CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology and Toxicology Data

Key Words: Diclofenac, NSAID, Actinic Keratosis

JUL 16 2000

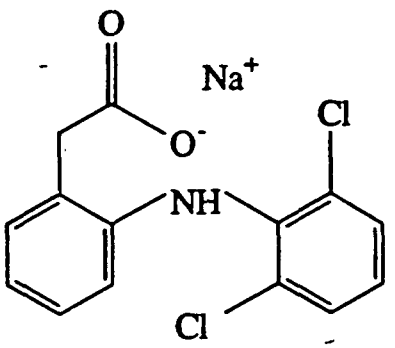
Reviewer: Lynnda Reid, Ph.D.
Division: Dermatologic and Dental Drug Products, HFD-540
Date: June 12, 2000

NDA No: 21,005
Amendment No. N000 - Addendum Review No. 2
Original and Amendments Dated: 1/18/99, 5/21/99, 7/7/99, 8/12/99, 1/21/00, 4/24/00

Information to Sponsor: Yes ( ) No (x)

Sponsor: SkyePharma INC. (Formerly Hyal Pharmaceutical Corporation)
10450 Science Center Drive
San Diego, CA 92121

Drug: Solarase™ 3% Gel
Code Name: HYAL-CT1101
Generic Name: Diclofenac sodium
Trade Name: Diclofenac
Chemical Names: 2-[2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt;
[o-(2,,6-dichloranilino)phenyl]acetic acid sodium salt; and
sodium [0-[2,6-diclorophenyl)amino]phenyl]acetate
CAS Number: CAS No. 15307-79-6
Molecular Formula: $C_{14}H_{10}Cl_2NO_2Na$
Molecular Weight: 318.14
Structure:



Description: White to Slightly Yellow crystallized powder, sparing soluble in H_2O
Absorption Spectrum: Diclofenac in methanol (0.03 mg/ml) absorbs between ——— nm
with peaks at ——— nm

Drug Class: Nonsteroidal Anti-inflammatory Drug (NSAID)

Indication: Treatment of Actinic Keratosis

Clinical Formulation: Diclofenac sodium 3% topical gel.

Ingredients	%w/w	Function
Diclofenac sodium	3.0	Prostaglandin Inhibitor
Sodium hyaluronate *	—	—
Polyethylene glycol monomethyl ether —	—	—
Benzyl alcohol	—	—
Purified Water	—	—

Route of Administration: Topical

Proposed Clinical Protocol or Use: Solarase™ gel is to be applied to actinic keratosis lesions twice daily and gently smoothed into the affected skin. The amount needed depends upon the size of the lesion site. Normally 0.5 g of gel will be used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from — to 90 days. Recommendations and indications for the use of Solarase™ have not been established.

Disclaimer: Note some material may be taken directly from Sponsor's submission.

BACKGROUND

The original Pharmacology/Toxicology Review was filed on October 20, 1999. At that time, it was concluded that the data provided on impurities and degradants was inadequate to evaluate the safety of Solarase 3% Gel. The following information was relayed to the Hyal Pharmaceutical Corporation on October 21, 1999:

> *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 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.*

Subsequent to filing the first Pharmacology/Toxicology review dated July 16, 1999, chemistry identified several issues which may impact the potential safety of the product, including a discernible

degradation product resulting in yellow discoloration of the product over time. The failure of the Sponsor to identify and/or quantify this strong ——— brought into question the validity of their analytical methods.

This review addresses chemistry amendments dated October 8, 1999, January 21, 2000 and April 24, 2000, as well as communications received from CDER chemistry reviewers regarding degradation and photo-degradation products (CMC Review #3 dated June 4, 2000).

DISCUSSION

CMC Findings:

1) ***Validation of Analytical Methods:*** Revised finished product specifications and methods of analysis for the finished drug product were found to be acceptable.

2) ***Quantification of Impurities and Degradants:*** Acceptable limits for drug product impurities are as follows: ——— of diclofenac sodium; no other single known or unknown impurity greater than — of diclofenac sodium; total impurities: ——— of diclofenac sodium.

   ——— aged diclofenac resulted in some peaks at — nm, that could account for the yellow color sometimes observed in aged drug product. Two peaks found at — nm were further analyzed using ——— The peaks corresponded to a molecular weight of — possibly an ——— formed by ——— The yellow impurity was found at levels of ——— in Lots VGD6 and VHD7, respectively, previously used in the dermal toxicity studies, and in Lot XPB292 used in the carcinogenicity study

3) ***Photo-degradants:*** The parent compound and – other compounds were identified following exposure of the diclofenac sodium raw material (Lot # 226500295) to direct sunlight for up to 12 hours. At 3, 6, 9 and 12 hours the parent compound was reduced from 100% to 82.7, 78.8, 76.1 and 70.5%, respectively. Based on molecular weight, 3 of the degradants were tentatively identified ——— unidentified peaks with molecular weights of ——— accounted for up to — of the degraded product at 12 hours, while the other peaks ranged between———

   Note: During the photo-irritation and 2-year photo-cocarcinogenicity studies in mice, there was no observed increase in adverse skin reactions which might be attributable to photo-degradation products.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY AND CONCLUSION

The Sponsor has adequately addressed the outstanding nonclinical concerns regarding impurities, degradants and method analysis. From a Pharmacology/Toxicology perspective, there are no remaining safety concerns. The application is considered approvable with minor recommended labeling changes.

APPEARS THIS WAY
ON ORIGINAL

/S/

6-12-00

Lynnda Reid, Ph.D.
Pharmacologist/Toxicologist

Date

Sent to DFS
6-15-00

cc:
NDA 21-005
HFD-540
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs
HFD-540/CSO/White
HFD-540/MO/Ko
HFD-540/Chem/Gautam-Basak

For Concurrence Only:
HFD-540/DD/JWilkin
HFD-540/TL/AJacobs

/S/ 6/15/00
/S/ 7/16/00

APPEARS THIS WAY
ON ORIGINAL

Executive CAC
Date of Meeting – June 15, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Ken Hastings, D.Sc., HFD-590, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Team Leader
Lynnda Reid, Ph.D., HFD-540, Presenting Reviewer

Author of Minutes: Lynnda Reid

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21-005
Drug Name: Diclofenac 3% Topical Gel
Sponsor: Hyal Pharmacutical Corporation, Ontario, Canada

Mouse 2-Year Dermal Carcinogenicity Study: Diclofenac 3% Topical Gel (with — Hyaluronate) is being developed for the Treatment of Actinic Keratosis. This dermal carcinogenicity study was initiated on 1/3/96 and terminated on 2/16/98. Groups of 60 albino Swiss Crl:CD®-I(ICR)BR mice/sex were administered topical doses of 0 to 0.035% diclofenac/ — sodium hyaluronate (HA), 0.2 ml, to the shaved interscapular region, 7 days/wk for up to 104 weeks. The MTD was based on gastro-intestinal effects (presumably due to oral consumption) resulting in mortality at concentrations of ≥0.09%. The incidence of tumors was generally low and distributed similarly between groups. Diclofenac has previously been tested for carcinogenicity potential following oral administration at doses up to 2 mg/kg/day in rats and 0.3 mg/kg/day in mice. Furthermore mutagenicity and genotoxicity studies demonstrated no evidence of genotoxicity.

Executive CAC Recommendations and Conclusions:

The Exec CAC concurred with the following review findings:

- There was no evidence of diclofenac-related skin or systemic tumorigenic effects at the highest concentration (0.035%) tested.
- The study was found to be adequate based on similar weight gain patterns between groups and acceptable survival up to approximately 88-90 weeks.

/S/ 6/16/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
NDA 21-005
HFD-540/Division File
HFD-540/Team leader/Jacobs
HFD-540/Reviewer/Reid
HFD-540/CSO/White
HFD-024/ASeifried

APPEARS THIS WAY
ON ORIGINAL

OCT 13 1999

Review and Evaluation of Pharmacology and Toxicology Data

Key Words: Diclofenac, NSAID, Actinic Keratosis

Reviewer: Lynnda Reid, Ph.D.
Division: Dermatologic and Dental Drug Products, HFD-540
Date: September 30, 1999

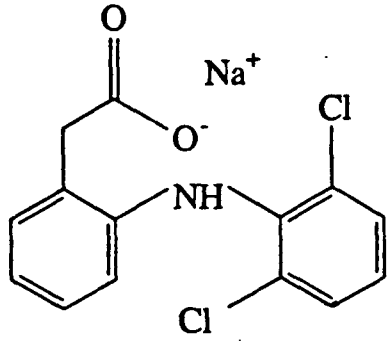
NDA No: 21,005
Amendment No. N000 - Addendum Review
Dated: October 20, 1998 and September 1, 1999

Information to Sponsor: Yes ( ) No (x)

Sponsor: Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
905-625-8181; FAX 905-625-1884

Drug:

Generic Name: Diclofenac sodium
Trade Name: Solarase 3% Gel
Chemical Names: 2-[2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt;
[o-(2,,6-dichloranilino)phenyl]acetic acid sodium salt; and
sodium [0-[2,6-diclorophenyl)amino]phenyl]acetate
CAS Number: CAS No. 15307-79-6
Molecular Formula: $C_{14}H_{10}Cl_2NO_2Na$
Molecular Weight: 318.14
Structure:



Description: White to Slightly Yellow crystallized powder, sparing soluble in H_2O
Absorption Spectrum: Diclofenac in methanol (0.03 mg/ml) absorbs between ——— nm
with peaks at ——— nm

Drug Class: Nonsteroidal Anti-inflammatory Drug (NSAID)

Indication: Treatment of Actinic Keratosis

Clinical Formulation: Diclofenac sodium 3% topical gel.

Ingredients	%w/w	Function
Diclofenac sodium	3.0	Prostaglandin Inhibitor
Sodium hyaluronate *	—	—
—		
Polyethylene glycol monomethyl ether —	—	—
—		
Benzyl alcohol	—	—
Purified Water	—	—

Note: The source of the hyaluronate for the nonclinical and clinical safety and PK studies was from — The source used for the pivotal clinical trials and the to be marketed formulation is — (See Discussion).

Route of Administration: Topical

Proposed Clinical Protocol or Use: Solarase™ gel is to be applied to actinic keratosis lesions twice daily and gently smoothed into the affected skin. The amount needed depends upon the size of the lesion site. Normally 0.5 g of gel will be used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from — to 90 days. Recommendations and indications for the use of Solarase™ have not been established.

Disclaimer: Note some material may be taken directly from Sponsor's submission.

BACKGROUND

The original Pharmacology/Toxicology Review was filed on October 20, 1999. At that time, it was concluded that there was insufficient information on the — hyaluronan to evaluate the safety of Solarase 3% Gel. The unresolved safety issues were as follows:

1) *Hyaluronate Sodium:* To date, the source of the hyaluronate used in all pivotal nonclinical studies appears to be from — and it is unclear what the source is for the many of the clinical studies including the dermal sensitization and irritation studies. At some point in the development of the 3% diclofenac/ — hyaluronate gel, the source of the hyaluronate was changed from — to — While the specifications for hyaluronate itself appear to be reasonably similar, safety information regarding and impurities and — contaminants from the — hyaluronate product has not been submitted. Also, due to the presence of —, there are concerns that this product may

be antigenic. Therefore, the following informational request was sent to the Sponsor on June 22, 1999:

(Please) provide material to assure the safety of the ——— hyaluronic acid (HA) and any potentially hazardous impurities which may result from the ——— process, such as ——— If data is not currently available to assure the safety of the ——— HA, a nonclinical toxicology study should be performed to bridge to the nonclinical studies performed with the HA ——— If the ——— HA was not used in formulations used for clinical sensitization studies, then the sensitization potential of the ——— HA should be evaluated nonclincially in an assay such as the Local Lymph Node Assay (LLNA). If further testing is necessary, we recommend submission of study protocols for review concurrence prior to initiation of studies.

2) ***Solarase Degradation Products or Any Other Issues Arising from the CMC Review:*** Any findings arising from the CMC review which may impact safety will need to be addressed by the Sponsor.

Subsequently, several amendments have been received from the Sponsor which address not only the safety concerns with the ——— hyaluronan, but also with chemistry questions regarding identification and quantitation of impurities and degradation products.

This review addresses amendments received on August 9, August 20 and September 3, 1999, as well as communications received from CDER chemistry reviewers.

Disclaimer: Note some material may be taken directly from Sponsor's submission.

APPEARS THIS WAY
ON ORIGINAL

SECTION I: DATA SUBMITTED IN SUPPORT OF THE HYALURONATE ———

Index of Supplemental Pharmacology and Toxicology Studies Submitted (9/3/99):

No.	Study Title	Study No.
1	Primary Dermal Irritation Study of Sodium Hyaluronic Acid (HYA-A)	61-Kei-19-2
2	Ocular Mucosa Irritation Study of Sodium Hyaluronic Acid (HYA-A)	61-Kei-19-3
3	Phototoxicity Study of Sodium Hyaluronic Acid (HYA-A)	— 86-1960
4	Contact Photosensitization Study of Sodium Hyaluronic Acid (HYA-A)	— 86-2008

Review of Submitted Studies: The following studies were performed for ——— using sodium hyaluronic acid ———

Study 1: **Primary Dermal Irritation Study of Sodium Hyaluronic Acid (HYA-A)**
Study No: 61-Kei-19-2
Volume and Page No.: BP, Page 104
Conducting Laboratory and Location: ———

Date of Study Initiation: August 11, 1986 to September 5, 1986
GLP Compliance: Yes
QA Report: Yes (x) No ( )
Methods and Dosing: HA (0.5 ml) was placed evenly on a piece of lint and attached to 2 areas of the upper or lower side of the clipped back. The other 2 areas on the other side were similarly treated with water soaked lint. All areas were then covered with oilpaper and rubber sheeting to prevent evaporation. Protective coverings and test material were removed after 4 hours.
Species/Strain: Japanese White Rabbits (JW-NIBS)
#/sex/group or time point: 6 males
Age: 2 months
Weight: 2.02 to 2.35 kg
Supplier: ———
Dosage Groups in Administered Units: 1.0%
Route, Form, Volume and/or Infusion Rate: 0.5 ml/site
Drug Lot #, Radiolabel, and % Purity: Lot S-10, Mo. Wt. = 1.5 to 2.5 x 10^6
Formulation/Vehicle: Sterile Water for Injection

Observations and Times: Observations were performed 4, 24, 48 and 72 hours after application and again on day 7 after application. The primary irritation rate was calculated based on observations made at the 4, 24 and 48 hour time points.

Results: The primary dermal irritation rate was 0 for both the test article and water treated groups.

Study 2: **Ocular Mucosa Irritation Study of Sodium Hyaluronic Acid (HYA-A)**
Study No: 61-Kei-19-3
Volume and Page No.: BP, Page 44
Conducting Laboratory and Location: ———

Date of Study Initiation: July 28, 1986 to September 5, 1986
GLP Compliance: Yes
QA Report: Yes (x) No ( )
Methods and Dosing: In Group 1, the eyes were rinsed with 50-100 ml saline approximately 5 minutes after applying HA. In Group II, the eyes were washed out 24 hours after applying the sample.
Species/Strain: Japanese White Rabbits (JW-NIBS)
#/sex/group or time point: 5 males/Group 1; 3 males/Group 2
Age: 2 months
Weight: 1.84 to 2.10 kg
Supplier: ———
Dosage Groups in Administered Units: 1.0%

Route, Form, Volume and/or Infusion Rate: 0.1 ml/eye
Drug Lot #, Radiolabel, and % Purity: Lot S-10, Mo. Wt. = 1.5 to 2.5 x 10^6
Formulation/Vehicle: Sterile Water for Injection

Observations and Times: Each animal was examined by macroscopic observation and the fluorescein test on the day preceding treatment, at 1, 24, 48 and 72 hours after washing and on the 7th day. The findings for cornea, conjunctiva and iris were assessed according to standard criteria.

Results: There were no signs of ocular irritation following instillation of an aqueous 1% HA solution to the cornea, conjunctiva or iris following either the 5-minute treatment or the 24-hour treatment.

Study 3: **Phototoxicity Study of Sodium Hyaluronic Acid (HYA-A)**
Study No: 86-1960
Volume and Page No.: BP, Page 71
Conducting Laboratory and Location: [redacted]

Date of Study Initiation: July 14, 1986 to September 12, 1986
GLP Compliance: Yes
QA Report: Yes (x) No ( )
Methods and Dosing: Phototoxicity of 1.0% HA was evaluated in female guinea pigs using a 24 hour closed patch method. After removing the patches, the shaved skin was exposed to UV radiation for 60 minutes. This was repeated every 24 hours for 5 days. Following a 2 week rest period, animals were challenged with three concentrations of HA applied under closed patches for 24 hours. animals were again irradiated for 60 minutes. 8-Methoxypsoralen was used as the positive control.
Species/Strain: Hartley Guinea Pigs
#/sex/group or time point: 10 females
Weight: 314-332 g
Supplier: [redacted]
Dosage Groups in Administered Units: 0.1 or 1%
Route, Form, Volume and/or Infusion Rate: 0.1 ml/site
Drug Lot #, Radiolabel, and % Purity: Lot S-10, Mo. Wt. = 1.5 to 2.5 x 10^6
Formulation/Vehicle: Sterile Water for Injection

UV Source: 300 to 400 nm

Observations and Times: Irradiated sites were macroscopically observed 24 to 72 hours after irradiation.

Results: There were no dermal signs of reaction at either concentration with or without UV radiation, whereas the positive control demonstrated a clear phototoxic response.

Study 4: **Contact Photosensitization Study of Sodium Hyaluronic Acid (HYA-A)**
Study No: 86-2008
Volume and Page No.: BP, Page 1

Conducting Laboratory and Location: [redacted]

Date of Study Initiation: August 28, 1986 to September 25, 1986
GLP Compliance: Yes
QA Report: Yes (x) No ( )
Methods and Dosing: Contact photosensitization of 1.0% HA was evaluated in female guinea pigs according to Adjuvant strip method. A clipped area on the back was first injected with Freund's complete adjuvant, tape stripped, treated with 1.0% HA, then exposed to UV radiation for 60 minutes. This was repeated every 24 hours for 5 days. Following a 2 week rest period, animals were challenged with three concentrations of HA applied under closed patches for 24 hours. animals were again irradiated for 60 minutes. Tetrachlorosalicylanilide (2%) was used as the positive control.
Species/Strain: Hartley Guinea Pigs
#/sex/group or time point: 12 females/group
Weight: 314-332 g
Supplier: [redacted]
Dosage Groups in Administered Units: 0.01, 0.1 or 1%
Route, Form, Volume and/or Infusion Rate: 0.1 ml/site
Drug Lot #, Radiolabel, and % Purity: Lot S-10, Mo. Wt. = 1.5 to 2.5 x 10^6
Formulation/Vehicle: Sterile Water for Injection

UV Source: 300 to 400 nm

Observations and Times: Animals were monitored daily for signs of toxicity and dermal irritation and challenged for signs of sensitization after two weeks of non-dosing. Evaluations were performed at 0, 24, 48 and 72 hours after irradiation.

Results: 1% HA applied topically did not cause erythema or edema in UV or non-UV irritated animals. Further more there were no signs of contact sensitization following reapplication 2 weeks after the induction phase.

Other Information:

1) The medical officer has confirmed that [redacted] hyaluronate was used in the clinical formulation used to test for contact hypersensitivity in humans, therefore no further nonclinical testing of the hyaluronate is recommended.

2) Impurities identified in [redacted] HA include the following:

- [redacted] [redacted] of final product)
- [redacted] [redacted]
- [redacted] Not quantified

[redacted] is a potential systemic toxicant, dermal irritant and sensitizing agent in humans. However, the quantities found in Solarase 3% gel are below the levels allowable in drinking

water (EPA) and below the levels known to cause contact sensitization reactions in humans

With regards to the ——— present, there is no ——— present. At present, CDER has no regulations regarding the presence of ——— — present in drug products. However, it is recommended that the — be quantified and a product limit be set by the Sponsor for this impurity.

Overall Summary and Discussion of the Safety of ——— Hyaluronan for Use in Solarase 3% Gel:

Acute topical studies performed for ——— indicate that the ——— hyaluronate did not produce any of the following dermal effects: primary skin or ocular irritation in rabbits, and phototoxicity or contact photosensitization in guinea pigs. These studies were all performed using 1.0 % concentrations of HA, whereas the Solarase formulation included — HA. However, since the ——— hyaluronate was used during the pivotal Phase III clinical studies, and therefore qualified at least to some extent in humans, further nonclinical qualification of this excipient will not be recommended at this time.

APPEARS THIS WAY
ON ORIGINAL

SECTION II: QUANTIFICATION AND QUALIFICATION OF PRODUCT IMPURITIES AND DEGRATANTS

Since filing the first Pharmacology/Toxicology review, chemistry has identified several issues which may impact the potential safety of the product, including a discernible degradation product resulting in yellow discoloration of the product over time. The failure of the Sponsor to identify and/or quantify this strong ——— has brought into question the validity of their analytical methods.

In the submission received August 20, 1999, Hyal has stated: "Finished product specifications dictate that throughout self life, related compounds, impurities and or degradants be ——— ———, any unidentified compound and——— total impurities." However, they have not submitted the documentation needed to support this statement. Without the proper documentation and validation of the analytical methods, this statement is insufficient to comply with the regulations concerning product impurities and degradants.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY AND CONCLUSION

In response to a request for information on impurities and degradation products at 6 months, Hyal submitted an amendment on August 19, 1999, stating that there were no "impurities or degradants present at — in the bulk drug substance or —— of the drug substance in the drug product,

(therefore) genotoxicity is not required". However, according to the chemistry reviewer, this statement is not supported by a validated analytical method.

The information on impurities and degradants remains inadequate to conclusively evaluate the safety of Solarase Gel. From a Pharm/Tox perspective, the NDA could be approved provided that the chemistry reviewer can confirm that there are no impurities or degradants present at concentrations a) greater than — of the bulk drug product; or b) greater than — of the drug substance in the drug product; or c) the Sponsor can demonstrate that impurities or degradants are present at less than or comparable levels in marketed diclofenac tablets. Furthermore, any impurities and/or degradants found at higher concentrations would need to be identified, tested for genotoxicity, and found to be nongenotoxic.

APPEARS THIS WAY
ON ORIGINAL

/s/ 9-30-99

Lynnda Reid, Ph.D. Date
Pharmacologist/Toxicologist

cc:
IND —
HFD 540
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs
HFD-540/CSO/White
HFD-540/MO/Ko
HFD-540/Chem/DeCamp
HFD-540/Biopharm/Tandon
HFD-540/Biostat/Freidlin
HFD-540/Biostat/Thomson

For Concurrence Only:
HFD-540/DD/JWilkin /s/ 10/13/99
HFD-540/TL/AJacobs /s/ 9/30/99

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Pharmacology and Toxicology Data

Key Words: Diclofenac, NSAID, Actinic Keratosis

Reviewer: Lynnda Reid, Ph.D.
Division: Dermatologic and Dental Drug Products, HFD-540
Date: July 16, 1999, (First Draft Completed 3/16/99)

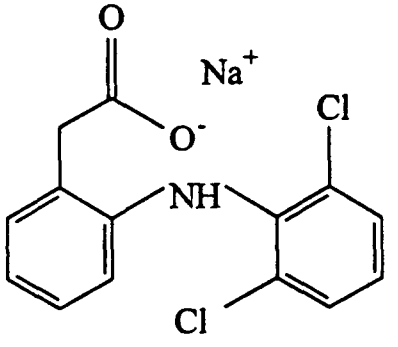
NDA No: 21,005
Amendment No. N000
Dated: October 20, 1998

Information to Sponsor: Yes ( ) No (X)

Sponsor: Hyal Pharmaceutical Corporation
2425 Skymark Avenue
Mississauga, Ontario
Canada L4W 4Y6
905-625-8181; FAX 905-625-1884

Drug:

Generic Name: Diclofenac sodium
Trade Name: Solarase 3% Gel
Chemical Names: 2-[2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt;
[o-(2,,6-dichloranilino)phenyl]acetic acid sodium salt; and
sodium [0-[2,6-diclorophenyl)amino]phenyl]acetate
CAS Number: CAS No. 15307-79-6
Molecular Formula: $C_{14}H_{10}Cl_2NO_2Na$
Molecular Weight: 318.14
Structure:



Description: White to Slightly Yellow crystallized powder, sparing soluble in H_2O
Absorption Spectrum: Diclofenac in methanol (0.03 mg/ml) absorbs between ——— nm
with peaks at ——— nm

Relevant IND and NDA Submissions:

No.	Product	Formulation	Sponsor
N20-142	Cataflam (diclofenac potassium)	Oral Tablets	Geigy Pharmaceuticals
N19-201	Voltaren	Oral Tablets	Geigy Pharmaceuticals
N20-254	Voltaren XR (diclofenac sodium)	Oral Tablets	Geigy Pharmaceuticals
N20-037	Voltaren Ophthalmic	Ophthalmic Solution	Ciba Vision
I			
I			
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I			

Drug Class: Nonsteroidal Anti-inflammatory Drug (NSAID)

Indication: Treatment of Actinic Keratosis

Clinical Formulation: Diclofenac sodium 3% topical gel.

Ingredients	%w/w	Function
Diclofenac sodium	3.0	Prostaglandin Inhibitor
Sodium hyaluronate *		
Polyethylene glycol monomethyl ether		
Benzyl alcohol		
Purified Water		

Note: The source of the hyaluronate for the nonclinical and clinical safety and PK studies was from *The source used for the pivotal clinical trials and the to be marketed formulation is* *(See Discussion).*

The following impurities were identified using *(See CMC Review)*:

- [redacted]

Route of Administration: Topical

Proposed Clinical Protocol or Use: Solarase™ gel is to be applied to actinic keratosis lesions twice daily and gently smoothed into the affected skin. The amount needed depends upon the size of the lesion site. Normally 0.5 g of gel will be used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from — to 90 days. Recommendations and indications for the use of Solarase™ have not been established.

Previous Clinical Experience: Diclofenac sodium has been marketed as an anti-inflammatory in the United States since 1988 under the trade names Voltaren and Cataflam. Approved formulations include immediate-, delayed- extended-release tablets in concentrations of 25, 50 and 75 mg tablets for oral administration and as a 0.1% solution for ophthalmic use.

Cataflam Immediate-Release Tablets and Voltaren Delayed-Release Tablets are indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Voltaren-XR Extended-Release Tablets are indicated for chronic therapy of osteoarthritis and rheumatoid arthritis. Cataflam Immediate-Release Tables are also approved for the management of pain and primary dysmenorrhea. The recommended doses range between 100 and 200 mg/kg/day (b.i.d., t.i.d. or q.i.d.) depending on patient responsiveness, tablet type, and condition treated. Voltaren Ophthalmic (0.1% diclofenac sodium solution) is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction and for the treatment of photophobia in patients undergoing incisional refractive surgery.

TABLE OF CONTENTS

Disclaimer: Note some material may be taken directly from Sponsor's submission.

INTRODUCTION

Solarase™ is under investigation for the treatment of actinic keratosis. The active ingredient is sodium diclofenac (hereafter referred to as diclofenac) which is accompanied by hyaluronate purportedly included to target and concentrate the drug at the site of action in the dermis. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) currently advocated for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. It is a potent inhibitor of cyclooxygenase activity and it's pharmacodynamic effects are thought to be due to reduced prostaglandin E_2 (PGE_2) synthesis. PGE_2 has been shown to inhibit polymorphonuclear leukocyte function by reducing chemotaxis, superoxide production, and protease production; natural killer cell cytotoxicity; and mitogen-induced lymphocyte proliferation.

Worldwide use of diclofenac since 1974 has yielded an extensive body of data on the safety of this drug in humans. Although the systemic toxicity associated with diclofenac has been well characterized in both non-clinical and clinical studies, topical formulations are new. It is currently available in a number of administration forms that can be given orally, rectally, or intramuscularly. Dosage adjustments are not required in the elderly or in those patients with renal or hepatic impairment.

Under IND ——— diclofenac was studied as a topical treatment for actinic keratosis. New studies specific to the dermal formulation have been conducted and will be reviewed here along with a brief summary evaluation of the previously available toxicology and pharmacology data used to support oral and ophthalmic formulations containing diclofenac.

Clinical use of the topical 3.0% preparation is estimated to be approximately 0.2 ml/application, or approximately 6 mg diclofenac/application (~0.1 mg/kg or 3.7 mg/m^2 for a 60 kg adult).

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INDEX OF PHARMACOLOGY AND TOXICOLOGY STUDIES and SUBMITTED PEER REVIEWED LITERATURE

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REVIEW OF SUBMITTED STUDIES AND LITERATURE

SECTION I: PHARMACOLOGY

Mechanism of Action: In pharmacologic studies, diclofenac has demonstrated anti-inflammatory, analgesic, and antipyretic activity. Its exact mode of action is unknown, however, it has been hypothesized to be related to its ability to inhibit prostaglandin (PGE_2) synthesis and cyclo-oxygenase activity. It also affects polymorphonuclear leukocyte function by reducing chemotaxis, superoxide production and protease production.

Himashu and colleagues (1987) have demonstrated *in vitro* diclofenac inhibition of arachidonic acid conversion to leukotriene products in human leukocytes. Follow-up studies with rat peritoneal leukocytes revealed that this effect was not mediated by inhibition of 5-lipooxygenase or phsopholipase A_2, but rather through modulation of arachidonic acid uptake and release, e.g., redistribution of arachidonic acid in lipid pools. The potency of this effect was dependent upon cell type; macrophages being more sensitive to the drug than neutrophils (IC_{50} values were 60 and 10 µM, respectively). In leukocytes treated with diclofenac, arachidonic acid released from phospholipids in response to A 23187 challenge was reincorporated into triacylglycerols. The drug enhanced the spontaneous uptake of arachidonic acid into the cellular triacylglycerol pool and, in this manner decreased the availability of intracellular arachidonic acid.

Drug Activity Related to Proposed Indication: With respect to the observed action of diclofenac-induced regression of actinic keratoses, there have been no specific pharmacological studies. However, NSAIDs, including diclofenac have reportedly been associated with prevention and/or regression of neoplastic or preneoplastic lesions in a number of *in vitro* and *in vivo* nonclinical test systems as well as in human populations (Donatini *et al.*, 1994; Hixson *et al.*, 1994; Lackner *et al.*, 1997; Peterson 1983, and Seed *et al.*, 1997). The pharmacodynamic mechanism with respect to antineoplastic activity has not been specifically studied, however, there is evidence that diclofenac may act through a PGE_2-dependent immunologic mechanism (Blomgren *et al.*, 1990; Ohnishi *et al.*, 1991; Viland and Blomgren, 1988). Antineoplastic activity may also be related to angiostasis, another activity that is thought to be at least partially mediated through PGE_2 inhibition (Moore and Willowghby, 1995).

The Sponsor originally proposed that sodium hyaluronate (HA) would enhance the transdermal delivery of diclofenac and sustain the release of diclofenac in the epidermis where a depot or reservoir of the drug is formed. Although hyaluronate is known to target a number of receptors (e.g., ICAM-1, RHAMM, CD-44) which increase in pathological states, the exact role and mechanism of action of sodium hyaluronate in enhancing drug delivery is unknown. One hypothesis seems to be that hyaluronate could specifically target the pathological site and either render it more permeable to the drug, or attract the drug to the pathological site of action (Brown *et al.*, 1995a). When ^{14}C-labeled diclofenac in a — HA formulation was applied to the surface of full thickness human skin in a Franz cell assay, a reservoir of retained diclofenac was shown to form in the area of the basement membrane and the basal layer of the epidermis. (Brown *et al.*, 1995-b and -c). These effects were never confirmed clinically.

Ancillary Pharmacology Studies:

Angiostasis Activity: Applications of topical hyaluronate and diclofenac in combination have been reported to enhance angiostasis and vascular regression in chronic granulomatous inflammation and in tumor tissues. Initial investigations in mice using a combination of hyaluronate and diclofenac, given either topically or directly into the lesion, demonstrated reduced vascular development and accelerated resolution during granulomatous inflammation (Alam *et al.*, 1995). This effect was similar to that observed following depletion of substance-P. It has been hypothesized that depletion of substance-P may also be involved in diclofenac/hyaluronate-induced angiostatic activity (Alam *et al.*, 1994). Following injection of Colon-26 cells in BALB/c mice, HYAL EX-0001 cream (0.18% diclofenac and 2.5% hyaluronate) was applied daily to the depilated dorsal skin covering the tumors at a dose of 6 mg diclofenac/kg/day (Freemantle *et al.*, 1995). Treatment resulted in complete cessation of tumor growth and vascular development, significant from day 10.

Antineoplastic Activity: Several reports in the literature suggest that NSAIDs may be useful for treatment and chemoprevention of human neoplastic lesions (Funhouser and Sharp, 1995; Giardiello *et al.*, 1995; Hanif *et al.*, 1996; Heath *et al.*, 1994; Lee *et al.*, 1994; Levy, 1997; Lupulescu, 1996; McCracken *et al.*, 1996; Rosenberg *et al.*, 1991). None of these studies deal specifically with diclofenac, but only with NSAIDs in general. The mechanism associated with the antineoplastic effects of NSAIDs is unknown, but most hypotheses involve inhibition of prostaglandin synthase enzymes and reduction on levels of PGE in tissues. Mechanisms postulated to explain the antiproliferative/antineoplastic effects of NSAIDs in addition to PGE include the following: substance-P modulation, interference with a spectrum of membrane-associated processes, including G protein function, transmembrane calcium flux, and cell-to-cell binding; inhibition of activity of other enzymes (in addition to cyclooxygenase), including phosphodiaesterase and cyclic AMP-dependent protein kinase which may be integral to cancer initiation and promotion; inhibition of cyclooxygenase co-oxidation of non-lipid substrates to carcinogenic derivatives during prostaglandin synthesis; enhancement of a multitude of immunological responses which may have an important role in restoring host antitumor immunity; and finally mechanisms related to the induction of cellular apoptosis (Alberts *et al.*, 1995; Kelloff *et al.*, 1994).

Numerous *in vivo* studies have been conducted in animal models to demonstrate the antineoplastic activity of NSAIDs (Djaldetti *et al.*, 1982; Jalbert and Castonguay, 1992; Knapp *et al.*, 1995; Okajima *et al.*, 1997; Piazza *et al.*, 1997; Shiff *et al.*, 1995; Valdex and Perdigon, 1991). Key studies with diclofenac are summarized below.

- When oral diclofenac was combined with intra-portal pirarubicin to treat liver VX2 tumors in rabbits, it was found to significantly ($p<0.02$) enhance the effectiveness of pirarubicin. However, the combination of diclofenac and pirarubicin was more toxic than pirarubicin alone and induced centrolobular necrosis and sclerosing cholangitis (Donatini *et al.*, 1994).

- Alexandrov and colleagues (1996) performed a 12-month post-natal study to examine the chemopreventive effect of indomethacin, Voltaren, theophylline and ε-aminocaptroic acid on ethylnitrosourea-induced transplacental carcinogenesis in rats. Voltaren (diclofenac, 20 ppm in drinking water) significantly decreased total tumor incidence (20%) and multiplicity, and specific tumor incidences in the following organs: brain – 27%, spinal cord – 9%, peripheral nerves – 10% and kidney – 14.2%. Mean survival was also increased by 22 days.

- Peterson (1983) studied the effects of prostaglandin synthesis inhibitors on tumor growth and vascularization in two transplantable rat tumors: a 20-methylcholanthrene-induced fibrosarcoma and a hepatoma. Growth rate was evaluated by mean tumor dry weight and vascularization by microangiography. Both types of tumors were significantly ($p<0.05$) reduced by diclofenac (0.75 mg/100g body weight) administered i.v. once daily, irrespective of whether the drug was administered early (days 1-7) or late (days 8-14) during tumor growth.

- Seed and colleagues (1997) investigated the inhibition of colon-26 adenocarcinoma development and angiogenesis by topical diclofenac (6 mg/kg) in 2.5% hyaluronate. In this study topical applications of diclofenac were shown to inhibit tumor prostaglandin synthesis and retard angiogenesis and tumor growth (ratio of treatment:control = 0.174) The mitotic index remained unaltered in vivo, whereas the apoptotic index and necrosis were increased.

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Summary of Pharmacology

Diclofenac has demonstrated anti-inflammatory, analgesic, and antipyretic activity. Its exact mode of action is unknown, however, it has been hypothesized to be related to its potent effects on cyclooxygenase activity and subsequent inhibit of prostaglandin (PGE_2) synthesis. It has also been shown to modulate arachidonic acid uptake and release, and polymorphonuclear leukocyte function by reducing chemotaxis, superoxide production and protease production. Along with other nonsteroidal antibiotic drugs, diclofenac has reportedly been associated with prevention and/or regression of neoplastic and preneoplastic lesions in a number of in vitro and in vivo nonclinical test systems as well as in human populations.

The inclusion of — sodium hyaluronate in the gel formulation was thought to enhance the transdermal delivery of diclofenac and was believed to control and sustain the release of diclofenac in the epidermis, forming a depot or reservoir of the drug in the area of the basement membrane and the basal layer. However, enhanced dermal residence time was never convincingly proven, nor is the exact mechanism of action by which sodium hyaluronate could result in enhanced drug delivery known.

The pharmacodynamic mechanism of action associated with the antineoplastic effects of NSAIDs is unknown, but most hypotheses involve inhibition of prostaglandin synthase enzymes and reduction of PGE levels in tissues. Topical applications of sodium hyaluronate and diclofenac in combination have been shown to enhance angiostasis and vascular regression in chronic granulomatous inflammation and in tumor tissues in rodents.

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SECTION II: PHARMACOKINETICS

Study 2.1 – Skin Residue Experiment — Cell Assay w/ — Diclofenac gel and Human Breast Skin). Report No. 92/188, conducted by _____, in compliance with Good Laboratory Practice regulations (CFR 21:58).

Study Design: — cells were used to study the rate of skin penetration of diclofenac from Diclofenac Gel, Diclofenac/HA Gel, and Voltarol Emulsion Gel. One piece of skin (female, 32 years, non-smoker, breast skin) was used for this experiment. Skin permeation cells were prepared containing an exposed skin surface area of 2.0 cm^2 and a constantly stirred receptor fluid consisting of 5.5 ml of ethanol:phosphate buffered saline (25:75 v/v). One cell from each sample was removed at each of the following time points: 0.3, 1.1, 2, 6 and 12. Following exposure, any gel remaining on the surface was removed and the skin was sectioned to obtain thin top and thicker lower sections of skin, approximating epidermal and dermal skin layers. Each skin section was weighed and residual diclofenac extracted. Receptor fluid and skin extracts were assayed using _____

Summary of Study Results:

Table 4: Diclofenac concentrations recovered from *in vitro* topical application of gel formulations to human skin using — cells.

Sample	Elapsed Time	Receptor Fluid (µg)	Top Skin (µg/g)	Bottom Skin (µg/g)
— Diclofenac Gel (XPB049)	0.3	ND	388	1.12
	1.1	ND	688	1.89
	2.0	ND	1153	4.71
	6.0	ND	1559	18.35
	12.0	3.30	2385	55.22
3% Diclofenac/ — HA Gel (EPDICLO1 – Hyal's formulation used in clinical trials)	0.3	ND	1756	3.35
	1.1	ND	1740	1.99
	2.0	ND	1867	2.77
	6.0	ND	1945	4.69
	12.0	15.51	4287	113.04
Voltarol Emulsion Gel (060400-10-93)	0.3	ND	539	1.72
	1.1	ND	669	1.25
	2.0	ND	1137	1.86
	6.0	ND	1028	7.77
	12.0	13.09	3321	110.94

Reviewer's Comments: *Hyal did not include summary conclusions of their results or formulations for the — diclofenac gel or the Voltarol Emulsion Gel. Without these formulations it is impossible to draw any definitive conclusions. However, if it is assumed that the Voltarol contains — diclofenac and that the only difference between the — Diclofenac Gel and 3% Diclofenac/HA Gel is the presence of — HA, then some conclusions can be drawn. The presence of hyaluronate increases absorption of diclofenac into the epidermis and dermis during*

the first (0-2) hours post application by approximately 2-3 fold when compared to formulations without HA. There does not appear to be any difference in the overall retention time between the 3% Diclofenac/HA Gel and the Voltarol Emulsion Gel, however, diclofenac appears to transfer more readily into the deeper skin layers at both 2 and 6 hours following absorption of the — Diclofenac Gel.

Study 2.2 – A Study of the Transdermal Drug Delivery Properties of Hyaluronan. ————

Study Design: This study was performed to assess the effect of —— hyaluronate on the diffusion of radio-labeled diclofenac through human skin. Fresh, surgically excised samples of skin were obtained directly after abdomino-plasties and surgery. The age of male and female donors ranged between 30 and 50 years. Skin was stored at 4°C up to a maximum of 24 hours after surgical excision prior to removal of epidermal membrane or stratum corneum, and subcutaneous fat. The epidermis and dermis were separated and samples stored at –20°C until required. Diffusion studies were carried out using full thickness, epidermal sheet and stratum corneum skin sections in the —— cell. The receptor compartment was filled with Sorenson's buffer (pH 7.4) maintained at 37°C. Skin samples were allowed to equilibrate for 48 hours prior to application of test materials. Sampling (0.5 ml) occurred over predetermined time intervals while maintaining a constant receptor fluid level. At the end of each experiment, methylene blue solution was placed on the upper surface to check sample viability.

Summary of Study Results: There was a marked difference in the diffusion characteristics of diclofenac in the — hyaluronan formulation when compared to Sorenson's buffer. When suspended in buffer, 10% of the radioactivity diffused into the receptor chamber within approximately 8-12 hours depending on sample type. In contrast, when the diclofenac/hyaluronate formulation was applied, it took well over a week (limit of viability) to reach this level of diffusion, suggesting that the diffusion of C^{14} labeled diclofenac is sustained and controlled by hyaluronate.

Study 2.3 – Absorption of Hyaluronan Applied to the Surface of the Skin. ————
———— Round Table Series No. 40, 1995.

Study Design: Hyaluronate was labeled with ^{3}H in its acetyl group and reduced by sonication to a modal molecular weight of 250,000 in the first preparation and of 400,000 in the second preparation. Preparation compositions (in water) are presented below:

Component	A	B
Hyaluronan	18.4 mg/ml (77.6 µCi)	17.0 mg/ml (250 µCi)
Polyethylene glycol	—	——
Benzyl alcohol	—	—
3H/Application of 50 mg gel	~3.9 µCi	~12.5 µCi

Test preparations (~50 mg) were gently rubbed in to an area ~5 to 6 cm^2 of dorsal skin of hairless mice. In the first series, test groups consisted of the following: 3 mice dosed with preparation A, 3 with non-radioactive Hyal gel, 2 with methycellulose gel, and 2 were left untreated. In the first study

of this series, 3 applications were made at 12 hourly intervals; in the second study, 11 or 12 applications were made. Animals were restrained (with food and water available *ad libitum*) to prevent oral ingestion and were sacrificed between 8 and 16 hours after the last application. In the second and third series tests, preparation B was applied with and without PEG, and the animals were sacrificed 1, 2, 4, 6 and 8 hours following constant observation.

Treated skin was excised and fixed. Samples were divided, with histology and ——— performed on half of the sample. In the first series, the other half of the sample was prepared for ——— and in the second series, the samples were further divided for chemical solubilization or proteolytic digestion prior to chromatographic analysis. Chromatographic analysis were also performed on extracted livers, blood serum and urine.

Summary of Study Results: Results from all three studies confirmed that when hyaluronan was applied to the surface of the skin it was capable of penetrating the epidermis to accumulate at least briefly in the dermis. Radio labeled hyaluronan was recovered from serum and liver extracts early after application. The molecular weight of absorbed hyaluronate was virtually identical with that applied.

(Review Note: The Sponsor contends that this is indicative that absorption was not restricted to the smaller ——— in the ——— material. However, it seems more likely that it is the result of transfer or incorporation of the radiolabeled hyaluronate by endogenous hyaluronate or reorganization of metabolized hyaluronate following absorption.)

The levels of activity in the specimens collected after 8 hours indicated absorption and catabolism of significant amounts of labeled hyaluronate. Accumulation of hyaluronan metabolic end products (labeled acetate and water) were not found in either the liver or serum, but were present in urine samples. Hyaluronate in the molecular weight range used in this study began to pass through epidermis to dermis within 1 hour of application. The transit time through the epidermis was short relative to turnover time in the dermis. Residual ^{3}H in the treated skin was only slightly higher after 11 or 12 than after 3 applications, suggesting that equilibrium is approached after only a few applications. PEG had no discernible effect on transit of hyaluronate through skin. The mode of transport of hyaluronate through the epidermis was not established by these studies.

Study 2.4 – Disposition of Radioactivity in Minipigs after a Single Dermal Application of 3% ^{14}C-Diclofenac. Report No. — -45235, dated 11/13/96, in life 2/2/96, conducted by ———————————————, in compliance with Good Laboratory Practice regulations (21 CFR 58).

Study Design: The purpose of this preliminary study in male Göttingen minipigs was to determine the radioactivity in the blood and plasma, urine and feces, and dermis following a single dermal application of formulated gel containing 3% ^{14}C-diclofenac. Two minipigs were each administered a target dose of 0.5 g of formulated gel containing 15 mg diclofenac (1.70 mg/kg), approximately ~1056 µCi/dose, to a site approximately 5.4 to 5.6 cm by 4.9 to 5.2 cm. Following dosing, each application site was occluded during the 24 hour collection interval for animal 1001 and 168 hour collection interval for animals 2001. Urine and feces were collected over the following intervals: 0-12 and 12-24 hours for both animals, and 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours

for animal 2001. Cage washings were collected daily and occlusion material at study termination. Following euthanasia, treated and untreated skin sites (2 cm x 4 cm) were collected for analysis.

Summary of Study Results: Plasma radioactivity was quantifiable in both animals: in animal 1001 Cmax (4.222 ng.eq/ml) was achieved at 24 hours while in animal 2001 Cmax (1.041 ng.eq/ml) was achieved at 6 hours post application. In animal 2001 the levels of radioactivity were near Cmax from 3 hours (0.868 ng.eq/ml) to 48 hours (0.840 ng.eq/ml) post application. At 168 hours post application radioactivity in plasma had declined to a level of 0.250 ng.eq/ml. The blood/plasma ratios ranged from ——— The recovery of radioactivity from skin and excreta was low.

Parameter	Animal 1001 (0-24 hrs)	Animal 2001 (0-168 hrs)
Plasma C_{max} (ng.eq/ml)	4.222	1.041
Plasma T_{max} (hrs)	24	6
% of Dose Recovered:		
Subcutaneous layer (fat)	0.216 %	0.031 %
Urine	0.125 %	0.766 %
Feces	0.0 %	0.115 %
Cage Wash	0.163 %	1.741 %
Dermis, Dressing and Wipes	80.67 %	88.16 %
Total Recovery	81.17 %	90.82 %

The minimum dermal radioactivity absorption was calculated at approximately 0.50 % of the dose over 24 hours (animal 1001) and 2.65 % of the dose following 168 hours of exposure (animals 2001).

Study 2.5 – Pilot Study: Absorption and Distribution of Diclofenac after Dermal Application on Guinea Pigs. Study No. 92 9756, Report dated 12/14/93, in life 1993, conducted by ———

Study Design: Approximately 50 mg gel containing 3% labeled Diclofenac in either a 5% CMC vehicle or a — HA vehicle was applied to approximately 0.25 cm^2 shaved area on Pirbright-White Guinea pigs. Blood samples and skin and muscle tissue were taken 0.5 hr and 2 hr post administration. Frozen tissue-blocks were cut into 100 µm thick slices with a — microtome and separated into skin and muscle sections. Samples were homogenized and ——— performed. Extractions were prepared from the tissue homogenates and ——— assays using ——— were performed. ——— were also prepared on intact shaved sections.

Summary of Study Results: Very low amounts of activity were detected in plasma at .5 and 2 hr post application (See Table 2.5.1). Individual guinea pig diclofenac absorption profiles were highly variable, and no significant differences could be clearly demonstrated between the two formulations. Muscle tissue concentrations were generally low, between 0.3 and 4.0 µg/g, with the exception of one animal which had muscle concentrations of 60 µg/g 2 hours post- treatment with 3% diclofenac and 5% CMC. The results obtained in the muscle cannot be used for further interpretations since the limit of quantitation was —µg/g. The copies of the submitted ——— were uninterpretable and no quantitation was included in this report, however, researchers concluded that

most of the radioactivity was found in the skin, probably at the boundary between skin and muscle. Researchers further concluded from the analysis of the — results, that under the conditions used in this system, the test substance was not metabolized, but bound to non-extractable parts of the skin.

Table 2.5.1 - Diclofenac Concentrations Following Topical Application in Guinea Pigs

Formulation	3%Diclofenac/5% CMC Gel				3% Diclofenac/ — HA Gel			
Time	0.5 h		2 h		0.5 h		2 h	
Animal	A1	A2	A3	A4	B1	B2	B3	B4
Amt (mg) Gel Applied to 0.5 cm^2 (250 µm)	68.5	57.8	56.2	57.1	52.5	45.3	44.4	52.5
Diclofenac Applied (mg/250 µm)	2.055	1.734	1.585	1.713	1.575	1.359	1.332	1.575
Recovered from plasma: µg/ml	0.015	0.001	0.004	0.001	0.001	0.002	0.006	0.002
Recovered from Skin: µg/200 µm	339	2102	1657	1609	147	266	1429	371
Recovered from muscle: µg/200 µm	1.26	1.83	59.78	3.56	1.97	0.3	2.1	0.4
Approximate Fraction Diclofenac Recovered	~17%	>100%	>100%	~94%	~9%	~20%	>100%	~24%

Reviewer's Comments: *Under the conditions of this study, the dermal absorption profile for diclofenac appears to be highly variable in guinea pigs. In this study, 5% CMC (Carboxymethylcellulose) actually appeared to more consistently and uniformly facilitate absorption of diclofenac than did the hyaluronate. It was not possible to distinguish any significant differences in dermal retention patterns between the two vehicles tested.*

Ancillary Pharmacokinetic Studies:

- There is *in vitro* evidence that suggests that hyaluronate may interfere with binding of diclofenac to serum albumin. If such a phenomenon occurs *in vivo*, it could have a marked effect on the concentration of free diclofenac available systemically (Brown *et al.*, 1995a). Studies have also demonstrated that concomitant administration of acetylsalicylic and salicylic acid can reduce diclofenac protein binding by approximately 1% (John, 1979). This may increase the amount of free (active) diclofenac bioavailability by 300%, with the potential of altering both the pharmacodynamic and toxicology profile of the drug.

- Both diclofenac and hyaluronate have been detected in lymphatic fluid following topical administration, where they are eliminated less rapidly than from plasma. The concentration of hyaluronate was usually higher in the peripheral lymph fluid relative to that in postnodal lymph or blood, and more or less represented that of hyaluronate in the tissues, at least in the more mobile tissue pools (Fraser, 1995).

- *In vitro* skin permeation rates for diclofenac were determined for Yucatan hairless micropig skin, rat skin, and human skin: 2.8 ± 0.9, 16 ± 3.0 and ~4.6 cm/sec, respectively (Fujii et al., 1997).

- Hyaluronate is found in normal tissues and plasma. The removal of hyaluronate from the circulation is very efficient with a half-life of 2-6 minutes and a total normal turnover of 10-100 mg/day in an adult human. Normal circulating levels of hyaluronate for various species of interest here are presented below (Lebel, 1991). Levels may vary during various disease states.

Species	Plasma Concentration (µg/ml)
Human – normal	0.010 – 0.10
w/neoplasias	>1.0
Pig - normal	0.1 – 0.23
Rabbit – normal	0.019 – 0.086
Rat - normal	0.05 – 0.26

Following i.v. infusion of hyaluronate, rapid uptake takes place in the liver endothelial cells, with degradation products appearing in the plasma within 10-20 minutes. Recent evidence suggests that hyaluronate may also undergo degradation in the kidneys. Accumulation of hyaluronate metabolic end products (labeled acetate and water) were not found in the liver, kidney or serum, but were present in urine and fecal samples.

- In man, monkey and baboon, the preferential metabolic pathways are similar and involve mostly aromatic hydroxylation of one or both of the aromatic rings to form several phenolic metabolites, most of which are converted to glucuronide conjugates. In dog, diclofenac appears to be converted directly to the glucuronide conjugate with a small fraction being converted to a taurine conjugate. In rats, diclofenac is metabolized by direct conjugation and aromatic hydroxylation. Also peculiar to the rat is the formation of a sulfuric acid ester of the 4'-hydroxy derivative, which is excreted only in urine. Furthermore, in dog and rat, diclofenac is subject to enterohepatic recirculation. (Stierlin and Faigle, 1979; John, 1979).

- The concentration of diclofenac and the major human hydroxy metabolites were determined in plasma following a 25 mg IV infusion and a 50 mg oral buffered solution dosage ro 4 Yucatan miniswine (YMS) and compared to the reported results of a 50 mg oral dose in humans (Das et al., 1989). Absolute bioavailability was 98% in YMS compared to approximately 50% in humans, whereas the 4'-hydroxy metabolite C_{max} was only 2% of the parent in YMS compared to 18% in humans. In contrast to humans, other hydroxy metabolites were either low or not detectable, suggesting that metabolism in Yucatan Miniswine may be more similar to dogs than humans.

PK Parameter	YMS		Human
	25 mg IV	50 mg Oral	50 mg Oral
AUC (µg.h/ml)	18.3	35.9	1.36
C_{max} (µg/ml)	-	9.1	2.4
T_{max} (hr)	-	0.5	0.25
$T_{1/2}$ (hr)	2.4	2.3	1.6

- Oberle et al., (Pharmaceutical Research 11:5, 1994) also compared the pharmacokinetics and metabolism of diclofenac following intravenous and oral administration in Yucatan miniature pigs with the historical data in man. Total plasma clearance in minipigs was fivefold slower than in humans; the plasma levels of the major metabolites (4'-hydroxy, 5-hydroxy, 3'-hydroxy, 4',5-dihydroxy, and 3'-hydroxy- 4'-methoxy diclofenac) were considerably lower in minipigs than in man after both iv and oral administration; the volume of distribution was 40% less in humans than in minipigs; and the terminal half-lives were similar (2.4 hr vs. 1.8 hr in pigs and humans, respectively). These results suggest slower metabolism and/or enterohepatic recirculation of the parent drug in minipigs.

  The 4'-hydroxy metabolite, although it is much less potent than the parent compound, may exhibit significant biological activity. In humans, it accounts for 30-40% of the total biotransformation products (Skoutakis et al., 1988).

- In a 2-way crossover multiple dose bioavailability study of Hyal Diclofenac Sodium 3% Topical Gel and Voltaren® 75 mg Diclofenac Sodium Film-Coated Tablets, healthy volunteers self-administered either 1 tablet/day for 6 days or applied approximately 2g gel 3 times/day for 5 days and 1 time on day 6. Only 12 of the 23 subjects had detectable levels of plasma diclofenac (limit of detection = – ng/ml) following topical applications, demonstrating little or no systemic absorption. Mean pharmacokinetic parameters from these 12 subjects and those following oral administration are listed below. K_{el}, $t_{1/2}$ and AUC_{inf} could be calculated following topical administration.

Bioavailability Parameter	3% Diclofenac/HA Gel	250 mg Tablet
AUC_{0-t}	9.09 ng-hr/ml *	1598.8 ng-hr/ml
AUC_{inf}	NA	1696.9 ng-hr/ml
C_{max}	4.49 ng/ml	316.05 ng/ml
T_{max}	4.5 hrs	4.72 hrs
K_{el}	NA	0.23 l/hr
$t_{1/2}$	NA	3.94 hrs

* C.V. = 175%, p = 0.05

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Summary of Nonclinical Pharmacokinetics

Diclofenac

Absorption: *When administered orally, diclofenac is 100% absorbed from the GI tract, however only 50% of each dose is systemically available due to first pass metabolism. It is highly bound to serum proteins (99.5%).*

Following oral administration of diclofenac, plasma C_{max}, AUC, $T_{1/2}$ and V_d were all considerably higher in Yucatan minipigs than in humans, and absolute bioavailability was approximately 98% in the minipigs compared to only approximately 50% in humans. The in vitro skin permeation rates for diclofenac were determined for Yucatan hairless minipig skin, rat skin and human skin were 2.8 ± 0.9, 16 ± 3.0 and ~4.6, respectively.

In a 2-way crossover multiple dose bioavailability study of Hyal Diclofenac Sodium 3% Topical Gel and Voltaren® 75 mg Diclofenac Sodium Film-Coated Tablets (administered q.i.d. for total daily dose of 250 mg) in healthy volunteers, plasma AUC levels were 150 fold greater following oral administration.

Distribution: *Following administration of ^{14}C labeled diclofenac, measurable levels of radioactivity were detectable in all mouse tissues within 1 minute of i.v. infusion. The highest levels occurred in the drug elimination organs (liver and kidney) and other highly profused organs, as well as in blood, bile and lymphatic fluid. Diclofenac has also been detected in lymphatic fluid following topical administration, where it is eliminated less rapidly than from plasma.*

Metabolism: *In man, monkey and baboon, the preferential metabolic pathways are similar and involve mostly aromatic hydroxylation of one or both of the aromatic rings to form several phenolic metabolites, most of which are converted to glucuronide conjugates. In dog, diclofenac appears to be converted directly to the glucuronide conjugate with a small fraction being converted to a taurine conjugate. In rats, diclofenac is metabolized by direct conjugation and aromatic hydroxylation. Also peculiar to the rat is the formation of a sulfuric acid ester of the 4'hydroxy derivative, which is excreted only in urine. Furthermore, in dog, rat, and swine diclofenac is subject to enterohepatic recirculation.*

Excretion: *Diclofenac has a relatively short terminal plasma half-life (1-4 hours). It is eliminated principally by hepatic metabolism with subsequent urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites. In rats approximately 65% of the drug is eliminated in the feces, while in dogs urinary and fecal elimination are approximately 1:1, and in nonhuman primates and man, approximately 60-75% of the drug is eliminated in the urine. In humans, 65% of an oral dose is excreted in urine and 35% in the feces (Skoutakis, 1988). Enterohepatic recycling may give rise to high steady-state levels of drug during chronic administration in species where the primary route of elimination is through bile, e.g., rat, dog and possibly swine. This is generally not observed in humans and monkeys, where the primary route of excretion is through the urine.*

Total plasma clearance in minipigs was fivefold slower than in humans and the plasma levels of the major metabolites (4'-hydroxy, 5-hydroxy, 3'-hydroxy, 4',5-dihydroxy, and 3'-hydroxy- 4'-

methoxy diclofenac) were considerably lower in minipigs than in man. These results suggest slower metabolism and/or enterohepatic recirculation of the parent drug in minipigs.

Sodium Hyaluronate (HA, Haluronan)

Radiolabel following topical applications of labeled hyaluronate has been observed in the dermis within 1 hour of application to the skin of hairless mice. The transit time through the epidermis was short relative to turnover time in the dermis, and equilibrium was reached after only a few applications. Labeled hyaluronate was subsequently recovered from serum and liver extracts, followed by rapid degradation, which appeared to occur primarily in the liver. Following i.v. infusion of labeled hyaluronate, degradation products appear in the plasma within 10-20 minutes. Following topical applications, accumulation of hyaluronate metabolic end products (labeled acetate and water) were not found in either serum or liver, but were present in urine samples.

Absorption Characteristics of Diclofenac/HA Gel

In vitro, — hyaluronate significantly increases the diffusion characteristics of diclofenac when compared to buffer. When suspended in buffer, 10% of the diclofenac associated radioactivity diffused into the receptor chamber within approximately 8-12 hours depending on skin sample type. In contrast, when the diclofenac/hyaluronate formulation was applied, it took well over a week (limit of viability) to reach this level of diffusion, suggesting that the diffusion of C^{14} labeled diclofenac is sustained and controlled by hyaluronate. However, in studies comparing absorption profiles of diclofenac suspended in the hyaluronate gel versus other gel formulations, it was not possible to distinguish any significant differences in dermal retention patterns between the vehicles tested.

There was a high degree of interanimal and interspecies variability in absorption profiles following topical applications of diclofenac/hyaluronate gels. Following topical applications of 3% ^{14}C-Diclofenac — hyaluronate gel to minipigs, quantifiable levels of radioactivity were found in the plasma within 1 hour of application. Levels of radioactivity were near Cmax between 3 and 48 hours post application. The blood/plasma ratios ranged from ——— The dermal radioactivity absorption was calculated at approximately 0.50 % of the dose over 24 hours, and 2.65 % of the dose following 168 hours of exposure.

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