CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

CHEMISTRY REVIEW(S)

JUL 19 1999

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-005	CHEM. REVIEW #: 1	REVIEW DATE: 1/10/99	
SUBMISSION/TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	10/20/98	10/23/98	12/8/98

NAME & ADDRESS OF APPLICANT: Hyal Pharmaceutical Corp.
2425 Skymark Avenue
Mississauga, Ontario, Canada L4W 4Y6

DRUG PRODUCT NAME

Proprietary:	Solarase
Nonproprietary/USAN:	Sodium Diclofenac Gel, 30 mg/g
Code Names/#'s:	CAS# 15307-79-6
Chemical Type:	
Therapeutic Class:	NSAID

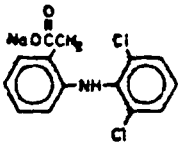
ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory drug (NSAID)

DOSAGE FORM: Gel
STRENGTHS: 3% W/W
ROUTE OF ADMINISTRATION: Topical
DISPENSED: XXX Rx ___OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Diclofenac Sodium [*1973*]. $C_{14}H_{10}Cl_2NNaO_2$. 318.14. (1) Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt; (2) Sodium [*o*-(2,6-dichloroanilino)phenyl] acetate. *CAS-15307-79-6*. JAN. *Anti-inflammatory*. Voltaren (Ciba-Geigy); Voltaren Ophthalmic (Ciba Vision Ophthalmics) ✧*GP 45840*



Structural Formula:

Molecular Weight: 318.13

RELATED DOCUMENTS (if applicable):

Related Document	Holder	Subject	LOA date	Review Status and date	Reviewed By
IND			n/a	Active	
IND			n/a	Active	Ho/HFD-550
DMF			12/31/96	ADEQUATE, 8/10/98; IR letter issued 8/12/98 for	
DMF			2/14/97	not reviewed; LOA replaced by corrected reference to DMF	
DMF			1/4/99	INADEQUATE, 6/28/99; IR letter issued, 6/30/99	Gautam-Basak
DMF			none; reviewed w/DMF	INADEQUATE, 6/28/99; IR letter issued, 6/30/99	Gautam-Basak
DMF			8/2/96	last review 5/10/95; ADEQUATE	assigned to Mamta Gautam-Basak, 7/16/99
DMF			11/12/96	INADEQUATE, 7/15/99; IR letter issued, 7/19/99	Shetty
DMF			9/24/96	not reviewed	

CONSULTS:

Dr. DeCamp of HFD-540 will request Methods Validation. Trade name (Solarase) confirmation has been requested by Dr. DeCamp.

REMARKS/COMMENTS:

Originally, the drug, diclofenac sodium was developed by Ciba Geigy and marketed as an oral formulation first in Japan in 1974. Diclofenac has a pka of 4.0 and a partition coefficient of 13.4. The structural elements include a phenyl acetic acid group, a secondary amino group and a phenyl ring containing chlorine atoms, which cause maximum twisting of the ring. The drug is synthesized by

Diclofenac is off patent and listed in the orange book. It has recently been listed in the USP. The present NDA is for the use of the

drug as a gel for topical treatment of active keratoses. The drug is a derivative of phenyl acetic acid and commonly classed as a non-steroidal anti-inflammatory drug (NSAID). It belongs to the group of arylacanoic acid NSAIDs. Other members of this group are bufexamac, mefenamic, ——— meclofenamic, flufenamic and tolfenamic. This NDA #21-005 belongs to HFD-540.

An IR letter has been issued to this applicant.

The DMF —— Type II has been reviewed. Deficiencies have been noted.

CONCLUSIONS & RECOMMENDATIONS:

The application is NOT APPROVABLE for manufacturing and controls under section 505 of the ACT. Specific items which are not approvable are identified under the following headings: ——— (deficient DMF), Drug Product (specifications for hyaluronate sodium), and Stability (development of color on storage at room temperature). Information request letters were issued to the applicant on July 9, 1999, and to ——— (the DMF holder ——— on June 30, 1999. A deficiency letter was issued to ——— on July 19, 1999.

/S/ 7/20/99

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 21-005
HFD-540/Division File
HFD-520/BVShetty
HFD-540/MO/Ko
HFD-540/Pharm/Reid
HFD-540/CSO/White
HFD-540/WHDeCamp /S/ 7/19/99
R/D Init by: WHDeCamp

See Chem TL /S/ 8/3/99
Review Addend—
dated 7/19/99

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: July 19, 1999

AUG 8 1999

To: Jonathan K. Wilkin, M.D., Director, HFD-540
Chi-Wan Chen, Director, HFD-830

From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Team Leader's Addendum, NDA 21-005, Chemistry Review #1

The following comments are my Team Leader's addendum to Dr. Shetty's Chemistry Review #1 for NDA 21-005, Solarase (diclofenac sodium) Gel, 3.0%. As noted in his review, an Information Request (IR) letter was issued to the Applicant on July 9; certain of the items in that letter are commented on below to provide a focus for the next review cycle. My concurrence with Dr. Shetty's review is subject to the comments noted below. My comments follow the usual outline of review notes; item, volume and page references are to the NDA.

A. Drug Substance

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D. Environmental Assessment

No comments.

E. Methods Validation

Dr. Shetty recommended that the Hyal method for related substances in diclofenac sodium and the product tests for diclofenac sodium assay and related substances be validated. I concur.

F. Labeling

This item was evaluated by Dr. Shetty as unacceptable. I DO NOT AGREE WITH THIS CONCLUSION. Given the numerous other deficiencies, there appears to be little regulatory utility in a detailed review of the package insert at this time.

G. Establishment Inspections
No comments.

/S/

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
Division of Dermatological and
Dental Drug Products

cc: Archival NDA 21-005
HFD-540/Div. Files
HFD-540/White
HFD-540/Ko
HFD-540/Walker
HFD-540/Reid
HFD-540/Jacobs
HFD-540/Gautam-Basak
HFD-540/DeCamp
HFD-520/Shetty
HFD-520/Katague
HFD-830/Dunn
HFD-830/Chen

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-005 **REVIEW #:** 2 **REVIEW DATE:** 23-SEP-1999 SEP 28 1999

SUBMISSION	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	07-JUL-99	09-JUL-99	16-JUL-99
Amendment	12-AUG-99	16-AUG-99	18-AUG-99

NAME & ADDRESS OF APPLICANT: Hyal Pharmaceuticals Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6

DRUG PRODUCT NAME

Proprietary:	Solarase
Established: Diclofenac Sodium	
Code Name:	HYAL-CT1101
Product Number:	
Chem.Type/Ther.Class:	NSAID

PHARMACOL. CATEGORY/INDICATION: Treatment of actinic keratoses

DOSAGE FORM:	Gel
STRENGTHS:	3% w/w
ROUTE OF ADMINISTRATION:	Topical
Rx/OTC:	_X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See Chemistry Review #1

SUPPORTING DOCUMENTS (if applicable): Same as listed in Chemistry Review #1

CONSULTS: Yes, Microbiology review dated 9/15/99

REMARKS/COMMENTS:
Hyal's response to the FDA's information request letter dated June 22, 1999 and CMC information request letter dated July 9, 1999 is the subject of this review. The response is incomplete.

We have not received updated information for Type II DMF — A deficiency letter was issued on July 19, 1999.

The updated information to DMF —— (submission dated 7/19/99) has been reviewed. Minor deficiencies noted will be forwarded to the DMF holder.

CONCLUSIONS & RECOMMENDATIONS:
The application is NOT APPROVABLE for manufacturing and controls under section 505 of the ACT. Data submitted are insufficient to establish the identity and amount of degradants and/or impurities present in the drug substance/drug product. For evaluation of the safety of the drug product we cannot confirm that there are no impurities or degradants present at concentrations a) greater than —— of the bulk drug substance or b) greater then —— of the drug substance in the drug product. Deficiencies identified as "Impurities and Degradants" for both Drug Substance and Drug Product constitute NA issues.

/S/ 9/27/99

Mamta Gautam-Basak, Ph.D.
Review Chemist, HFD-540

cc:
Org. NDA 21-005
HFD-540/Division File
HFD-540/Ko
HFD-540/White
HFD-540/Walker
HFD 540/Tandon
HFD-540/Reid
HFD-540/Jacobs
HFD-540/Gautambasak
HFD-540/DeCamp
HFD-830/Dunn
HFD-830/Chen

/S/ 9/28/99 - see addendum

R/D Init by: TEAMLEADER

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ON ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: September 28, 1999

SEP 28 1999

To: Jonathan K. Wilkin, M.D., Director, HFD-540
Chi-Wan Chen, Director, HFD-830

From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Team Leader's Addendum, NDA 21-005, Chemistry Review #2

In addition to the comments from Dr. Gautam-Basak's Chemistry Review #2 for NDA 21-005, Solarase (diclofenac sodium) Gel, 3.0%, the following should be added to the action letter:

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:
(1) your description of the drug substance describes it as ——— , hygroscopic, and sparingly soluble in water;
(2) in at least one development batch, ——————— of diclofenac was observed (vol. 1.3, pg. 3); and
(3) it is unclear from the data whether ——————————— of diclofenac sodium are known.

/S/

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
Division of Dermatological and
Dental Drug Products

cc: Archival NDA 21-005
HFD-540/Div. Files
HFD-540/White
HFD-540/Ko
HFD-540/Walker
HFD-540/Reid
HFD-540/Jacobs
HFD-540/Gautam-Basak
HFD-540/DeCamp
HFD-830/Dunn
HFD-830/Chen

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUN 9 2000

NDA #: 21-005 **REVIEW #:** 3 **REVIEW DATE:** 04-JUN-2000

SUBMISSION	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	20-OCT-1998	23-OCT-1998	Chem. Rev. #1
Amendment	07-JUL-1999	09-JUL-1999	Chem. Rev. #2
Amendment	12-AUG-1999	16-AUG-1999	Chem. Rev. #2
Amendment	08-OCT-1999	12-OCT-1999	25-OCT-1999
Amendment	21-JAN-2000	24-JAN-2000	02-FEB-2000
Amendment	24-APR-2000	25-APR-2000	24-MAY-2000

NAME & ADDRESS OF APPLICANT: SkyePharma Inc.
(formerly Hyal)
10450 Science Center Drive
San Diego, CA 92121

DRUG PRODUCT NAME
Proprietary: Solarase™
Established: Diclofenac Sodium
Code Name: HYAL-CT1101
Product Number:
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Treatment of actinic keratoses

DOSAGE FORM: Gel
STRENGTHS: 3% w/w
ROUTE OF ADMINISTRATION: Topical
Rx/OTC: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Same as in USP/USAN (see Chemistry Review #1)

SUPPORTING DOCUMENTS (if applicable): Type II DMFs ——— (Also see Chemistry Reviews #1 and #2)

DMF #	Holder	Subject

CONSULTS: NA

REMARKS/COMMENTS:
SkyePharm's response to FDA's Not Approvable (NA) letter dated October 21, 1999, and a partial response to CMC information request (IR) letter dated July 19, 1999, are the subject of this review. Deficiencies are reviewed in the original NDA format and may not follow the order in which they appeared in the NA letter.

Dr. G. Bykadi (HFD-623, OGD) reviewed (Chemistry Review #2) the response to our deficiency letter dated July 19, 1999 (DMF [redacted] for a [redacted] Per Chemistry Review #2 of the DMF the holder has addressed all deficiencies as listed in deficiency letter dated July 19, 1999, satisfactorily except the issue of [redacted] Overall the DMF was found to be Inadequate. Since additional supporting information for [redacted] was submitted in the NDA, the new DMF deficiencies are not considered as the approvability issue for the subject NDA (see review notes).

Type II DMF [redacted] is considered adequate to support the NDA 21-005 (see Microbiologist's review dated 9/17/99).

The applicant has satisfactorily addressed all CMC deficiencies listed in the agency's NA letter dated 10/21/99 (NDA 21-005). Method validation data submitted for the assay of the finished drug product dosage form are found to be suitable.

Methods Validation Package is under review and upon completion the methods will be forwarded to district for validation.

Information regarding labeling is incomplete (submission dated 4/24/00). A proof copy is requested.

The cGMP status of both DS and DP manufacturing facilities is acceptable (see EER attached).

APPEARS THIS WAY
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CONCLUSIONS & RECOMMENDATIONS:

An APPROVAL action is recommended from the CMC standpoint provided a proof copy of the container and carton labeling is submitted for our review. The comments listed on page 18 should be forwarded as Phase 4 commitments.

/S/ 5/9/00

Mamta Gautam-Basak, Ph.D.
Review Chemist, HFD-540

cc:
Org. NDA 21-005
HFD-540/Division File
HFD-540/Ko
HFD-540/White
HFD-540/Walker
HFD 540/Tandon
HFD-540/Reid
HFD-540/Jacobs
HFD-540/Gautambasak
HFD-540/DeCamp /S/ 6/9/00
HFD-830/Dunn
HFD-830/Chen

R/D Init by: TEAMLEADER /S/ 7/16/00

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ON ORIGINAL

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21005/000
Stamp: 22-OCT-1998 Regulatory Due: 24-JUL-2000
Applicant: HYAL
L4W 4Y6
MISSISSAUGA, ONTARIO, CA

Priority: 3S Org Code: 540
Action Goal: District Goal: 23-JUN-1999
Brand Name: SOLARASE(DICLOFENAC SODIUM)3%W/W TOP GEL
Established Name:
Generic Name: DICLOFENAC SODIUM
Dosage Form: GEL (GEL)
Strength: 0.3%

FDA Contacts:			
R. BLAY	(HFD-46)	301-827-7378	, Project Manager
B. SHETTY	(HFD-520)	301-827-2187	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

ACCEPTABLE on 08-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: ———
DMF No: —
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: ———

Establishment: ———
DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: ———

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21005/000
Stamp: 22-OCT-1998 Regulatory Due: 22-AUG-1999
Applicant: HYAL
2425 SKYMARK AVE, L4W 4Y6
MISSISSAUGA, ONTARIO, CA

Priority: 3S Org Code: 540
Action Goal: District Goal: 23-JUN-1999
Brand Name: SOLARASE(DICLOFENAC SODIUM)3%W/W TOP GEL
Established Name:
Generic Name: DICLOFENAC SODIUM
Dosage Form: GEL (GEL)
Strength: 0.3%

FDA Contacts:			
R. BLAY	(HFD-540)	301-827-2023	, Project Manager
B. SHETTY	(HFD-520)	301-827-2187	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

ACCEPTABLE on 08-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: ——
DMF No: —
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment: ——
DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 08-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities:

APPEARS THIS WAY
ON ORIGINAL