 (21)
ABDOMINAL PAIN	0 (0)	1 (2)
ACCIDENTAL INJURY	1 (2)	3 (5)
ALLERGIC REACTION	3 (5)	0 (0)
ASTHENIA	0 (0)	1 (2)
BACK PAIN	2 (3)	2 (3)
FACE EDEMA	0 (0)	1 (2)
FEVER	1 (2)	0 (0)
FLU SYNDROME	3 (5)	1 (2)
HEADACHE	5 (9)	4 (7)
INFECTION	2 (3)	1 (2)
PAIN	0 (0)	1 (2)
PHOTOSENSITIVITY REACTION	0 (0)	1 (2)
CARDIOVASCULAR SYSTEM	0 (0)	2 (3)
HYPERTENSION	0 (0)	1 (2)
MIGRAINE	0 (0)	1 (2)
DIGESTIVE SYSTEM	6 (10)	5 (9)
CONSTIPATION	2 (3)	0 (0)
DIARRHEA	3 (5)	2 (3)
DYSPEPSIA	2 (3)	3 (5)
NAUSEA	1 (2)	0 (0)
RECTAL DISORDER	1 (2)	1 (2)
VOMITING	1 (2)	0 (0)
HEMIC AND LYMPHATIC SYSTEM	1 (2)	1 (2)
EOSINOPHILIA	0 (0)	1 (2)
LEUKOCYTOSIS	1 (2)	0 (0)
METABOLIC AND NUTRITIONAL DISORDERS	2 (3)	8 (14)
BUN INCREASED	1 (2)	0 (0)
CREATINE PHOSPHOKINASE INCREASED	1 (2)	4 (7)
CREATININE INCREASED	1 (2)	0 (0)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0 (0)	1 (2)
HYPERCHOLESTEREMIA	0 (0)	1 (2)
HYPERGLYCEMIA	0 (0)	1 (2)
LACTIC DEHYDROGENASE INCREASED	0 (0)	1 (2)
SGOT INCREASED	0 (0)	3 (5)
SGPT INCREASED	0 (0)	2 (3)
MUSCULOSKELETAL SYSTEM	3 (5)	2 (3)
ARTHRALGIA	2 (3)	0 (0)
ARTHRITIS	1 (2)	0 (0)
MYALGIA	0 (0)	2 (3)

* US-AK study

All Adverse events reported during CT-1101-03 trial

Body & Costart	CT-1101-03 * Gel Vehicle, N (% N=69	Solaraze, N (%) N = 58
NERVOUS SYSTEM	4 (7)	2 (3)
DIZZINESS	4 (7)	0 (0)
HYPERTONIA	0 (0)	1 (2)
NERVOUSNESS	1 (2)	0 (0)
SOMNOLENCE	0 (0)	1 (2)
VERTIGO	0 (0)	1 (2)
RESPIRATORY SYSTEM	6 (9)	4 (7)
BRONCHITIS	1 (2)	1 (2)
COUGH INCREASED	1 (2)	0 (0)
DYSPNEA	0 (0)	1 (2)
PHARYNGITIS	3 (5)	2 (3)
PNEUMONIA	1 (2)	0 (0)
RHINITIS	1 (2)	1 (2)
SKIN AND APPENDAGES	40 (66)	47 (81)
APPLICATION SITE REACTION	39 (66)	46 (79)
CONTACT DERMATITIS	1 (2)	7 (12)
DRY SKIN	7 (12)	15 (26)
EDEMA	0 (0)	3 (5)
EXFOLIATION	8 (14)	15 (26)
HYPERESTHESIA	0 (0)	1 (2)
HYPERTONIA	1 (2)	0 (0)
LACRIMATION DISORDER	0 (0)	1 (2)
MACULOPAPULAR RASH	0 (0)	1 (2)
PAIN	15 (25)	18 (31)
PARESTHESIA	12 (20)	12 (21)
PHOTOSENSITIVITY REACTION	0 (0)	1 (2)
PRURITUS	28 (48)	31 (63)
PURPURIC RASH	0 (0)	1 (2)
RASH	11 (19)	26 (46)
VASODILATATION	1 (2)	0 (0)
VESICULOBULLOUS RASH	0 (0)	3 (5)
DRY SKIN	0 (0)	3 (5)
PAIN	0 (0)	1 (2)
PARESTHESIA	0 (0)	1 (2)
PRURITUS	1 (2)	4 (7)
RASH	0 (0)	3 (5)
SEBORRHEA	0 (0)	1 (2)
SKIN CARCINOMA	1 (2)	2 (3)
SKIN HYPERTROPHY	1 (2)	1 (2)
SKIN ULCER	0 (0)	1 (2)
URTICARIA	0 (0)	1 (2)
SPECIAL SENSES	1 (2)	4 (7)

* US-AK study

All Adverse events reported during CT-1101-03 trial

Body & Costart	CT-1101-03 * Gel Vehicle, N (% N=59	Solaraze, N (%) N = 58
CONJUNCTIVITIS	1 (2)	3 (5)
EYE PAIN	0 (0)	2 (3)
UROGENITAL SYSTEM	6 (10)	2 (3)
DYSMENORRHEA	1 (2)	0 (0)
EPIDIDYMITIS	1 (2)	0 (0)
HEMATURIA	1 (2)	2 (3)
PYURIA	1 (2)	0 (0)
URINARY FREQUENCY	1 (2)	0 (0)
URINARY TRACT INFECTION	1 (2)	0 (0)

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* US-AK study

ATTACHMENT 3

Clinical Study CT-1101-07 (90-day treatment)

using

COSTART terms with expanded ASRs

All Adverse events reported during CT-1101-07 trial

Body & Costart	CT-1101-07 * Gel Vehicle, N (% N=55	Solaraze, N (%) N = 56
OTHER	1 (2)	0 (0)
PROCEDURE	1 (2)	0 (0)
BODY AS A WHOLE	8 (15)	11 (20)
ACCIDENTAL INJURY	1 (2)	1 (2)
ALLERGIC REACTION	0 (0)	1 (2)
ASTHENIA	0 (0)	1 (2)
CHEST PAIN	0 (0)	1 (2)
FEVER	0 (0)	1 (2)
FLU SYNDROME	1 (2)	0 (0)
HEADACHE	2 (4)	4 (7)
INFECTION	4 (7)	4 (7)
MALAISE	1 (2)	0 (0)
NECK PAIN	0 (0)	2 (4)
PAIN	2 (4)	1 (2)
CARDIOVASCULAR SYSTEM	1 (2)	1 (2)
CARDIOMYOPATHY	0 (0)	1 (2)
CONGESTIVE HEART FAILURE	1 (2)	0 (0)
CORONARY ARTERY DISORDER	0 (0)	1 (2)
DIGESTIVE SYSTEM	3 (6)	2 (4)
DYSPEPSIA	2 (4)	0 (0)
MOUTH ULCERATION	0 (0)	1 (2)
NAUSEA	0 (0)	1 (2)
STOMACH ULCER	1 (2)	0 (0)
VOMITING	0 (0)	1 (2)
MUSCULOSKELETAL SYSTEM	1 (2)	1 (2)
MYALGIA	1 (2)	1 (2)
NERVOUS SYSTEM	2 (4)	0 (0)
ANXIETY	1 (2)	0 (0)
DIZZINESS	1 (2)	0 (0)
RESPIRATORY SYSTEM	2 (4)	4 (7)
DYSPNEA	0 (0)	1 (2)
PHARYNGITIS	1 (2)	0 (0)
RHINITIS	1 (2)	1 (2)
SINUSITIS	0 (0)	2 (4)
SKIN AND APPENDAGES	41 (75)	51 (91)
ACNE	1 (2)	0 (0)
APPLICATION SITE REACTION	41 (75)	50 (89)
ACNE	0 (0)	1 (2)
ALOPECIA	1 (2)	1 (2)
CONTACT DERMATITIS	3 (6)	30 (54)
DRY SKIN	12 (22)	14 (25)
EXFOLIATION	7 (13)	12 (21)

* Del Rosso study

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All Adverse events reported during CT-1101-07 trial

Body & Costart	CT-1101-07 * Gel Vehicle, N (% N=55	Solaraze, N (% N = 56
HYPERESTHESIA	1 (2)	2 (4)
PAIN	19 (35)	12 (21)
PARESTHESIA	11 (20)	11 (20)
PHOTOSENSITIVITY REACTION	0 (0)	2 (4)
PRURITUS	23 (42)	28 (50)
RASH	8 (15)	24 (43)
SKIN CARCINOMA	0 (0)	1 (2)
VESICULOBULLOUS RASH	1 (2)	1 (2)
RASH	0 (0)	1 (2)
SKIN CARCINOMA	1 (2)	0 (0)
SPECIAL SENSES	1 (2)	1 (2)
CONJUNCTIVITIS	0 (0)	1 (2)
EAR PAIN	1 (2)	0 (0)
UROGENITAL SYSTEM	0 (0)	3 (5)
NEPHRITIS	0 (0)	1 (2)
PROSTATIC CARCINOMA	0 (0)	1 (2)
URINARY TRACT INFECTION	0 (0)	1 (2)

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* Del Rosso study

ATTACHMENT 4

Overall AEs for CT-1101-03 and CT-1101-07 (90-day treatment)

using

COSTART terms with expanded ASRs

All Adverse events reported during 90-day treatment

Body & Costart	90-day Treatment ** Del Vehicle, N (% N=59	Solaraze, N (%) N = 58
OTHER	3 (3)	0 (0)
PROCEDURE	3 (3)	0 (0)
BODY AS A WHOLE	20 (18)	23 (20)
ABDOMINAL PAIN	0 (0)	1 (1)
ACCIDENTAL INJURY	2 (2)	4 (4)
ALLERGIC REACTION	3 (3)	1 (1)
ASTHENIA	0 (0)	2 (2)
BACK PAIN	2 (2)	2 (2)
CHEST PAIN	0 (0)	1 (1)
CHILLS	0 (0)	0 (0)
EYE PAIN	0 (0)	0 (0)
FACE EDEMA	0 (0)	1 (1)
FEVER	1 (1)	1 (1)
FLU SYNDROME	4 (4)	1 (1)
HEADACHE	7 (6)	8 (7)
INFECTION	6 (5)	5 (4)
MALAISE	1 (1)	0 (0)
NECK PAIN	0 (0)	2 (2)
PAIN	2 (2)	2 (2)
PHOTOSENSITIVITY REACTION	0 (0)	1 (1)
CARDIOVASCULAR SYSTEM	1 (1)	3 (3)
CARDIOMYOPATHY	0 (0)	1 (1)
CONGESTIVE HEART FAILURE	1 (1)	0 (0)
CORONARY ARTERY DISORDER	0 (0)	1 (1)
HYPERTENSION	0 (0)	1 (1)
MIGRAINE	0 (0)	1 (1)
PHLEBITIS	0 (0)	0 (0)
DIGESTIVE SYSTEM	9 (8)	7 (6)
CONSTIPATION	2 (2)	0 (0)
DIARRHEA	3 (3)	2 (2)
DYSPEPSIA	4 (4)	3 (3)
MOUTH ULCERATION	0 (0)	1 (1)
NAUSEA	1 (1)	1 (1)
RECTAL DISORDER	1 (1)	1 (1)
STOMACH ULCER	1 (1)	0 (0)
VOMITING	1 (1)	1 (1)
HEMIC AND LYMPHATIC SYSTEM	1 (1)	1 (1)
EOSINOPHILIA	0 (0)	1 (1)
LEUKOCYTOSIS	1 (1)	0 (0)
METABOLIC AND NUTRITIONAL DISORDERS	2 (2)	8 (7)
BUN INCREASED	1 (1)	0 (0)
CREATINE PHOSPHOKINASE INCREASED	1 (1)	4 (4)

** US-AK study and Del Rosso study

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All Adverse events reported during 90-day treatment

Body & Costart	90-day Treatment ** Gel Vehicle, N (% N=59	Solaraze, N (%) N = 58
CREATININE INCREASED	1 (1)	0 (0)
EDEMA	0 (0)	0 (0)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0 (0)	1 (1)
HYPERCHOLESTEREMIA	0 (0)	1 (1)
HYPERGLYCEMIA	0 (0)	1 (1)
LACTIC DEHYDROGENASE INCREASED	0 (0)	1 (1)
SGOT INCREASED	0 (0)	3 (3)
SGPT INCREASED	0 (0)	2 (2)
MUSCULOSKELETAL SYSTEM	4 (4)	3 (3)
ARTHRALGIA	2 (2)	0 (0)
ARTHRITIS	1 (1)	0 (0)
ARTHROSIS	0 (0)	0 (0)
MYALGIA	1 (1)	3 (3)
NERVOUS SYSTEM	6 (5)	2 (2)
ANXIETY	1 (1)	0 (0)
DIZZINESS	5 (4)	0 (0)
HYPERTONIA	0 (0)	1 (1)
HYPOKINESIA	0 (0)	0 (0)
NERVOUSNESS	1 (1)	0 (0)
SOMNOLENCE	0 (0)	1 (1)
VERTIGO	0 (0)	1 (1)
RESPIRATORY SYSTEM	7 (6)	8 (7)
ASTHMA	0 (0)	0 (0)
BRONCHITIS	1 (1)	1 (1)
COUGH INCREASED	1 (1)	0 (0)
DYSPNEA	0 (0)	2 (2)
PHARYNGITIS	4 (4)	2 (2)
PNEUMONIA	1 (1)	0 (0)
RHINITIS	2 (2)	2 (2)
SINUSITIS	0 (0)	2 (2)
SKIN AND APPENDAGES	81 (71)	98 (86)
ACNE	1 (1)	0 (0)
APPLICATION SITE REACTION	80 (70)	96 (84)
ACNE	0 (0)	1 (1)
ALOPECIA	1 (1)	1 (1)
CONTACT DERMATITIS	4 (4)	37 (33)
DRY SKIN	19 (17)	29 (25)
EDEMA	0 (0)	3 (3)
EXFOLIATION	15 (13)	27 (24)
HYPERESTHESIA	1 (1)	3 (3)
HYPERTONIA	1 (1)	0 (0)
LACRIMATION DISORDER	0 (0)	1 (1)

** US-AK study and Del Rosso study

All Adverse events reported during 90-day treatment

Body & Costart	90-day Treatment ** Gel Vehicle, N (% N=59	Solaraze, N (%) N = 58
MACULOPAPULAR RASH	0 (0)	1 (1)
PAIN	34 (30)	30 (26)
PARESTHESIA	23 (20)	23 (20)
PHOTOSENSITIVITY REACTION	0 (0)	3 (3)
PRURITUS	51 (45)	59 (52)
PURPURIC RASH	0 (0)	1 (1)
RASH	19 (17)	52 (46)
SKIN CARCINOMA	0 (0)	1 (1)
VASODILATATION	1 (1)	0 (0)
VESICULOBULLOUS RASH	1 (1)	4 (4)
CONTACT DERMATITIS	0 (0)	0 (0)
DRY SKIN	0 (0)	3 (3)
HERPES SIMPLEX	0 (0)	0 (0)
MACULOPAPULAR RASH	0 (0)	0 (0)
PAIN	0 (0)	1 (1)
PARESTHESIA	0 (0)	1 (1)
PRURITUS	1 (1)	4 (4)
RASH	0 (0)	4 (4)
SEBORRHEA	0 (0)	1 (1)
SKIN CARCINOMA	2 (2)	2 (2)
SKIN HYPERTROPHY	1 (1)	1 (1)
SKIN NODULE	0 (0)	0 (0)
SKIN ULCER	0 (0)	1 (1)
URTICARIA	0 (0)	1 (1)
SPECIAL SENSES	2 (2)	5 (4)
CONJUNCTIVITIS	1 (1)	4 (4)
EAR PAIN	1 (1)	0 (0)
EYE PAIN	0 (0)	2 (2)
UROGENITAL SYSTEM	6 (5)	5 (4)
DYSMENORRHEA	1 (1)	0 (0)
EPIDIDYMITIS	1 (1)	0 (0)
HEMATURIA	1 (1)	2 (2)
NEPHRITIS	0 (0)	1 (1)
PROSTATIC CARCINOMA	0 (0)	1 (1)
PYURIA	1 (1)	0 (0)
URINARY FREQUENCY	1 (1)	0 (0)
URINARY TRACT INFECTION	1 (1)	1 (1)

** US-AK study and Del Rosso study

ATTACHMENT 5

Clinical Study CT-1101-04 (30- and 60-day treatment)

using

COSTART terms with expanded ASRs

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All Adverse events reported during 30-day treatment in CT-1101-04 trial

Body & Costart	30-day Treatment * Gel Vehicle, N (% N=49	Solaraze, N (%) N = 49
OTHER	0 (0)	1 (2)
PROCEDURE	0 (0)	1 (2)
BODY AS A WHOLE	5 (10)	2 (4)
ACCIDENTAL INJURY	0 (0)	1 (2)
ASTHENIA	1 (2)	0 (0)
FLU SYNDROME	1 (2)	0 (0)
HEADACHE	2 (4)	0 (0)
HIV TEST POSITIVE	1 (2)	0 (0)
INFECTION	1 (2)	0 (0)
NECK PAIN	0 (0)	1 (2)
CARDIOVASCULAR SYSTEM	1 (2)	1 (2)
ANGINA PECTORIS	1 (2)	0 (0)
HYPERTENSION	0 (0)	1 (2)
DIGESTIVE SYSTEM	1 (2)	3 (6)
COLITIS	0 (0)	1 (2)
DIARRHEA	1 (2)	0 (0)
NAUSEA	0 (0)	1 (2)
RECTAL DISORDER	0 (0)	1 (2)
ULCERATIVE STOMATITIS	0 (0)	1 (2)
HEMIC AND LYMPHATIC SYSTEM	1 (2)	0 (0)
LYMPHADENOPATHY	1 (2)	0 (0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0)	1 (2)
WEIGHT LOSS	0 (0)	1 (2)
NERVOUS SYSTEM	1 (2)	0 (0)
INSOMNIA	1 (2)	0 (0)
RESPIRATORY SYSTEM	4 (8)	1 (2)
BRONCHITIS	2 (4)	0 (0)
COUGH INCREASED	0 (0)	1 (2)
PHARYNGITIS	1 (2)	1 (2)
PNEUMONIA	1 (2)	0 (0)
SKIN AND APPENDAGES	37 (76)	38 (78)
APPLICATION SITE REACTION	34 (69)	37 (76)
CONTACT DERMATITIS	0 (0)	1 (2)
DRY SKIN	5 (10)	7 (14)
EXFOLIATION	0 (0)	3 (6)
MACULOPAPULAR RASH	0 (0)	1 (2)
PAIN	7 (14)	15 (31)
PARESTHESIA	7 (14)	8 (16)
PRURITUS	28 (61)	19 (39)
RASH	10 (20)	14 (29)
SKIN HYPERTROPHY	0 (0)	2 (4)
DRY SKIN	1 (2)	0 (0)

* Subset of CDN-AK study

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All Adverse events reported during 30-day treatment in CT-1101-04 trial

Body & Costart	30-day Treatment * Gel Vehicle, N (%) N=49	Solaraze, N (%) N = 49
HERPES SIMPLEX	1 (2)	0 (0)
PAIN	1 (2)	0 (0)
PRURITUS	2 (4)	1 (2)
RASH	2 (4)	0 (0)
SKIN CARCINOMA	2 (4)	0 (0)
UROGENITAL SYSTEM	1 (2)	0 (0)
HEMATURIA	1 (2)	0 (0)

* Subset of CDN-AK study

All Adverse events reported during 60-day treatment in CT-1101-04 trial

Body & Costart	60-day Treatment * Gel Vehicle, N (% N=49	Solaraze, N (%) N = 48
BODY AS A WHOLE	10 (20)	10 (21)
ABDOMINAL PAIN	0 (0)	1 (2)
BACK PAIN	0 (0)	2 (4)
CHEST PAIN	0 (0)	1 (2)
CHILLS	1 (2)	0 (0)
EYE PAIN	1 (2)	0 (0)
FLU SYNDROME	3 (6)	5 (10)
HEADACHE	3 (6)	0 (0)
INFECTION	3 (6)	2 (4)
PAIN	0 (0)	1 (2)
CARDIOVASCULAR SYSTEM	2 (4)	1 (2)
HYPERTENSION	0 (0)	1 (2)
MIGRAINE	1 (2)	0 (0)
PHLEBITIS	1 (2)	0 (0)
DIGESTIVE SYSTEM	0 (0)	2 (4)
DIARRHEA	0 (0)	1 (2)
DYSPEPSIA	0 (0)	1 (2)
METABOLIC AND NUTRITIONAL DISORDERS	4 (8)	1 (2)
CREATININE INCREASED	1 (2)	1 (2)
EDEMA	1 (2)	0 (0)
HYPERCHOLESTEREMIA	1 (2)	0 (0)
HYPERGLYCEMIA	1 (2)	0 (0)
MUSCULOSKELETAL SYSTEM	0 (0)	2 (4)
ARTHRALGIA	0 (0)	1 (2)
ARTHROSIS	0 (0)	1 (2)
MYALGIA	0 (0)	1 (2)
NERVOUS SYSTEM	1 (2)	1 (2)
ANXIETY	1 (2)	0 (0)
HYPOKINESIA	0 (0)	1 (2)
RESPIRATORY SYSTEM	4 (8)	4 (8)
ASTHMA	0 (0)	1 (2)
DYSPNEA	0 (0)	1 (2)
PHARYNGITIS	4 (8)	1 (2)
PNEUMONIA	0 (0)	1 (2)
RHINITIS	1 (2)	1 (2)
SKIN AND APPENDAGES	42 (86)	36 (75)
ACNE	1 (2)	0 (0)
APPLICATION SITE REACTION	35 (71)	36 (76)
ACNE	2 (4)	0 (0)
ALOPECIA	0 (0)	1 (2)
CONTACT DERMATITIS	2 (4)	9 (19)
DRY SKIN	8 (12)	13 (27)

* Subset of CDN-AK study

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All Adverse events reported during 60-day treatment in CT-1101-04 trial

Body & Costart	60-day Treatment * Gel Vehicle, N (% N=49	Solaraze, N (%) N = 46
EDEMA	0 (0)	2 (4)
EXFOLIATION	2 (4)	3 (6)
PAIN	11 (22)	7 (15)
PARESTHESIA	2 (4)	4 (8)
PHOTOSENSITIVITY REACTION	1 (2)	0 (0)
PRURITUS	29 (59)	15 (31)
RASH	10 (20)	17 (35)
CONTACT DERMATITIS	0 (0)	1 (2)
DRY SKIN	2 (4)	0 (0)
HERPES SIMPLEX	1 (2)	0 (0)
MACULOPAPULAR RASH	1 (2)	0 (0)
PAIN	1 (2)	1 (2)
PRURITUS	3 (6)	2 (4)
RASH	6 (10)	1 (2)
SKIN CARCINOMA	3 (6)	0 (0)
SKIN NODULE	1 (2)	0 (0)
SKIN ULCER	0 (0)	1 (2)
SPECIAL SENSES	0 (0)	1 (2)
CONJUNCTIVITIS	0 (0)	1 (2)

* Subset of CDN-AK study

ATTACHMENT 6

All Adverse Events Reported

during the

Phase 3 Clinical Studies

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All Adverse events reported during Solaraze phase 3 clinical trials
Incidences in the 3 pivotal studies

Body & Costart	All AWC studies * Gel Vehicle, N (%) N=212	Solaraze, N (%) N = 211
OTHER	3 (1)	1 (1)
PROCEDURE	3 (1)	1 (1)
BODY AS A WHOLE	35 (17)	35 (17)
ABDOMINAL PAIN	0 (0)	2 (1)
ACCIDENTAL INJURY	2 (1)	5 (2)
ALLERGIC REACTION	3 (1)	1 (1)
ASTHENIA	1 (1)	2 (1)
BACK PAIN	2 (1)	4 (2)
CHEST PAIN	0 (0)	2 (1)
CHILLS	1 (1)	0 (0)
EYE PAIN	1 (1)	0 (0)
FACE EDEMA	0 (0)	1 (1)
FEVER	1 (1)	1 (1)
FLU SYNDROME	8 (4)	6 (3)
HEADACHE	12 (6)	8 (4)
HIV TEST POSITIVE	1 (1)	0 (0)
INFECTION	10 (5)	7 (3)
MALAISE	1 (1)	0 (0)
NECK PAIN	0 (0)	3 (1)
PAIN	2 (1)	3 (1)
PHOTOSENSITIVITY REACTION	0 (0)	1 (1)
CARDIOVASCULAR SYSTEM	4 (2)	5 (2)
ANGINA PECTORIS	1 (1)	0 (0)
CARDIOMYOPATHY	0 (0)	1 (1)
CONGESTIVE HEART FAILURE	1 (1)	0 (0)
CORONARY ARTERY DISORDER	0 (0)	1 (1)
HYPERTENSION	0 (0)	3 (1)
MIGRAINE	1 (1)	1 (1)
PHLEBITIS	1 (1)	0 (0)
DIGESTIVE SYSTEM	10 (5)	12 (6)
COLITIS	0 (0)	1 (1)
CONSTIPATION	2 (1)	0 (0)
DIARRHEA	4 (2)	3 (1)
DYSPEPSIA	4 (2)	4 (2)
MOUTH ULCERATION	0 (0)	1 (1)
NAUSEA	1 (1)	2 (1)
RECTAL DISORDER	1 (1)	2 (1)
STOMACH ULCER	1 (1)	0 (0)
ULCERATIVE STOMATITIS	0 (0)	1 (1)
VOMITING	1 (1)	1 (1)
HEMIC AND LYMPHATIC SYSTEM	2 (1)	1 (1)

* CT-1101-03, CT-1101-04 & CT-1101-07

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All Adverse events reported during Solaraze phase 3 clinical trials
Incidences in the 3 pivotal studies

Body & Costart	All AWC Studies * Gel Vehicle, N (%) N=212	Solaraze, N (%) N = 211
EOSINOPHILIA	0 (0)	1 (1)
LEUKOCYTOSIS	1 (1)	0 (0)
LYMPHADENOPATHY	1 (1)	0 (0)
METABOLIC AND NUTRITIONAL DISORDERS	6 (3)	10 (5)
BUN INCREASED	1 (1)	0 (0)
CREATINE PHOSPHOKINASE INCREASED	1 (1)	4 (2)
CREATININE INCREASED	2 (1)	1 (1)
EDEMA	1 (1)	0 (0)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0 (0)	1 (1)
HYPERCHOLESTEREMIA	1 (1)	1 (1)
HYPERGLYCEMIA	1 (1)	1 (1)
LACTIC DEHYDROGENASE INCREASED	0 (0)	1 (1)
SGOT INCREASED	0 (0)	3 (1)
SGPT INCREASED	0 (0)	2 (1)
WEIGHT LOSS	0 (0)	1 (1)
MUSCULOSKELETAL SYSTEM	4 (2)	5 (2)
ARTHRALGIA	2 (1)	1 (1)
ARTHRITIS	1 (1)	0 (0)
ARTHROSIS	0 (0)	1 (1)
MYALGIA	1 (1)	4 (2)
NERVOUS SYSTEM	8 (4)	3 (1)
ANXIETY	2 (1)	0 (0)
DIZZINESS	5 (2)	0 (0)
HYPERTONIA	0 (0)	1 (1)
HYPOKINESIA	0 (0)	1 (1)
INSOMNIA	1 (1)	0 (0)
NERVOUSNESS	1 (1)	0 (0)
SOMNOLENCE	0 (0)	1 (1)
VERTIGO	0 (0)	1 (1)
RESPIRATORY SYSTEM	15 (7)	13 (6)
ASTHMA	0 (0)	1 (1)
BRONCHITIS	3 (1)	1 (1)
COUGH INCREASED	1 (1)	1 (1)
DYSPNEA	0 (0)	3 (1)
PHARYNGITIS	9 (4)	4 (2)
PNEUMONIA	2 (1)	1 (1)
RHINITIS	3 (1)	3 (1)
SINUSITIS	0 (0)	2 (1)
SKIN AND APPENDAGES	160 (76)	172 (82)
ACNE	2 (1)	0 (0)
APPLICATION SITE REACTION	149 (70)	169 (80)

* CT-1101-03, CT-1101-04 & CT-1101-07

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All Adverse events reported during Solaraze phase 3 clinical trials
Incidences in the 3 pivotal studies

	All AWC Studies *	
	Gel Vehicle, N (%) N=212	Solaraze, N (%) N = 211
Body & Costart		
ACNE	2 (1)	1 (1)
ALOPECIA	1 (1)	2 (1)
CONTACT DERMATITIS	6 (3)	47 (22)
DRY SKIN	30 (14)	49 (23)
EDEMA	0 (0)	5 (2)
EXFOLIATION	17 (8)	33 (16)
HYPERESTHESIA	1 (1)	3 (1)
HYPERTONIA	1 (1)	0 (0)
LACRIMATION DISORDER	0 (0)	1 (1)
MACULOPAPULAR RASH	0 (0)	2 (1)
PAIN	52 (25)	52 (25)
PARESTHESIA	32 (15)	35 (17)
PHOTOSENSITIVITY REACTION	1 (1)	3 (1)
PRURITUS	105 (50)	93 (44)
PURPURIC RASH	0 (0)	1 (1)
RASH	39 (18)	83 (39)
SKIN CARCINOMA	0 (0)	1 (1)
SKIN HYPERTROPHY	0 (0)	2 (1)
VASODILATATION	1 (1)	0 (0)
VESICULOBULLOUS RASH	1 (1)	4 (2)
CONTACT DERMATITIS	0 (0)	1 (1)
DRY SKIN	3 (1)	3 (1)
HERPES SIMPLEX	2 (1)	0 (0)
MACULOPAPULAR RASH	1 (1)	0 (0)
PAIN	2 (1)	2 (1)
PARESTHESIA	0 (0)	1 (1)
PRURITUS	6 (3)	7 (3)
RASH	7 (3)	5 (2)
SEBORRHEA	0 (0)	1 (1)
SKIN CARCINOMA	7 (3)	2 (1)
SKIN HYPERTROPHY	1 (1)	1 (1)
SKIN NODULE	1 (1)	0 (0)
SKIN ULCER	0 (0)	2 (1)
URTICARIA	0 (0)	1 (1)
SPECIAL SENSES	2 (1)	6 (3)
CONJUNCTIVITIS	1 (1)	5 (2)
EAR PAIN	1 (1)	0 (0)
EYE PAIN	0 (0)	2 (1)
UROGENITAL SYSTEM	7 (3)	5 (2)
DYSMENORRHEA	1 (1)	0 (0)
EPIDIDYMITIS	1 (1)	0 (0)

* CT-1101-03, CT-1101-04 & CT-1101-07

All Adverse events reported during Solaraze phase 3 clinical trials
Incidences in the 3 pivotal studies

Body & Costart	All AWC Studies * Gel Vehicle, N (%) N=212	Solaraze, N (%) N = 211
HEMATURIA	2 (1)	2 (1)
NEPHRITIS	0 (0)	1 (1)
PROSTATIC CARCINOMA	0 (0)	1 (1)
PYURIA	1 (1)	0 (0)
URINARY FREQUENCY	1 (1)	0 (0)
URINARY TRACT INFECTION	1 (1)	1 (1)

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* CT-1101-03, CT-1101-04 & CT-1101-07

ATTACHMENT 7

Patient Listings sorted by

COSTART terms with expanded ASRs

Please note: The fax submission does not include the 71 pages of the patient listing. It will be included in the hard copy submission, sent via Fed Ex

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ATTACHMENT 8

Clean Copy of Revised Package Insert

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WITHHOLD 6 PAGE (S)

Draft

Labeling

SkyePharma Inc.
10450 Science Center Drive
San Diego, CA 92121
Phone: (858) 625-2424
Fax: (858) 625-2439

FACSIMILE COVER PAGE

DATE: 10/12/00 Number of Pages Including Cover: 2

TO: Kevin Darryl White FROM: Pearl Amos

FDA (HFD-340)

Phone: 301-827-2020 Phone: (858) 625-2424 x 3231

Fax: 301-827-2075 Fax: (858) 625-2439

REMARKS:

☒ Urgent ☐ For Your Review ☐ Reply ASAP ☐ Please comment

Kevin Darryl,

Per our telecon today, attached is our commitment to revise the Solaraze tube + carton labels.

-Pearl

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SkyePharma

October 12, 2000

Kevin Darryl White
Project Manager (HFD-540)
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

Via Facsimile - (301) 827-2075

Attention: Document Control Room

Dear Mr. White,

RE: NDA 21-005 – Solaraze™ (diclofenac sodium) Gel, 3%
Product Labeling – tube and carton labels

Reference is made to the NDA amendment submitted October 3, 2000, in which SkyePharma provided revised product labeling. Reference is also made to the teleconference held today, October 12, 2000, between the Agency and SkyePharma.

As requested by the Agency during the October 12 teleconference, SkyePharma, hereby commits to revise the Solaraze tube and carton labels as follows:

1) In accordance with 21 CFR 201.10(g)(2), the established name, "diclofenac sodium," will be printed in a font size that is at least half as large as the font size used in the tradename, Solaraze.

2) Under excipients, the number — listed with the ingredient polyethylene glycol monomethyl ether — will be removed to be consistent with the ingredient as listed in the package insert.

As discussed via telephone, SkyePharma is submitting this information to the Agency via fax, with a hard copy being sent via Federal Express.

If you have further questions, please contact me at (858) 625-2424, ext. 3370.

Sincerely,

Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical Research and Regulatory Affairs

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered no 107582 England. Registered office 105 Piccadilly, London W1V 9FN

SkyePharma Inc.
10450 Science Center Drive
San Diego, CA 92121
Phone: (858) 625-2424
Fax: (858) 625-2439

FACSIMILE COVER PAGE

DATE: 10-12-00 **Number of Pages Including Cover:** 7

TO: Kevin Darryl White
FDA (HFD-540)

FROM: Pearl Amos

Phone: 301- 827-2020 **Phone:** (858) 625-2424 xt 3231

Fax: 301- 827-2075 **Fax:** (858) 625-2439

REMARKS:

☒ Urgent ☐ For Your Review ☐ Reply ASAP ☐ Please comment

Kevin Darryl -

As discussed, the following editorial changes were made to the Solaraze PI.

- edits under PK/Absorption section.
- AEs for EYE PAIN were consolidated in Table 1.

-Pearl-

BEST POSSIBLE COPY

SkyePharma

NDA ORIG AMENDMENT

April 3, 2000

Kevin Darryl White
Project Manager
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard (HFD-540)
Rockville, MD 20857

Attention: Central Document Room

Subject: Solarase™ (diclofenac sodium) Gel, 3% (NDA 21-005) BM
Amendment – Response to "not approvable" letter

Dear Mr. White:

Reference is made to our telephone conversation on April 3, 2000 and to the January 21, 2000 submission in which we responded to the not approvable letter for NDA 21-005. As stated in the cover letter of the January 21, 2000 submission, we did not provide updated safety information as requested on page 4 of the Agency's not approvable letter. All available safety data were reported in the NDA for this product, and there are no ongoing clinical trials from which patient data is available to report.

Solarase™ has been approved for marketing in six countries including Canada, United Kingdom, Sweden, Italy, Germany and France. Solarase has not yet been launched in these markets.

Should you have any questions regarding this meeting package please contact me by telephone at (858) 625-2414 ext. 3370, or by FAX at (858) 558-6617.

Sincerely,

Gordon L. Schooley, Ph.D.
Sr. Vice President,
Clinical Research & Regulatory Affairs

ORIGINAL

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
[illegible] Registered office 105 Piccadilly London W1V 9FN

Safety Update

NDA 21.005 Solarase™
Diclofenac Gel
March 17, 1999
Hyal Pharmaceutical Corporation

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Solarase™ has yet to be marketed in those jurisdictions where it has been approved. ———

——— Information on the number of patients treated has been included in Appendix 1. Other than AEs previously reported there have been no adverse events **arising** from this program since the NDA filing.

For further information, we are presenting the safety data from a clinical study completed, AT2101-15 - Diclofenac Gel in the Treatment of ——— AT2101-15 was a randomized, double blind vehicle controlled trial with a duration of 28 days and a dose of 2 gm q.i.d. This information has not yet been merged into the overall safety database, but is presented in summary tables with safety data from — studies database to allow comparison. The summary tables are presented below with supporting patient data appended.

TABLE A:
Demographics and Duration (Data Limiting- Appendix 2)

	No. of patients		Number of males (%)		Mean (SD) Duration - days		Mean (SD) Age (years)	
	Diclofenac	Vehicle	Diclofenac	Vehicle	Diclofenac	Vehicle	Diclofenac	Vehicle
Study AT2101-15	304	313	96 (32)	102 (33)	27 (6)	28 (6)	62 (10)	62 (10)
— Studies in Safety database	684	550	250 (37)	201 (37)	16 (10)	17 (10)	60 (12)	62 (12)

APPEARS THIS WAY
ON ORIGINAL

TABLE B:Number and Percent of Patients with Adverse Events from Clinical Studies By COSTART Body Systems

Body System	Study AT2101-15		— Studies in Safety Database	
	Active n=304	Vehicle n=313	Active n=684	Vehicle n=550
Body as a Whole	59 (20%)	74 (24%)	75 (11%)	67 (12%)
Cardiovascular System	7 (2%)	6 (2%)	7 (1%)	7 (1%)
Digestive System	12 (4%)	9 (3%)	33(5%)	18 (5%)
Hemic and Lymphatic System	1 (0%)	1 (0%)	3 (0%)	1 (0%)
Metaboiic and Nutritional	2 (1%)	3 (1%)	9 (1%)	8(1%)
Muscoskeletal	10 (3%)	8 (3%)	5 (1%)	4(1%)
Nervous	9 (3%)	9 (3%)	12 (2%)	6 (1%)
Respiratory	17 (6%)	16 (5%)	17 (2%)	20 (4%)
Skin and Appendages (application site reactions)	27 (9%)	50 (16%)	112 (16%)	150 (27%)
Skin and Appendages (others)	23 (8%)	19 (6%)		
Special senses	7 (2%)	8 (3%)	7(1%)	4 (1%)
Urogenital	4 (1%)	1 (0%)	11 (2%)	7 (1%)

TABLE C:
Number and Percent of Patients with Skin and Appendages: Application Site Reactions (Data Listing Appendix 3)

Skin and Appendages Application Site Reactions (ASRs)	AT-2101-15		— Studies in Safety Data Base	
	Active n=304	Vehicle n=313	Active n=684	Vehicle n=550
alopecia			1 (0)	2 (0)
arthrosis	0	1 (0)		
conjunctivitis			1 (0)	0
contact dermatitis			2 (0)	4 (1)
cyst			0	1 (0)
dry skin	2 (1)	4 (1)	7 (1)	10 (2)
edema	0	1 (0)	4 (1)	5 (1)
exfoliation	1 (0)	4 (1)	3 (0)	4 (0)
hypaesthesia	0	1 (0)	2 (0)	1 (0)
maculopapular rash	5 (2)	1 (0)	4 (0)	0
nail disorder			0 (0)	1 (0)
pain	3 (1)	9 (3)	20 (3)	29 (5)
paraesthesia	1 (0)	3 (1)	10 (1)	17 (3)
petechial rash			1 (0)	0
photosensitivity reaction	1 (0%)	0		
pruritus	5 (2%)	26 (8)	30 (4)	72 (13)
pustular rash	1 (0)	0	0	1 (0)
rash	15 (5)	20 (6)	48 (7)	59 (11)
urticaria			2 (0)	0
vasodilation	0	1 (0)	5 (1)	1 (0)
vesiculobullous rash			2 (0)	0

Photosensitivity reaction was not previously reported during clinical investigations for ——— — but has been previously reported during the actinic keratosis trials. Arthrosis was noted in a patient treated with vehicle but causality was not assessed as likely to drug therapy. No new skin and appendage adverse reactions were noted during this trial.

TABLE D: Number and Percent of Patients with Skin and Appendage Adverse Events (other than application site reactions)(Data Listing Appendix 3)

Skin and Appendages	Study AT-2101-15		— Studies in Safety Data Base	
	Active n=304	Vehicle n=313	Active n=684	Vehicle n=550
acne	1 (0)	0		
angioedema	0	0	1 (0)	0
arthrosis	3 (1)	0		
contact dermatitis	2 (1)	0		
dry skin	0	1 (0)	3(0)	2(0)
edema	0	1 (0)		
herpes simplex	0	1 (0)		
herpes zoster	1 (0)	0		
maculopapular rash	0	1 (0)	0	1 (0)
pain	8 (3)	8 (3)		
paraesthesia	4 (2)	2 (1)		
photosensitivity reaction	0	2 (0)		
pruritus	1 (0)	3 (1)	3 (0)	4 (1)
rash	4 (1)	2 (1)	9 (1)	4 (1)
skin benign neoplasm			0	1 (0)
skin disorder	1 (0)	0	1 (0)	0
skin nodule	0 (0)	1 (0)	0	1 (0)
skin ulcer			1 (0)	0

sweating			1 (0)	0
urticaria			2 (0)	2 (0)
vesiculobullous rash			0	4 (1)

Arthrosis was noted as a new adverse event experienced during the treatment with diclofenac gel. However, causality was assessed as not likely due to drug treatment. New skin and appendage (other than ASRs) adverse events experienced during this trial for the indication of ——— — were previously seen during the clinical trials for the treatment of actinic keratoses they are: acne, contact dermatitis, edema, herpes simplex, herpes zoster, pain, paraesthesia, and photosensitivity reaction. Of these, Edema, herpes simplex and photosensitivity reaction were not seen in patients treated with the 3% diclofenac gel.

TABLE E: Adverse Events in AT 2101-15 not previously seen in Safety Database (number and percent of patients) (Appendix 4)

Body System	AT 2101-15	
	Active n=304	Vehicle n=313
Body as a Whole		
viral infection	1 (0)	0
Cardiovascular System		
tachycardia	1 (0)	0
arrhythmia	0	1 (0)
atriai fibrillation	0	1 (0)
Digestive System		
cholecystitis	1 (0)	0
gingivitis	***1 (0)***	0
Hemic and Lymphatic System		
anaemia	1 (0)	0
Skin and Appendages (others)		
arthrosis	3 (1)	0
Special senses		
cataract specified	1 (0)	0
Urogenital		
salpingitis	1 (0)	0
bladder stenosis	0	1 (0)
kidney calculus	0	1 (0)

Adverse Events coded as related to drug treatment have been bolded and italicized

TABLE F: AE's Number and Percent of Patients with Adverse Events by Severity (Data Appendix 5)

Body System	Study AT 2101-15		Studies in Database	
	Active n=304	Vehicle n=313	Active n=684	Vehicle n=550
Body as a Whole	28 mild (9) 30 mod (10) 1 sev (0)	35 mild (11) 32 mod (10) 7 sev (2)	28 mild (4) 31 mod (5) 10 sev (1)	26 mild (5) 28 mod (5) 8 sev (1)
Cardiovascular System	3 mild (1) 3 mod (1) 1 sev (1)	2 mild (1) 4 mod (1) 0 sev	2 mild (0) 2 mod (0) 3 sev (0)	3 mild (1) 3 mod (1)
Digestive System	4 mild (1) 6 mod (2) 2 sev (1)	2 mild (1) 5 mod (2) 2 sev (1)	13 mild (2) 13 mod (2) 6 sev (1)	6 mild (1) 7 mod (1) 4 sev (1)
Hemic and Lymphatic System	1 mild (0)	1 mod (0)	2 mod (0)	1 mild (0)
Metabolic and Nutritional	1 mild (0) 1 mod (0)	1 mild (0) 2 mod (1)	1 mild (0) 5 mod (1)	5 mild (1) 2 mod (0)
Muscoskeletal	6 mild (2) 1 mod (0) 3 sev (1)	5 mild (2) 2 mod (1) 1 sev (0)	2 mild (0) 2 mod (0) 1 sev (0)	2 mild (0) 2 sev (0)
Nervous	2 mild (1) 5 mod (2) 2 sev (1)	2 mild (1) 5 mod (2) 2 sev (1)	7 mild (1) 3 mod (0) 2 sev (0)	1 mild (0) 1 mod (0) 4 sev (1)
Respiratory	7 mild (2) 10 mod (3)	6 mild (2) 9 mod (3) 1 sev (0)	10 mild (1) 5 mod (1) 2 sev 90)	8 mild (1) 8 mod (1) 4 sev (1)
Skin and Appendages (total)	28 mild (9) 21 mod (7) 1 sev (0)	56 (18) 11 mod (4) 2 sev (1)	74 mild (11) 30 mod (4) 7 sev (1)	93 mild (17) 45 mod (8) 9 sev (2)
Skin and Appendages (application site reactions) Skin and Appendages (others)	17 mild (6) 10 mod (3) 11 mild (4) 11 mod (4) 1 sev (0)	41 mild (13) 8 mod (3) 1 sev (0) 15 mild (5) 3 mod (1) 1 sev (0)		
Special senses	4 mild (1) 3 mod (1)	6 mild (2) 2 mod (1)	3 mild (0) 3 mod (0) 1 sev (0)	3 mild (0) 1 mod (0)

Urogenital	2 mild (1) 1 mod (0) 1 sev (0)	2 mild (1) 1 mod (0) 1 sev (0)	5 mild (1) 5 mod (1) 1 sev (0)	2 mild (0) 5 mod (1)

The severity profile of adverse events experienced in Study AT 2101-15 was not different than that seen in the safety database for the pain studies.

TABLE G: Discontinuations from Clinical Studies (Data- Appendix 6)

	AT 2101-15		**— Studies in Safety Database**	
	Active n=304	**Vehicle n=313**	**Active n= 550**	**Vehicle n= 684**
Discontinuations (for any reason)	37 (12.2%)	36 (11.5%)	83 (12.1%)	83 (15.1%)
Discontinuations due to AEs	11 (3.6%)	11 (3.5%)	22 (3.2%)	33 (6.0%)

No increase in the overall discontinuation rate or in discontinuation rate due to AEs was seen in this study in comparison to that seen in the safety database for the — studies.

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Serious Adverse Events from AT 2101-15 (CRF's for these patients have been included in Appendix 7)

Four patients from AT 2101-15 experienced serious adverse events. All events were assessed as unlikely to be due to drug treatment.

Patients treated with Active

Patient 131 Site 21 — was a 45 year old female who experienced abdominal pain (RLQ tenderness) on 10/22/97 for 6 days. Intensity of AE was mild. Patient underwent exploratory laparoscopy with subsequent salpingo-oophorectomy due to (severe intensity) salpingitis. Patient recovered. Patient had entered study on 9/24/97 and completed trial 10/22/97.

Patient 359H Site 26 — was a 74 year old female who experienced cholecystitis 8/22/97 (severe intensity) lasting six days with complete recovery after surgery (cholecystotomy). Patient had entered study on 8/11/97 and patients last dose was 8/22/97. Patient was terminated early due to this adverse event.

Patient 494H Site 32 — was a 67 year old female who experienced congestive heart failure (severe intensity) on 9/10/97. Patient had a previous history of irregular heartbeat. Diclofenac gel treatment was started 8/29/97 and the last treatment was administered 9/10/97. Treatment was discontinued due to heart condition. Patient was treated with drug therapy and scheduled for follow-up work including possible pacemaker and/or heart catheterization.

Patients treated with Vehicle

Patient 627 Site 39, — was an eighty year old male who experienced severe kidney stones on 9/20/97 with complete recovery two days later on 9/22/97. There was no interruption of treatment and patient completed study. The patient started the gel therapy on 9/9/97 and completed the study on10/09/97.

Conclusion:

The safety data submitted herein is consistent with the data already submitted in the NDA and does not affect the overall safety profile of Solarase™.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 20, 2000

To: Kevin D. White
Division of Dermatological and Dental Products

From: Cheryl Roberts, M.S., J.D.
Division of Drug Marketing, Advertising, and Communications

Re: Solarase (Sodium Diclofenac 3% w/w) Topical Gel

I found many problems with the content and wording of the Solarase draft labeling. I know your division will revise much of the labeling, therefore, I limited my comments to the problems I viewed as directly related to promotion and advertising.

The efficacy rates presented in *Clinical Trial Data* section of the product labeling (PI) are misleading because they fail to present results for patients in the vehicle-arm. This presentation therefore overstates the effectiveness of Solarase.

In the *Warnings* section of the PI, it states, [redacted] The sponsors should include what the more severe skin reactions are.

In the *Information for Patients* section of the PI, it states [redacted] treatment with [redacted] may be [redacted] interrupted until the condition subsides. Are there any instances where Solarse should be stopped? If so, it should be stated.

In the *Adverse Reaction* section of the PI, the sentence stating, [redacted] " should be omitted. The sponsor seems to be making an efficacy claim out of an adverse reaction statement.

The sponsors should simply state if no drug interactions have been found in patients taking oral NSAIDS such as acetylslicylic acid, ketorolac, tiaprofenic acid and indomethacin, instead of stating that patients who took these drugs have been treated

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Draft

Labeling

Meeting I.D. 1930

Minutes of Meeting

Date: January 7, 1998, 10:00 AM
Sponsor: Hyal Pharmaceuticals
Agent: Diclofenac, IND ——
Purpose: Chemistry Pre-NDA Meeting

FDA Attendees:

Jonathan Wilkin, M.D., Division Director, DDDDP
Roy Blay, Ph.D., Project Manager
Janet Higgins, Chemist
Wilson DeCamp, Ph.D., Chemistry Team Leader

Sponsor Attendees:

Patricia Anderson, Director, Regulatory Affairs
Marc Cohen, Senior V.P., Chief Medical Officer
Catherine Tung, Regulatory Associate

The following sponsor questions (in italics) were answered by the chemists.

1. *Previous communications have agreed upon an abbreviated EA. Is this still acceptable/required?*

It is possible that this application might now fall under the current Final Rule published on July 29, 1997. The proposed NDA might be able to claim categorical exclusions under this final rule published in the Federal Register. Our recommendation is to review this final rule and assess if you can claim a categorical exclusion.

2. *Diclofenac has recently been added to the USP. Our raw material meets both BP and EP standards. While we have tested against USP standards and met them, must we use USP over BP methodology?*

It is our recommendation that the USP specifications and methodology be utilized in your NDA. However, it is acceptable to include tests additional to the USP tests so that you can also meet the BP and EP. A comparison of all monographs involved should also be included in the NDA.

3. *Can we submit the CMC section early?*

Yes, however, this document will be reviewed based on workload at the time of submission. Please be advised that if review of this section is begun prior to the submission of the NDA, you will be contacted and asked to submit a statement that no major changes will be introduced, and that this is the identical CMC section that will be provided in the NDA submission. Of course, if changes need to be made due to a risk to the public safety, then those modifications will be welcomed and reviewed.

4. *Are proposed changes to the drug product impurity stability testing acceptable?*

Most of the changes are acceptable. However, it is not appropriate to delete possible drug product impurities at this point in the drug product history. Please investigate all impurities until several commercial lots illustrate that the impurities of concern are not present. If you decide to delete these impurities at the NDA stage, then a justification for the change will need to be included in the NDA. It is our opinion that these impurities should be included unless they are shown not to be degradation products in the bulk drug substance.

The following additional comments were made by FDA.

1. The component, sodium hyaluronate, does not have a USP monograph. Please assure that this component is completely characterized in the NDA. The source of this component and the name and address of the supplier should also be provided. We are also interested in the prion status of this component. The sponsor noted that the sodium hyaluronate component is produced through ——— processes.

2. The NDA should have a statement claiming that all facilities connected with the manufacturing, packaging and testing of the drug substance and drug product are ready for inspection. Additionally, any foreign firms requiring inspection should be identified as soon as possible. Identification should include the phone number of the firm, the name of the appropriate contact person, and the I.D. # from Form 2656

3. FDA is interested in all the investigational formulations and the history of these formulations which includes: lot size, manufacturing site, use of lot (clinical study, pivotal study), formulation, packaging, date of manufacturing, and batch number. FDA suggested that the sponsor be aware of relevant SUPAC rules, particularly as they regard scale-up procedures.

4. The product development report would also be helpful during the review of this NDA.

5. The chemistry presubmission should precede the NDA by 90-120 days. The sponsor anticipated submitting the NDA in July, 1998.

Regarding the applicability of the combination drug policy to this particular drug product, the following comments were made:

1. The sponsor was requested to provide additional information on sodium hyaluronate containing OTC drug products such as Eucerin and Stephan Bio Ultra.

2. FDA discussed the possible distinctions between a penetration enhancer and a vehicle, the claims made for either component, and the applicability of 21 CFR 300.50(a)(1). The sponsor indicated that they did not wish to make any claims regarding the activity of sodium hyaluronate in their drug product. FDA encouraged the sponsor to submit any prior agreement made with the Agency regarding the combination drug status of their drug product. The sponsor provided a copy of minutes of a meeting between the sponsor and FDA on November 5, 1992, in which FDA states that the sponsor's formulation does not have to meet the requirements of the combination drug policy. FDA said that sodium hyaluronate will not be considered an active component of this drug product provided that no claims regarding its activity are made in the labeling for the drug product.

Meeting I.D. 1967

Minutes of Meeting

Date: December 15, 1997, 3:00 PM
Sponsor: Hyal Pharmaceuticals
Agent: Diclofenac, IND
Purpose: Pre-NDA Meeting

FDA Attendees:

Jonathan Wilkin, M.D., Division Director, DDDDP
Roy Blay, Ph.D., Project Manager
Hon-Sum Ko, M.D., Medical Officer
Shahla Farr, M.S., Statistician
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader
Mary Fanning, M.D., Office of Generic Drugs
Lynnda Reid, Ph.D., Pharmacologist
Abby Jacobs, Ph.D. Pharmacology team Leader
Rajagopolan Srinivasan, Ph.D., Biostatistics Team Leader

Sponsor Attendees:

Patricia Anderson, Director, Regulatory Affairs
Marc Cohen, Senior V.P., Chief Medical Officer
Michael Vanzieleghelm, Director, Clinical Services
Jennifer Ellis, Regulatory Affairs Associate
_____ Clinical, Statistical Consultant
Jason Rivers, U.B.C., Clinical Investigator
_____ Consultant

Pharmacology

The sponsor listed the various pharmacology/toxicology studies it had conducted including mutagenicity assays, dermal toxicity assays, photocarcinogenicity assays, 2 year rodent carcinogenicity assays, etc. The sponsor asked if the pharmacology studies presented would be adequate for filing. FDA said that on its face, the studies presented would be adequate for filing.

FDA said that draft reports for the carcinogenicity studies, which should include histopathology, would be acceptable at the time of the NDA submission, provided the final reports were received by the NDA filing date (approximately 6 weeks later). "Draft" was later defined to mean complete reports that had not yet undergone quality assurance. In addition to the standard carcinogenicity study report which includes summary data as well as individual animal data, specifically formatted data will need to be submitted for statistical analysis by the Division of Biometrics. The format for submission of this data will be communicated to the sponsor under separate cover.

Although anomalous levels of the drug were detected in the control group during the 6 month dermal toxicology study performed in minipigs, a decision on the need for repetition of this study would await evaluation of other long-term studies submitted with the NDA. If the other long-term studies are deemed adequate, repetition will not be necessary.

Biopharmaceutics

The sponsor listed the PK studies performed . FDA asked for clarification of the term, "compromised" epidermis. The sponsor said that compromised skin was generally eczematous skin, and said that they would provide more data describing "compromised" skin. The sponsor noted that treatment for PK studies was generally confined to the back of the hand. FDA said that it would like to see data reflecting a worst-case scenario; i.e., treatment of the severest expression of the disease over the largest body surface possible in order to examine upper limit of drug exposure.

FDA said that it would view the studies on compromised epidermis as pivotal pharmacokinetic (PK) studies where the primary issue would be systemic availability. The sponsor said that 8 of 11 subjects were treated with the drug on their hands. The need for studies evaluating other anatomic sites and surface areas was repeated.

Clinical

The sponsor listed the clinical dermal safety studies that were conducted. FDA clarified the point that the subjects as described on page 124 of the meeting package were not on oral NSAIDS.

The sponsor listed its clinical studies. The sponsor confirmed that it intended to conduct its primary analysis 30 days post-treatment. The sponsor presented 4 supportive studies and noted that only one study also utilized subjects using concomitant sunscreens.

The sponsor said that the same complete vehicle was used for all studies. FDA requested that copies of all referenced publications be submitted.

FDA said that the NDA must be complete upon submission for successful filing.

In response to the questions contained in the sponsor's facsimile of October 1, 1997, the FDA said that in response to the first question, all studies would need to be submitted. In response to the second question, the FDA said that it was interested in safety data for other indications but this information could be submitted in less detail than that information for relevant indications. With regard to the third question, FDA noted that a 30 day, a 60 day, and a 90 day study had been conducted. FDA emphasized the need for 2 adequate and well-controlled studies and noted that these studies may or may not support the labeling: this would be a review issue, not a flexibility issue.

FDA questioned the role of sodium hyaluronate in the drug. FDA quoted the sponsor's minutes describing the need for a study arm to describe the role of this agent. FDA pointed out the relevant passages from 21 CFR 300.50 describing the combination drug policy. FDA said that the sponsor would not need to conduct a complete factorial design study but would need to demonstrate that the combination of agents is more effective than the drug alone. This issue could not be resolved through labeling revisions. The sponsor said that it did not have any studies of its drug product without the hyaluronate component. FDA said that without an appropriate description of this component of the drug product, the application might not be fileable. FDA said it would seek guidance from its internal experts on the combination policy. FDA asked the sponsor to submit any prior correspondence or agreements made with the FDA concerning the characterization of hyaluronate

FDA said that the studies varied from one another in terms of its primary endpoint variables. FDA said that it would need only complete clearance of all target lesions in the specific region as a primary endpoint variable. FDA said that it would need to know the proportion of subjects exhibiting complete clearance. FDA suggested that data be analyzed using the Cochran-Mantel-Haenszel test while controlling for center effects. FDA said that the duration of treatment was unclear from the pivotal studies, and follow-up was not mentioned in the first protocol. FDA suggested that the sponsor look at time to complete cure for use in labeling. FDA asked the sponsor to define its sample size calculations. FDA said that ANOVA would not be needed for comparison of the active arm vs. the placebo. FDA noted typographical errors on pages 93 and 94 of the briefing package. The sponsor said that it would correct these errors.

Summary

1. The pharmacology studies presented are adequate on their face for filing.

2. Draft carcinogenicity studies (complete except for Q.A.) including histopathology are acceptable for submission with the NDA.

3. The sponsor should clarify the term, "compromised " skin.

4. Pharmacokinetic studies should reflect a greatest possible exposure under labeled conditions scenario; i.e., maximal systemic absorption.

5. Copies of all referenced publications should be submitted.

6 The NDA must be complete upon submission for successful filing.

7. All clinical studies conducted for this indication should be submitted with the NDA.

8. Two adequate and well-controlled studies are needed for approval; the studies presented by the sponsor may or may not support labeling depending on the data.

9. Unless the sponsor can submit prior agreements with the FDA to the contrary, the sponsor will need to demonstrate that the combination of agents (drug and hyaluronate) is more effective than the drug alone. Failure to do so may affect the fileability of the NDA. FDA will seek internal guidance regarding the combination drug policy.

10. For statistical analysis, only complete clearance is needed as a primary endpoint variable. The sponsor should indicate the proportion of subjects exhibiting complete clearance.

11. The sponsor should analyze its data using the Cochran-Mantel-Haenszel test while controlling for center effects.

12. The sponsor should define its sample size calculations.