CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

ADMINISTRATIVE DOCUMENTS

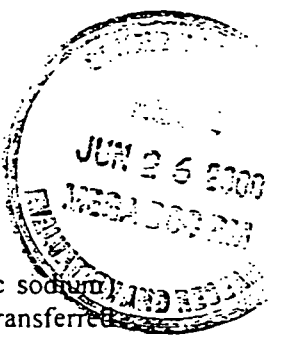
SkyePharma

June 23, 2000

Jonathan K. Wilken, 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

NEW CORRESP
NC

Desk Copy: Kevin Darryl White
Project Manager



Attention: Document Control Room

Dear Dr. Wilken,

RE: NDA 21-005 – Transfer of Ownership
IND — - Transfer of Sponsor Obligation

In accordance with 21 CFR 314.72, the rights to NDA 21-005 for Solarase™ (diclofenac sodium) Gel. 3% have been sold, effective October 28, 1999. The ownership of the NDA has been transferred from Hyal Pharmaceutical Corporation (Hyal), Mississauga, Ontario, Canada to SkyePharma Inc., San Diego, California. A signed application form, 356h, is attached.

SkyePharma Inc. is a wholly-owned subsidiary of SkyePharma PLC. London, England, who acquired all assets of Hyal Pharmaceutical Corporation. As such, Hyal has provided SkyePharma Inc. with a complete copy of the NDA, IND and all correspondence between Hyal and the FDA. SkyePharma Inc. is aware of, and commits to the reporting requirements and sponsor obligations required to maintain both the NDA and IND. The _____ will continue to take place at the contract manufacturer. _____

The former NDA owner, Hyal, filed bankruptcy under Canadian law. PricewaterhouseCoopers Inc. was the court-appointed receiver and manager of all of the assets, property and undertaking of Hyal. In lieu of a letter from Hyal confirming this transfer of ownership, as required per 21 CFR 314.72(a)(1), a copy of the bill of sale between SkyePharma and PricewaterhouseCoopers Inc. is provided (see Attachment 1). Please note page 6 of Attachment 1, paragraph 4 stating that the court ordered all of Hyal's rights, title and assets be vested in SkyePharma.

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

Sincerely,

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

cc: Caryn Everly, Investigator
Los Angeles District Office

ORIGINAL

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

WITHHOLD 4 PAGE (S)

SCHEDULE B

Court File No. 99-CL-3479

SUPERIOR COURT OF JUSTICE
COMMERCIAL LIST

THE HONOURABLE MR. JUSTICE FARLEY	))	SUNDAY, THE 24TH DAY OF OCTOBER, 1999

BETWEEN:

SKYEPHARMA PLC

Plaintiff

- and -

HYAL PHARMACEUTICAL CORPORATION

Defendant

ORDER APPROVING SALE

THIS MOTION, made by PricewaterhouseCoopers Inc., the Court-appointed receiver and manager (the "Receiver") of Hyal Pharmaceutical Corporation ("Hyal"), for an order approving the sale of certain of the assets of Hyal was heard on October 20, 1999 at 393 University Avenue, Toronto, Ontario.

ON READING THE NOTICE OF MOTION dated October 13, 1999, the report of the Receiver to this Court dated October 13, 1999 (the "Receiver's Report") and the confidential supplement to the Receiver's Report dated October 13, 1999 and all appendices thereto, each as filed, and upon reading the affidavits of service on SkyePharma PLC ("Skye"), Cangene Corporation ("Cangene"), Bioglan Pharma PLC ("Bioglan"), and Ivor M. Hughes as filed, and upon hearing the submissions of counsel for the Receiver, Skye, Cangene and Bioglan, no one appearing for Ivor M. Hughes:

Service

1 THIS COURT ORDERS that the time for service of the Notice of Motion, and the Motion Record herein be and it is hereby abridged and validated such that this Motion is properly returnable today.

2. THIS COURT ORDERS that service of the Notice of Motion and Motion Record herein upon persons other than those persons served be and is hereby dispensed with.

Sale of Assets

3. THIS COURT ORDERS that the Receiver's acceptance of and entering into the asset purchase and sale agreement between Skye and the Receiver (the "APS") (defined as Plan C in the Receiver's Report) for the sale of the Receiver's and Hyal's right title and interest, if any, in certain of the assets of Hyal (the "Purchased Assets", as defined in the APS and hereby recitified to include the Visible Youth product raw material, work in progress and finished goods inventory and related assets identified as Parcel 1 in the Receiver's Confidential Information Memorandum with respect to the assets of Hyal) be and is hereby authorized and approved.

4. THIS COURT ORDERS that all of the Receiver's and Hyal's right, title and interest, if any, in and to the Purchased Assets be and are hereby vested in Skye absolutely and forever, free and clear of and from any and all right, title, interest, security interests, estate, trusts or deemed trusts (whether contractual, statutory or otherwise), liens (whether contractual, statutory or otherwise), assignments, executions, options, adverse claims, levies, agreements, taxes, claims provable in the estates of Hyal, claims, charges, encumbrances or any other rights, rights of use, claims, disputes and debts of all persons or entities of any kind whatsoever, whether secured creditors of Hyal, unsecured or contingent creditors of Hyal or otherwise (collectively, the "Encumbrances").

5. THIS COURT ORDERS that the net proceeds of sale of the Purchased Assets shall stand in the place and stead of the Purchased Assets and shall be held by the Receiver until further Order of this Honourable Court, without prejudice to any claim being advanced against such net proceeds as could have been advanced against the Purchased Assets and that any such

claim against the net proceeds shall be subject to the same priorities as could have been claimed against the Purchased Assets.

General

6. **THIS COURT ORDERS** that the sales process outlined in the Receiver's Report and the Receiver's conduct in completing same were commercially reasonable and are hereby approved.

7. **THIS COURT ORDERS** that the Receiver be and is hereby authorized and empowered to execute any transfers, assignments, bills of sale, conveyances and all other documents and do all other acts as may be usual, customary, appropriate or necessary to evidence the sale of the Purchased Assets.

8. **THIS COURT ORDERS** that the transactions set out in the APS and the completion of such transactions in accordance with the Orders made herein shall be considered in all respects to be judicial sales.

9. **THIS COURT ORDERS** that this Order shall have full force and effect in all provinces and territories in Canada.

10. **THIS COURT REQUESTS** the aid and recognition of any court or administrative body in any Province or territory of Canada, any Canadian federal court or administrative body any federal or state court or administrative body in the United States of America and any court or administrative body in the United Kingdom and in any other jurisdiction in which such aid and recognition is necessary or desirable in order to assist the Receiver or to act in aid of and be complementary to this Court in carrying out the terms of this Order.

11. **THIS COURT ORDERS** that the Receiver be and is hereby authorized to seek such further and additional direction or Orders from this Court as may be necessary or desirable in the Receiver's opinion to carry out the transactions contemplated herein.

REGISTRAR

ENTERED AT/INSCRIT À TORONTO
ON/BOOK NO:
LE/DANS LE REGISTRE NO:

OCT 25 1999

PER/PAR:

EXCLUSIVITY SUMMARY for NDA # 21-005 SUPPL # _____

Trade Name SOLARAZE Generic Name DICLOFENAC SODIUM

Applicant Name SKYEPHARMA HFD- 540

Approval Date 10/16/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CT 1101-03

Investigation #2, Study # CT 1101-04

Investigation #3, Study # CT 1101-07

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # CT 1101-03

Investigation #2, Study # CT 1101-04

Investigation #3, Study # CT 1101-07

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ——— YES /___/ NO /✓/ Explain: SKYEPHARMA ACQUIRED THE IND FROM HYAL PHARMACEUTICAL 10/28/99. THE IND WAS ORIGINALLY OPENED BY HYAL PHARM.

Investigation #2

IND # ——— YES /___/ NO /✓/ Explain: NOTE: ALL OF HYAL'S RIGHTS, TITLE, AND ASSETS ARE VESTED IN SKYEPHARM.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

/S/ 10/12/00

Signature Date

Title: PROJ. MGR

/S/ 10/15/00

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-005 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: _____ Action: AP AE NA

Applicant SKYEPHARMA Therapeutic Class NSAID

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application TREATMENT OF ACTINIC KERATOSIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ ___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. AK's ARE VERY RARE IN PEDIATRIC PATIENTS

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ PROJ MGR 10/11/00

Signature of Preparer and Title Date

/S/ 10/15/00

cc: Orig NDA/BLA #_____
HF_____/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-005 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

D-540 SOLARASE (~~sodium~~ diclofenac sodium)

HF____ Trade and generic names/dosage form: _____ Action: AP (AE) NA

Applicant SKYEPHARMA Therapeutic Class NSAID

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate__ inadequate__

Proposed indication in this application TREATMENT OF ACTINIC KERATOSIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

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__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ __4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. AKs ARE VERY RARE IN PEDIATRIC PATIENTS.

__5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ /PROJ MGR 7/17/00

Signature of Preparer and Title Date

/S/ 7/18/00

: Orig NDA/BLA # 21-005
HF D 540 Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

N/BLA # 21-005 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: SOLARASE (SODIUM DICLOFENAC GEL) Action: AP AE (NA)

Applicant HYAL Therapeutic Class NSAID

Indication(s) previously approved TOPICAL TREATMENT OF ACTINIC KERATOSIS

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application _____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

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__c. The applicant has committed to doing such studies as will be required.

- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. Actinic Keratoses are very rare in pediatric patients and occur in the presence of very rare conditions such as Xeroderma pigmentosa

__5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ LPM /S/ 10/20/99

Signature of Preparer and Title Date

Orig NDA/BLA # 21-005
HFD 540 Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

13 PATENT INFORMATION

Solarase™ is covered by the following U.S. patents. Hyal Pharmaceutical Corporation believes that these patents would be infringed if a person not licensed by the owner engaged in the manufacture, use or sale of the drug composition described in this application:

United States Patent Number	Expiration Date
5,639,738	June 17, 2014
5,792,753	August 11, 2015

N21-005

HPC

Hyal Pharmaceutical Corporation

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

ORIGINAL

NEW CORRESP

NC

Oct. 29, 1998

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

Dear Dr. Blay,

Re: Question Regarding Investigators - Solarase NDA 21.005

This is a certification that Hyal has not and will not use any investigator in its Solarase Clinical Development Program or in any other of its clinical developments that has been disbarred as listed in the Blacklist published by the FDA.

Sincerely

PAnderson

Patricia Anderson
Director Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

By Courier and by fax

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

Oct. 29, 1998

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

Dear Dr. Blay,

Re: Question Regarding Investigators - Solarase NDA 21.005

This is a certification that Hyal has not and will not use any investigator in its Solarase Clinical Development Program or in any other of its clinical developments that has been disbarred as listed in the Blacklist published by the FDA.

Sincerely

PAnders

Patricia Anderson
Director Regulatory Affairs

By Courier and by fax

APPEARS THIS WAY
ON ORIGINAL

CSV / Rozma-tornaro 15-40

MENT OF HEALTH AND HUMAN SERVICES
UBLIC HEALTH SERVICE
D AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

NTS NAME AND ADDRESS
HARMACEUTICAL CORPORATION
5KYMARK AVENUE
SISSAUGA, ONTARIO
4Y2

3. PRODUCT NAME
SOLARASE 3% DICLOFENAC GEL

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IF FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM
IF RESPONSE IS 'YES' CHECK THE APPROPRIATE BOX BELOW:
[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION
[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
(APPLICATION NO. CONTAINING THE DATA)

HONE NUMBER (Include area code)
)625-8181

EE I.D. NUMBER
54

6. LICENSE NUMBER/NDA NUMBER
21.005

APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSION? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] LARGE VOLUME PARENTERAL DRUG PRODUCT PPROVED UNDER SECTION 505 OF THE FEDERAL OOD, DRUG, AND COSMETIC ACT BEFORE 91/92
elf Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See Item 7, reverse side before checking box)

[ ] HE APPLICATION QUALIFIES FOR THE ORPHAN XCEPTION UNDER SECTION 736(A)(1)(E) of the federal, food, ug and cosmetic Act
ee item 7, reverse side before checking box)

[ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(A)(1)(F) of the Federal Food, Drug and Cosmetic Act
(See item 7, reverse side before checking box)

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

[ ] HOLE BLOOD OR BLOOD COMPONENT FOR RANSFUSION

[ ] A CRUDE ALLERGENIC EXTRACT PRODUCT

[ ] N APPLICATION FOR A BIOLOGICAL PRODUCT OR FURTHER MANUFACTURING USE ONLY

[ ] AN 'IN VITRO' DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHASE ACT

[ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
r is attached

[X] YES [ ] NO
(See reverse side if answered YES)

ompleted form must be signed and accompany each new drug or biologic product application and each new lement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment

OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
PAnders	Director, Regulatory Affairs	September 4, 1998

BEST POSSIBLE COPY

NDA 21-005

Hyal Pharmaceutical Corporation
Attention: Patricia Anderson
Director of Regulatory Affairs
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6

OCT 21 1999

Dear Ms. Anderson:

Please refer to your new drug application (NDA) dated October 20, 1998, received October 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Solarase (diclofenac sodium) Gel, 3%.

We acknowledge receipt of your submissions dated October 29, 1998; and January 18, February 8 and 17, March 17 and 26, May 21, July 7, August 5, 12, 19 (two) and 25, September 1 and 3, 1999.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

A. Chemistry:

1. Please identify and quantitate impurity/degradant responsible for development of yellow color of the drug product at accelerated, as well as room temperature, storage conditions. In addition, the percentage of each of the impurities should be determined in the drug substance. Impurities and degradants present at concentration greater than — in the bulk drug substance should be quantitated.

   Your amendment dated August 12, 1999, in response to the Information Request Letter of July 9, 1999, was incomplete. According to the 1993 forced degradation study report "the yellowing in the drug product may be caused by a strong ——— that was below the level of the detection in any of the assays run". There is no technical reason why a strong ——— should not be detected by ——— method, if the detection ——— is properly chosen. Furthermore, the source of this yellowing is suspected to be impurity A or a decomposition product of impurity A from the drug substance. Data submitted are insufficient to establish not only the identity and amount of degradant/impurity but also whether it is a single chemical substance that is responsible for the discoloration of the product. Also, the analytical method used for generating stability data, to support the shelf life of the drug product, is inappropriate for assessing product stability.

2. ——— method used for determination of diclofenac related substances should be modified to include a variable ——————— to obtain the maximum ——— and retention time for various impurities and degradants. After the method is validated you should analyze reserved samples from pre-clinical lots to identify and quantitate the impurities and degradants present in the drug product.

3. Test results for related substances are not reported on your certificate of analysis. In the absence of test results your conclusion that "there were no related impurities that exceeded —— ' is not supported. Submit test results (with ——— of related substances for Lot Numbers 226500195, 226500295 and 226500395. Specification limits cannot substitute for submission of test results.

4. The specification for related substances or impurities in the drug product should be revised to conform to current USP requirements and ICH guidelines. Any unidentified impurity should be limited to —

5. We note that in item 3.2.8, ——— of the Drug Substance, of your original submission, you claimed that this item was not applicable to the application. We disagree with this statement and request that you submit a revised item 3.2.8. Our reasons for this are as follows:
   a) your description of the drug substance describes it as ——— hygroscopic, and sparingly soluble in water;
   b) in at least one development batch, ——— of diclofenac was observed (vol. 1.3, pg. 3); and,
   c) it is unclear from the data whether ——————— of diclofenac sodium are known.

B. Pharmacology/Toxicology

Data on impurities and degradants are inadequate to evaluate the safety of the drug product. Provide supportable evidence to demonstrate that there are no impurities or degradants (reference chemistry deficiencies noted above) present at concentrations greater than — of the bulk drug substance or greater than —— of the drug substance in the drug product; or else demonstrate that impurities and/or degradants are present at less than or comparable levels in marketed diclofenac tablets.

Any impurities and/or degradants found at concentrations higher than —— in the bulk drug substance or greater than —— of the drug substance in the drug product will require genotoxicity testing.

Although not the basis for the not approvable action of this application, the following issue should be addressed in any resubmission:

A. Chemistry

1. Individual specifications for [redacted] and [redacted] should also be submitted.

2. Specification test results of related substances by the [redacted] method and chromatographic purity by the USP method (along with the [redacted] should be submitted.

3. Raw data (e.g., lab notes) to support various corrections included in Stability Report Table should be submitted. In addition, in several cases, stability results for product description specification are reported simply as "conforms". Please provide an explanation.

4. Please submit a justification for an unusually broad range of retention time indicated for the diclofenac peak on page 69 (between [redacted] minutes).

5. In-process specifications test results, including pH and viscosity, for the batches listed in the table entitled [redacted] of Bulk 3% Diclofenac Gel' (amendment dated August 12, 1999, p. 49) should be provided.

6. Specifications for [redacted] hyaluronate sodium should be revised to also include a specification for [redacted] and the absence of [redacted] and [redacted] These specifications should apply to both [redacted] hyaluronate sodium.

B. Clinical

1. Please provide the following items which were not provided in the original NDA submission:
   a) Photography of the phase 3 studies CT1101-03 and CT1101-04 (Appendix 16.4 of these studies).
   b) Tables on complete clearance of lesions by covariates (Tables 11.1-11.9 in Integrated Summaries of Safety and Efficacy, vol 1.46), and
   c) Tables in the integrated report on safety data in actinic keratosis [redacted] studies (Tables 14 and 18, vol 1.50)
2. An analysis contrasting the proportion of patients showing complete clearance of lesions (cumulative lesion number score=0) in the diclofenac group vs that in the vehicle group 30 days post-treatment should be presented for each MBA (major body area) for the three phase 3 studies, for each study separately and for all studies combined.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

APPEARS THIS WAY
ON ORIGINAL

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 10/21/99

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-005
HFD-540/Div. Files
HFD-540/White
HFD-540/Kozma-Fornaro
HFD-540/Ko
HFD-540/Walker
HFD-540/Reid
HFD-540/Jacobs
HFD-540/DeCamp
HFD-540/Shetty
HFD-540/Gautam-Basak
HFD-540/Bashaw
HFD-880/Tandon
HFD-725/Freidlin
HFD-725/Srinivasan
HFD-002/ORM
HFD-105/ADRA
HFD-830/DNDC Division Director
DISTRICT OFFICE

Drafted by: KDW/October 7, 1999
Initialed by:
final:
filename: NALTR

NOT APPROVABLE (NA)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 19 1999

John E. Wolf, M.D.
Department of Dermatology
Baylor College of Medicine
6560 Fannin Street, Suite 802
Houston, Texas 77030

Dear Dr. Wolf:

Between May 11 and 13, 1999, Ms. Kara Lemons, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # CT-1101-03) of the investigational drug Solarase (3% diclofenac in —— hyaluronan gel, HYAL-CT-1101), performed for Hyal Pharmaceutical Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Lemons during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practices II, HFD-344
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

JUN 6 1999

MEMO

NDA: 21-005
PRODUCT: Solarase (Diclofenac Sodium 3% w/w topical gel)

REVIEWER: Veneeta Tandon

Re: Two different sources of hyaluronic acid used in the formulation
[redacted] vs. [redacted]

This memo supplements the NDA pharmacokinetic review regarding the use of two different sources of hyaluronic acid [redacted] versus [redacted]. Two clinical PK studies were done with diclofenac gel that used the [redacted] form of hyaluronic acid (Study EP105 in subjects with compromised skin and study BP 329 in healthy subjects). A retrospective analysis was done with three well-controlled clinical trials (CT-1101-03, CT-1101-04 and CT-1101-07) which used the [redacted] form of the hyaluronic acid. The formulation used in these clinical trials is the to-be-marketed formulation. The duration of study EP105 was 7 days, while the duration of the controlled clinical trials was 30, 60 and 90 days respectively. The area treated in study EP105 was 4 times more than that used in the clinical trials and the dosing schedule was 2 gm gel q.i.d in a 10x10 cm block. In comparison, the dosing schedule for the controlled clinical trials was 0.5 g of gel b.i.d. in up to three 5x5 cm blocks (depending upon severity).

Comparable mean serum diclofenac levels over the first 6 hours were seen from both the Clinical PK study as well as the Controlled Clinical study. The mean C_{max0-6} in the compromised skin from Study EP105 was 24.51 ng/ml (%CV 178). The mean C_{max0-6} from patients treated twice daily on three application blocks in the controlled clinical trials was 19.9 ng/ml. Thus, even with a higher dose, the absorption of diclofenac is not significantly different, suggesting that attainment of thermodynamic equilibrium between the viscosity of the gel, the resistance of the skin and the elimination of the drug has been reached. Therefore the source of hyaluronic acid is not likely to impart any changes in the absorption behavior of diclofenac from the drug product.

In regards to the elimination of diclofenac, there is indirect evidence that there is continued absorption of diclofenac from the skin. This is evidenced by a very slow elimination half-life for topically applied diclofenac (~11hrs) relative to orally absorbed diclofenac (~2hr half-life). This prolonged elimination is due to continued absorption of residual diclofenac across the skin. In any event, the net result of in vivo biostudies using topical formulations of diclofenac with hyaluronic acid from both sources is to produce roughly equivalent levels of diclofenac in the plasma, suggesting that the source of hyaluronic acid is not a factor in bioavailability.

As to the effect of source of hyaluronic acid on the local availabilty of diclofenac, the sponsor has not conducted any study to assess the topical retention of the drug product. However, one could infer that as the plasma levels are roughly equivalent, that based on the princples of diffusion (i.e. Fick's Law) that the equilibrium set up at the gel-skin interface is also roughly equivalent regardless of the source of the hyaluronic acid.

/S/

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 6/24/99

APPEARS THIS WAY
ON ORIGINAL

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%
Request for Waiver of Pediatric Assessment

As a follow-up to our telephone conversation on October 12, 2000, attached is a copy of the formal request for waiver of pediatric studies, as previously submitted to NDA 21-005 on April 24, 2000.

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

If you need additional information, please contact me at (858) 625-2424, ext. 3231.

Sincerely,

Pearl T. Amos
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON 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 0FN

SkyePharma

Request for Waiver of Pediatric Assessment
21 CFR 314.55(c)(2)(i)

As provided in §314.55(c)(2)(i) SkyePharma Inc., the applicant, requests a full waiver of the requirement to assess the safety and effectiveness of Solarase™ (Sodium Diclofenac 3% w/w) Topical Gel (NDA #21-005) for the claimed indication of the topical treatment of actinic keratoses (AK) in all pediatric subpopulations.

AK lesions are induced by excessive exposure to ultraviolet light and are typically found in patients who are middle-aged or older. SkyePharma Inc. certifies that Solarase does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

APPEARS THIS WAY
ON ORIGINAL

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

April 24, 2000
Date

APPEARS THIS WAY
ON ORIGINAL

SkyePharma Inc. 10450 Science Center Drive. San Diego. California 92121. USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com
Registered in England No. 3076928 Registered office 105 Piccadilly London W1V 9FN