CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-122

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum

NDA NUMBER:	**22-122**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**20-DEC-2006**
PRODUCT:	**Voltaren Gel (Diclofenac Sodium Topical Gel, 1%)**
INTENDED CLINICAL POPULATION:	**Osteoarthritis** *(For ——— ,oints amenable to .reatment, such as the hands and knees)*
SPONSOR:	**Novartis Consumer Health**
REVIEW DIVISION:	**Division of Analgesia, Anesthesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Lawrence S. Leshin, DVM, Ph.D.**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Lauren Tornetta**

Date of review submission to Division File System (DFS): October 5, 2007

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on approvability

NDA 22-122 for Voltaren Gel (diclofenac sodium gel, 1%) may be approved based on the nonclinical pharmacology/toxicology evaluation pending agreement on nonclinical labeling recommendations and with Sponsor's agreement to conduct post-marketing studies as described below.

B. Recommendation for nonclinical studies

I am in agreement with Dr. Leshin's recommendation for a Phase 4 Post-Marketing Commitment to conduct a dermal carcinogenicity evaluation of cocoyl caprylocaprate and have additional recommendations as described below:

1) The excipient cocoyl caprylocaprate contained in the Voltaren Gel formulation is considered *novel* by the Agency. Therefore, unless an adequate scientific rationale establishes this information is not necessary, the following safety information is requested as a post-marketing commitment consistent with FDA guidance "*Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*":
   a. Provide a dermal carcinogenicity evaluation of cocoyl caprylocaprate in two species. One of these studies may be conducted in a transgenic mouse model with concurrence from the Agency.
   b. Provide a full reproductive toxicology evaluation of the cocoyl caprylocaprate consistent with ICH-S5A unless the topical route can be demonstrated to produce non-detectable systemic exposure.

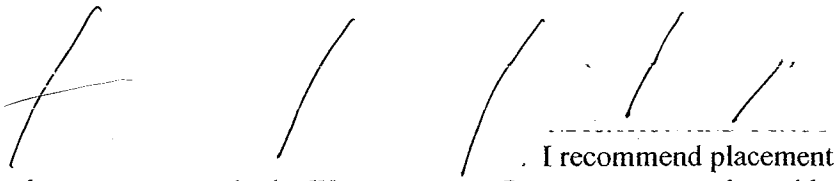
   You may refer to the FDA guidance described above for suggested components of a justification that such data are not necessary.

2) Provide a toxicologic risk assessment on photo-degradants which are considered unique or are found at substantially greater levels when compared against a characterization of photo-degradants in the referenced drug Solaraze.

C. Recommendations on labeling

I am in general agreement with Dr. Leshin's recommended changes to the nonclinical sections of the label with the exception of the placement(s) of the warnings to avoid sun exposure. Based on an evaluation of other topically applied drugs approved by the Agency (e.g. Elidel Cream 1% (2001); Benzaclin Topical Gel (2000); Protopic Ointment (2000); Aldara (1997)) which have positive photo-cocarcinogenicity results described in their label, the recommendations on sun/artificial light exposure avoidance are contained in the PRECAUTIONS section (and under the old labeling format sometimes within the

INFORMATION FOR PATIENTS subsection).



. I recommend placement of this precautionary statement in the WARNINGS AND PRECAUTIONS section with the following language:

> **5.XX Sun Exposure**
> Patients should minimize or avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicate diclofenac can reduce the time to onset of ultraviolet light-induced skin tumors. The potential effects of Voltaren Gel on skin response to ultraviolet damage in humans are not known.

I also suggest the following language be included in section 17 PATIENT COUNSELING INFORMATION:

> Patients should be instructed to minimize or avoid exposure of treated areas to natural or artificial sunlight.

Additionally, nonclinical safety margins have been included for section 8 USE IN SPECIAL POPULATIONS: *Pregnancy* as well as in *Labor and delivery* in order to provide risk information for the prescribing physician.

II. SUMMARY OF NONCLINICAL FINDINGS

A. Regulatory Background (Pharmacology/Toxicology)

The IND for Voltaren Gel (diclofenac sodium gel, 1%) was opened November 2003 subsequent to a Pre-IND meeting held in February of that year. The initial clinical indication for which the nonclinical program was developed as discussed at the PIND meeting was for '

". At the time of submission of IND 64,334 this indication had been simplified and clarified to an

joints amenable to treatment, such as the hands and knees". The API, diclofenac sodium, is a NSAID used in a number of pharmaceutics approved for the U.S. market as well as in foreign markets; therefore, the clinical experience with diclofenac is extensive. The present NDA references Novartis' Voltaren® enteric-coated tablets (NDA 19-201) for the majority of the nonclinical support with use of Novartis' NDAs 20-254 for Voltaren-XR (diclofenac sodium extended release tablets) and 20-142 Cataflam (diclofenac potassium tablets) for support where needed. The Sponsor additionally references NDA 21-005 for Solaraze® (diclofenac sodium topical gel, 3%) via the 505(b)(2) route for information and data related to dermal carcinogenicity and photo-cocarcinogenicity. Notably the owner of Solaraze, Bioglan Pharmaceuticals, initially contested the use of their data but during the review period withdrew their patent infringement suit against Novartis.

A highly similar diclofenac gel product, Voltaren® Emulgel, is approved in Europe and other foreign markets (100 countries according to the Sponsor) where it has been in use for over 20 years. Voltaren® Emulgel contains a different diclofenac salt (diclofenac diethylamine, 1.16%) and a slightly modified formulation relative to Voltaren Gel, principally a different Carbomer —

A request for additional pharmacology/toxicology information was sent to the Sponsor during the review cycle, June 15, 2007, and contained the following items:

1. Cocoyl caprylocaprate is a novel excipient for drug products marketed in the United States. As a novel excipient, the safety of cocoyl caprylocaprate should be established for use according to the following Guidance for Industry: ***Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*** which may be found at http://www.fda.gov/cder/guidance. Provide toxicological information about cocoyl caprylocaprate, especially genetic, dermal, photodermal, and systemic toxicology. Alternatively, provide support from published literature or the use of topical products containing similar or greater amounts of cocoyl caprylocaprate that this compound meets FDA criteria of safety.

2. The list of components of — comprises only those that are equal or greater than 5% of the total composition. This only totals to 78% of the — composition by weight. There is no threshold for reporting excipients or excipient components. Provide the entire composition for —

3. Impurities and degradants appear incompletely qualified and/or controlled. Since Voltaren® was approved in 1988, the Agency's chemistry and toxicology guidelines have been updated to ensure the safety of marketed products. In particular, these now include qualification of impurities containing structural alerts for genotoxicity [see FDA position paper *Regulation of genotoxic and carcinogenic impurities in drug substances and products* (McGovern and Jacobson-Kram: Trends in Analytical

Chemistry, 2006)] and the qualification of degradants observed in stability testing as described below.

[redacted] are [redacted] and contain structural alerts for genotoxicity. According to current Agency policy, such impurities must be controlled to [redacted] total daily intake or be toxicologically qualified consisting of negative findings in two in vitro genotoxicity studies (point mutation and clastogenicity assays) [redacted] while not containing a structural alert, exceeds the threshold for qualification (NMT [redacted] on stability and requires a similar genotoxicity evaluation unless levels can be reduced. Review of submitted studies present in the NDA does not identify evaluations of these impurities in both assays. Furthermore, impurities have not been toxicologically qualified in repeat-dose studies, up to 3 months duration, recommended to support a chronic indication. Provide further data and/or information to support the safety of the identified impurities at the levels proposed.

4. Provide information that the photodegradants for which you are relying on the Agency's prior findings of safety are the same and do not exceed the levels of those produced by the 505(b)(2) reference compound, Solaraze.

5. Submit to the NDA the 12-week rabbit dermal study using Voltaren Emulgel which was submitted to IND 64,334 in Jan 2004 to support the safety of clinical studies longer than 4 weeks. Also, provide the concentrations of impurities in the formulation used in this study, if available.

In response, the Sponsor provided a letter of authorization to DMF [redacted] for toxicology studies and chemistry and manufacturing information regarding the novel excipient cocoyl caprylocaprate [redacted] to address issue #1 as well as noting the use of the excipient in Voltaren® Emulgel in over 100 countries at the identical strength.

To address issue #2, on request of the Sponsor, the manufacturer of the fragrance used in the drug product supplied the Agency with a full listing of components in the excipient.

The impurities and degradants information request (point #3) response from Novartis was that all of the impurity [redacted] and degradation products [redacted] with the exception of [redacted] have been described as impurities in the US Pharmacopoeia and the Sponsor proposes the same limits ([redacted] any individual impurity [redacted], and sum of all impurities [redacted]. They note that as the Voltaren-XR daily dose is 150 mg by the oral dose, the 320 mg topical dose proposed should lead to at most similar levels of exposure to degradants and likely much less as diclofenac exposure is 8-fold lower due to bioavailability differences through the topical route. The Sponsor notes that Voltaren® Emulgel limits are set to [redacted]

With regard to the request for a comparison of photodegradants in Voltaren Gel with that of Solaraze (point #4), the Sponsor initially responded by

proposing a dermal phototoxicity evaluation to functionally compare the toxicity between the two drug products. The Division responded in an e-mail sent on August 15, 2007:

> **Your proposal to rely on a short-term comparative phototoxicity study of Diclofenac Sodium Gel and Solaraze to serve as a bridge to utilize the Solaraze photococarcinogenicity data is not acceptable. We are requesting that you compare the identities and amounts of degradants formed over time from solar or simulated solar exposure of Diclofenac sodium 1% gel and Solaraze.**
>
> **A short-term toxicity study as proposed, may not accurately predict comparability to a 2-year dermal photococarcinogenicity bioassay. Thus, we are requesting the demonstration of degradant profiles between your drug product and Solaraze.**

Finally, the Sponsor submitted the study report of the 12-week rabbit dermal study as requested in point #5.

B. Brief overview of nonclinical findings

As the NDA 19-201 which is owned by Novartis and was referenced in support of Voltaren® tablets contained a significant amount of supporting nonclinical studies for systemic exposure to diclofenac, the nonclinical program to support the present NDA was designed principally to characterize the dermal safety of the topical route of administration. The Sponsor additionally conducted a number of studies in order to characterize the safety of an excipient, [redacted] and several impurities and degradants which are present at levels above ICH thresholds for qualification studies.

Dermal tolerance and repeated dose dermal toxicity studies

Diclofenac gel was evaluated for dermal irritation in the rabbit and was found to produce a transient, mild irritation consisting exclusively of an erythematic response. In the longest dermal tolerance study conducted with the proposed drug product (four weeks) erythema was observed to be greatly reduced or absent after 2 weeks of continuous exposure. A similar observation of transient erythema was noted when applied to the eye of a rabbit with transient reversible swelling. A 12-week repeated-dose dermal toxicity study was conducted in the rabbit which included histopathology but used the Voltaren Emulgel formulation, as noted previously a similar but not identical product, which was compared to a placebo Emulgel formulation. Skin findings included edema, erythema, and papules among other observations but were found in both the Voltaren and placebo Emulgel formulations. Dr. Leshin notes that no other changes were noted which appeared to be related to treatment and due to the presence of skin findings in both groups agrees with Sponsor that the findings are due to the daily application and removal of occlusive dressings. It seems possible, however, that the findings could be due to the formulation itself (as the placebo group was a true vehicle group) but this could not be determined based on the design of the study.

Sensitization studies with diclofenac sodium gel formulations including one which, although not identical, was very close in formulation to the final drug product formulation. These studies were considered by the reviewer to indicate a negative response overall though methodologic issues were noted and which were

problematic in several earlier studies, especially in an initial study which produced a positive response. It is known that sensitization studies in animals are themselves not highly predictive of the human propensity to develop hypersensitivity and therefore the human data must be relied upon though the animal data may be helpful in support.

Photosafety studies

Photosafety testing involved photoirritation and photosensitivity tests of diclofenac applied to the guinea pig under conditions of UV or non-UV light exposure. Methodologic issues were again noted by Dr. Leshin, principally that the absorption maxima for diclofenac resides at the lower end of the spectrum tested and therefore in standard testing would not be administered at the highest intensity when compared with wavelengths above this in the spectrum. Slight irritation was noted in the diclofenac/UV exposed group but this finding was replicated to a lesser extent in the diclofenac/control light group. The reviewer noted that the positive response under both conditions may indicate a sensitizing potential of diclofenac and the addition of UV radiation may enhance the effect though subsequent studies to evaluate photo-sensitization failed to demonstrate any effect of UV light exposure. It is noted that the label for diclofenac products contains photosensitivity events in humans and a Phase 4 PMC for a photo-allergic potential evaluation is being requested by the primary medical reviewer.

Excipients

(also called Carbomer Homopolymer Type C), a , was evaluated in dermal sensitization studies in guinea pigs and was determined to have no sensitizing potential under the conditions of the assay. It is noted that it is included in the formulation at ; a concentration within or below that of approved topical products (up to 7.5%) as listed in the FDA Inactive Ingredient Database.

Impurities/Degradants

Four related impurities were reported as impurities in both the synthesis of diclofenac and as degradation products, three of which exceeded ICH threshold for qualification specifications on stability. Three of these degradant impurities also contained structural alerts for mutagenicity . Qualification studies for the impurities included acute oral toxicity studies as well as a single mutation (Ames) assay. Additionally, one impurity, which is considered novel to the drug product, was subjected to an in vitro clastogenicity evaluation. Genetic toxicology evaluation as performed was negative, acute oral toxicity evaluation indicated an absence of acute systemic toxicity with dosing up to 2000 mg/kg.

C. Nonclinical safety issues relevant to clinical use

1. No long-term nonclinical dermal toxicology study conducted in support of clinical trials & NDA

The Sponsor did not conduct a nonclinical dermal toxicology study of 3 months duration with the drug product formulation in a single non-rodent species to support pivotal clinical efficacy trials nor was a chronic dermal toxicity study performed to support long-term safety studies and the marketing application. Current Agency and Division policy, which has not been finalized in a public guidance, is to request such an evaluation. The reasons for this departure are not entirely clear but seem likely to have been the result of a change in proposed indication between two PIND meetings held on February 10, 2003 and November 18, 2003, respectively in which a [redacted] " to [redacted] At the time the [redacted] indication was proposed, nonclinical response to the adequacy of the proposed nonclinical program as captured in the meeting minutes was to note this deficiency and that they were "advised to compare and to correlate the local toxicities of diclofenac sodium gel and diclofenac diethylammonium gel [the latter representing the API of Voltaren® Emulgel] from the existing animal data. Depending on the outcome of the analysis, additional animal toxicity studies may be required." The Sponsor noted they had a 3-month study in rabbits and agreed to submit this data to the Agency. This study was informally evaluated by Dr. Conrad Chen who recommended in a memo (July 2, 2004) for the EOP2 meeting that no additional nonclinical dermal toxicology studies were necessary with diclofenac sodium gel. The memo was signed without comment by Dr. Josie Yang, supervisory pharmacologist/toxicologist of HFD-550. This study was reviewed by Dr. Leshin as part of his primary NDA review. Methodologic issues appear to confound interpretation of the study (repeated occlusive dressing application and removal were thought to produce dermal observations as these were noted in both treated and control groups). No additional studies were requested by the Division at the EOP2 meeting or through subsequent communication with the Sponsor.

Although not ideal, the absence of long-term nonclinical dermal toxicology studies are not considered to rise to the level of a deficiency at this time due to sufficient clinical safety data derived from studies of Voltaren Gel in 8- and 12-week duration efficacy trials as well as long-term open label safety studies up to 1 year or more in duration. The additional human clinical safety data with the Emulgel formulation which contains a diclofenac salt form (diethylamine) considered to possess inherently greater toxicity due to known concerns with the diethylamine moiety, including dermal toxicity, principally manifested as irritation but also in animal studies demonstrates neurotoxicity, respiratory toxicity, hepato- and renal toxicity with inhaled and oral routes of administration.

2. Use of Solaraze data; labeling issues

The Sponsor did not conduct dermal carcinogenicity or photo-cocarcinogenicity studies of Voltaren Gel but instead used the 505(b)(2) pathway to rely upon on the data contained in Bioglan's Solaraze Gel (diclofenac sodium 3% topical gel) for this information. It is notable that the formulation used in the dermal carcinogenicity study in mice contained significantly lower concentrations of diclofenac (0.035% maximum) than in the Solaraze product (or for that matter Voltaren Gel) due to systemic tolerability issues, contained a ——— hyaluronate sodium) and used different excipients. Despite these issues, it is clear from the referenced dermal carcinogenicity study that the severe GI toxicity encountered in long-term animal studies of this type renders these studies of limited value as the concentrations of diclofenac which can be used do not approach that of the clinical formulation. As a result, it is not possible to use the negative results in animals to provide meaningful exposure margins for a human risk assessment. A similar situation is encountered with the utility of the referenced photo-cocarcinogenicity study. Nevertheless, according to Agency guidance on Photosafety Testing, photo-cocarcinogenicity studies are not considered a requirement if the product can be labeled such that patients may be advised to avoid significant sun exposure.

The Voltaren Gel label will largely retain the language used in the Solaraze label for the dermal and photo-cocarcinogenicity studies with modifications appropriate for Voltaren Gel. Carcinogenicity data obtained through dietary administration studies in the mouse and rat as described in NDA 19-201 (Voltaren tablets) will be reported in the Voltaren Gel label with modification to safety margins appropriate for the maximum recommended human topical dose of Voltaren Gel based on a bioavailability of 6% and a body surface area comparison.

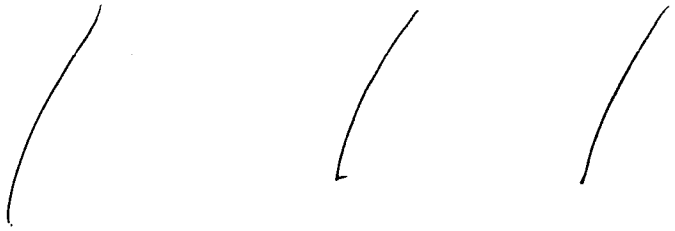
3. Impurities/Degradants

The four impurities and degradation products identified by the Sponsor which exceed ICH specifications at release and/or 36 month stability ——— were the subject of several toxicologic characterization studies as described by Dr. Leshin in his review. An additional synthesis impurity ——— contains a structural alert for genotoxicity as does ——— Compounds with structural alerts are required to be toxicologically qualified with negative genotoxicity studies or the levels set below ICH thresholds to allow for a maximal — g/day total daily intake. The toxicologic characterization of all impurities/degradants were considered incomplete by Dr. Leshin according to current ICH Q3A and Q3B(R) guidelines (Impurities in New Drug Substances and Impurities in New Drug Products, respectively). The Sponsor was asked to provide additional genetic toxicology data as well as repeat-dose toxicity data if available to qualify these compounds in an RFI letter of June 15, 2007 as noted previously. The Sponsor committed to providing the missing genotoxicity data in a subsequent submission (which was received by the Agency on September 27, 2007) but argued 3 of the impurities/degradants (——— , are found in Voltaren

and Voltaren-XR tablets for oral administration and propose the same specifications be allowed for these products, reasoning that systemic exposure with topical administration of the drug product would achieve at worst comparable levels of exposure and likely up to 8-fold lower systemic exposure (using the 6% bioavailability of diclofenac with topical administration as a guide for extrapolation). The Sponsor also notes that the European formulation, Voltaren Emulgel, has been available with specifications of NMT for these three degradant impurities.

The specifications for these three impurities/degradants are considered acceptable for the following reasons: 1) diclofenac sodium used for Voltaren Gel is obtained from the same manufacturing process as Voltaren and Voltaren-XR tablets. Requiring the Sponsor to reduce the specifications of these compounds in the current NDA would effectively change the specifications of these degradant impurities in the already approved oral tablet products; 2) use of the same diclofenac sodium API containing the same level of impurities in the topical product as found in the oral tablets would be expected to produce a lower systemic exposure to such compounds than what has already been allowed on the U.S. market for over 20 years; and, 3) no signals have emerged through the available genetic toxicology testing performed. Therefore further qualification of these impurities/degradants is considered unnecessary for approval of the present marketing application.

The degradant impurity is which, unlike the previously described impurities, is not found in other marketed Voltaren products but is specific to Voltaren Gel . Therefore, this impurity would be subject to current ICH thresholds for qualification. The acceptance criteria specifications for this degradant were above ICH thresholds for qualification at expiry (NMT threshold for full qualification > and with the presence of a structural alert for genotoxicity required qualification through negative genotoxicity studies to avoid being controlled to μg/TDI as a potentially genotoxic impurity. Mutagenicity and clastogenicity studies were performed and were negative which allows for use of standard ICH thresholds for qualification (NMT Upon review, however, it was noted that the due to the drug product batches representative of the commercial process contained very little of the degradant even at the proposed 36 month expiry (, as shown in the Sponsor's following table:



The Sponsor was contacted and agreed to reduce the acceptance criteria to NMT , for which renders further qualification studies unnecessary for marketing approval.

4. Photodegradants

During the review cycle, the Sponsor was asked through the RFI letter of June 15, 2007 to provide comparative photo-degradant data with the referenced Solaraze Gel product in order to rely on the Agency's prior findings of safety and efficacy for this product. The Sponsor initially proposed to conduct a short-term repeated-dose phototoxicity study comparing Voltaren Gel to Solaraze Gel in a nonclinical model in order to demonstrate comparable dermal phototoxicity. The Division responded in an e-mail of August 15, 2007 that this did not provide assurance that reliance on the dermal photo-cocarcinogencity data from the Solaraze product was appropriate. The Division requested the demonstration of an equivalent degradation profile between Voltaren Gel and Solaraze.

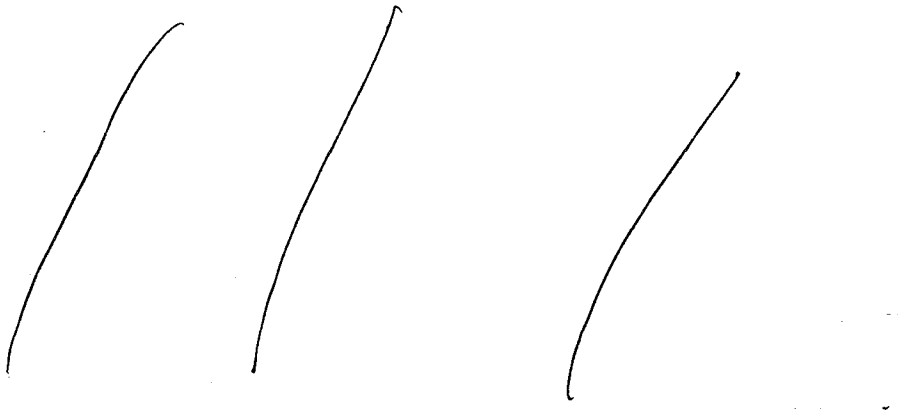
Upon further consideration, this comparison is not considered necessary for marketing approval since the dermal carcinogenicity study is used to evaluate the API and the dermal photo-cocarcinogenicity study can be avoided with appropriate labeling to avoid or minimize sun exposure. Furthermore, both the dermal carcinogenicity and photo-cocarcinogenicity studies referenced in the Solaraze label do not provide assurance or evidence of safety due to the significantly lower concentration of diclofenac utilized in these studies than is found in Voltaren Gel and, in the photo-cocarcinogenicity study, was even at this low concentration (~ 30-fold lower concentration than Voltaren Gel) associated with a more rapid onset of dermal tumors. However, utilization of the photo-cocarcinogenicity data described in the label for Solaraze should be supported by data which establishes the similarity of photodegradants profile between the two products.

5. Novel excipient(s)

The Voltaren Gel formulation contains a novel excipient, identified as cocoyl caprylocaprate . Cocoyl caprylocaprate is manufactured and serves as in the drug product at a level

of —. Cocoyl caprylocaprate is described as carpylic (decanoic)/capric (octanoic) acid esters of saturated fatty alcohols C_{12-18} derived from —. The Sponsor requested input on the acceptability of this excipient based on conformance with the European Pharmacopoeia in a CMC-directed EOP2 meeting held in 2005. At that time the Division indicated this was acceptable. During the NDA review, however, the current pharm/tox review team requested the Sponsor provide support for the use of the novel excipient with an emphasis on toxicologic data as the novel excipient would be listed in the Agency Inactive Ingredient Guide. This request was transmitted in the June 15, 2007 RFI letter. In response, the Sponsor provided a LOA to utilize the Type IV DMF — which

DMF — was reviewed by Drs. Leshin and Sue-Ching Lin (Dr. Lin is the current CMC primary reviewer). The DMF



Overall, this DMF cannot be used as supportive data

Cocoyl caprylocaprate is listed in the Cosmetics, Toiletries, and Fragrances Association database as a "Skin-Conditioning Agent – Emollient" and is found in a wide range of cosmetics and toiletries including (but not limited to): aftershave lotions, bath oils, blushes, body and hand preparations, cleansing products such as cold creams, eye shadows, foundations, hair conditioners, indoor tanning preparations, moisturizers, and suntan lotions. Products in these classes are in some cases used chronically and/or are applied over large body surface areas; however, data is not provided which would describe the concentration at which the excipient is used in such products. Cosmetics are not regulated to the same standards as drugs by the FDA and inactive ingredients are not the subject of safety testing for marketing of a cosmetic product. The presence of cocoyl

caprylocaprate in sunscreens, which are regulated by the FDA Office of Nonprescription Products, is not evidence of an assessment of safety as sunscreens are the subject of a final monograph (21 CFR 352; stayed indefinitely, however) which lists acceptable active ingredients, labeling requirements, and testing procedures. A Federal Register notice put forth in 2007 contains a proposed rule for the formulating, testing and labeling of sunscreens against UV-A as well as UV-B light. The acceptability of specific inactive ingredients is not a subject of the monograph or the Proposed Rule and therefore the presence of cocoyl caprylocaprate in marketed sunscreens does not represent or imply a determination of safety by the Agency.

Despite the absence of data to indicate concentrations of cocoyl caprylocaprate used in cosmetics and toiletries, as well as the inability to rely on data contained in the manufacturer's DMF, the dermal tolerability of the excipient is considered supported by the widespread use of products containing this excipient including products used chronically and/or over large surface areas, combined with clinical safety data from the studies conducted in support of Voltaren Gel as well as the two decades of marketing of the analogous product Voltaren Emulgel containing the same [redacted] concentration of the excipient. There is no data, however, on the reproductive toxicity or carcinogenicity potential of the product available and the [redacted] DMF cannot be used to address this concern. The Sponsor has not provided, nor does the DMF contain, data to form a scientific argument that the excipient would be benign in such evaluations and safety cannot be assumed based on the information and usage data provided. Approval of Voltaren Gel for the U.S. market would result in listing this excipient in the FDA's Inactive Ingredient Guide and allow Sponsor's of any topical preparation the ability to use this excipient up to the [redacted] concentration. Therefore the Sponsor should commit to performing the reproductive and carcinogenicity evaluations as part of a post-marketing agreement in order to assure the Agency of the safety of this excipient as used in topical preparations. Although the absence of usable genetic toxicology data would normally be required as part of the safety assessment, proper carcinogenicity evaluation through dermal studies would be considered to supersede this need. Reproductive toxicity evaluation could be avoided if systemic exposure to the components of the excipient is not detected.

Agency policy as described in the May 2005 "*Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*" is to require evaluation of novel excipients prior to a marketing approval though this can be delayed to post-approval under certain circumstances such as when the drug product is for a life-saving indication. Flexibility in the Agency policy is reflected in the guidance and excipients are to be considered on a case-by-case basis. I believe a post-marketing commitment to perform reproductive toxicology studies as well as carcinogenicity evaluation is acceptable for the following reasons:

1) The nature of the excipient [redacted] does not present an outright safety concern based on structural similarity to

other known compounds which have been approved for use in topical products (see CMC review of Dr. Lin).

2) The function of the excipient in the drug product. Cocoyl caprylocaprate would be expected to largely be retained on the surface of the skin and therefore systemic absorption would be expected to be very limited if not absent by standard detection methods. Unlike other types of excipients such as penetration enhancers, which may present additional risks due to direct absorption and the potential for increasing absorption of other inactive ingredients in the formulation, cocoyl caprylocaprate would be expected to have little effect on other excipients contained in the formulation.

3) There are no known significant or serious safety signals associated with use of this compound as can be determined from clinical trials with Voltaren Gel, the more than 20 years of foreign marketing experience of Voltaren Emulgel, and the widespread use of cocoyl caprylocaprate in cosmetics and sunscreens some of which may be applied to large body surface areas and/or may be applied chronically.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Adam Wasserman
10/5/2007 02:32:44 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-122**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Dec 20, 2006**
PRODUCT:	**Voltaren Gel (Diclofenac Sodium Topical Gel, 1%)**
INTENDED CLINICAL POPULATION:	**joints amenable to ——— treatment, such as the hands and knees.**
SPONSOR:	**Novartis Consumer Health**
DOCUMENTS REVIEWED:	**e-submisssion, Module 4**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**L.S. Leshin, DVM, PhD**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, PhD**
DIVISION DIRECTOR:	**Bob Rappaport, MD**
PROJECT MANAGER:	**L. Tornetta**

Date of review submission to Division File System (DFS): Sept 27, 2007

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW 19

2.6.1 INTRODUCTION AND DRUG HISTORY 19

2.6.2 PHARMACOLOGY 38
2.6.2.1 Brief summary 38
2.6.2.2 Primary pharmacodynamics 39
2.6.2.3 Secondary pharmacodynamics 41
2.6.2.4 Safety pharmacology 41
2.6.2.5 Pharmacodynamic drug interactions 41

2.6.4 PHARMACOKINETICS/TOXICOKINETICS 46
2.6.4.1 Brief summary 46
2.6.4.2 Methods of Analysis 51
2.6.4.3 Absorption 51
2.6.4.4 Distribution 61
2.6.4.5 Metabolism 61
2.6.4.6 Excretion 61
2.6.4.7 Pharmacokinetic drug interactions 61
2.6.4.8 Other Pharmacokinetic Studies 61
2.6.4.9 Discussion and Conclusions 61
2.6.4.10 Tables and figures to include comparative TK summary 62

2.6.5 PHARMACOKINETICS TABULATED SUMMARY 64

2.6.6 TOXICOLOGY 67
2.6.6.1 Overall toxicology summary 67
2.6.6.2 Single-dose toxicity 77
2.6.6.3 Repeat-dose toxicity 81
2.6.6.4 Genetic toxicology 98
2.6.6.5 Carcinogenicity 118
2.6.6.6 Reproductive and developmental toxicology 125
2.6.6.7 Local tolerance 130
2.6.6.8 Special toxicology studies 138
2.6.6.9 Discussion and Conclusions 190
2.6.6.10 Tables and Figures 195

2.6.7 TOXICOLOGY TABULATED SUMMARY 195

OVERALL CONCLUSIONS AND RECOMMENDATIONS 196

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

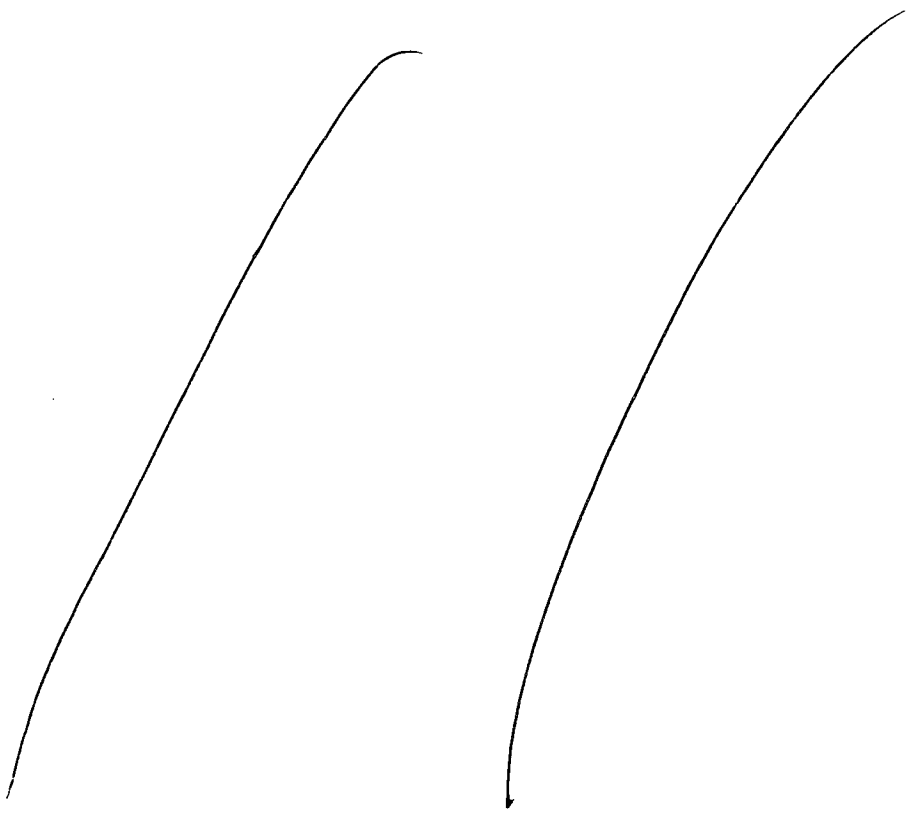
Approve with the provision that product be labeled to avoid sun exposure of the treated sites of application as well as pending agreement on other proposed drug product labeling recommendations.

B. Recommendation for nonclinical studies

A Phase 4 Commitment to determine the dermal carcinogenicity potential of cocoyl caprylocaprate, an novel excipient of Voltaren Gel.

C. Recommendations on labeling

The following labeling changes are recommended (wording to be removed is indicated by strikeouts and new wording is underlined) but are preliminary. The final label may reflect changes upon further discussion with review team and subsequent negotiation with the Sponsor.

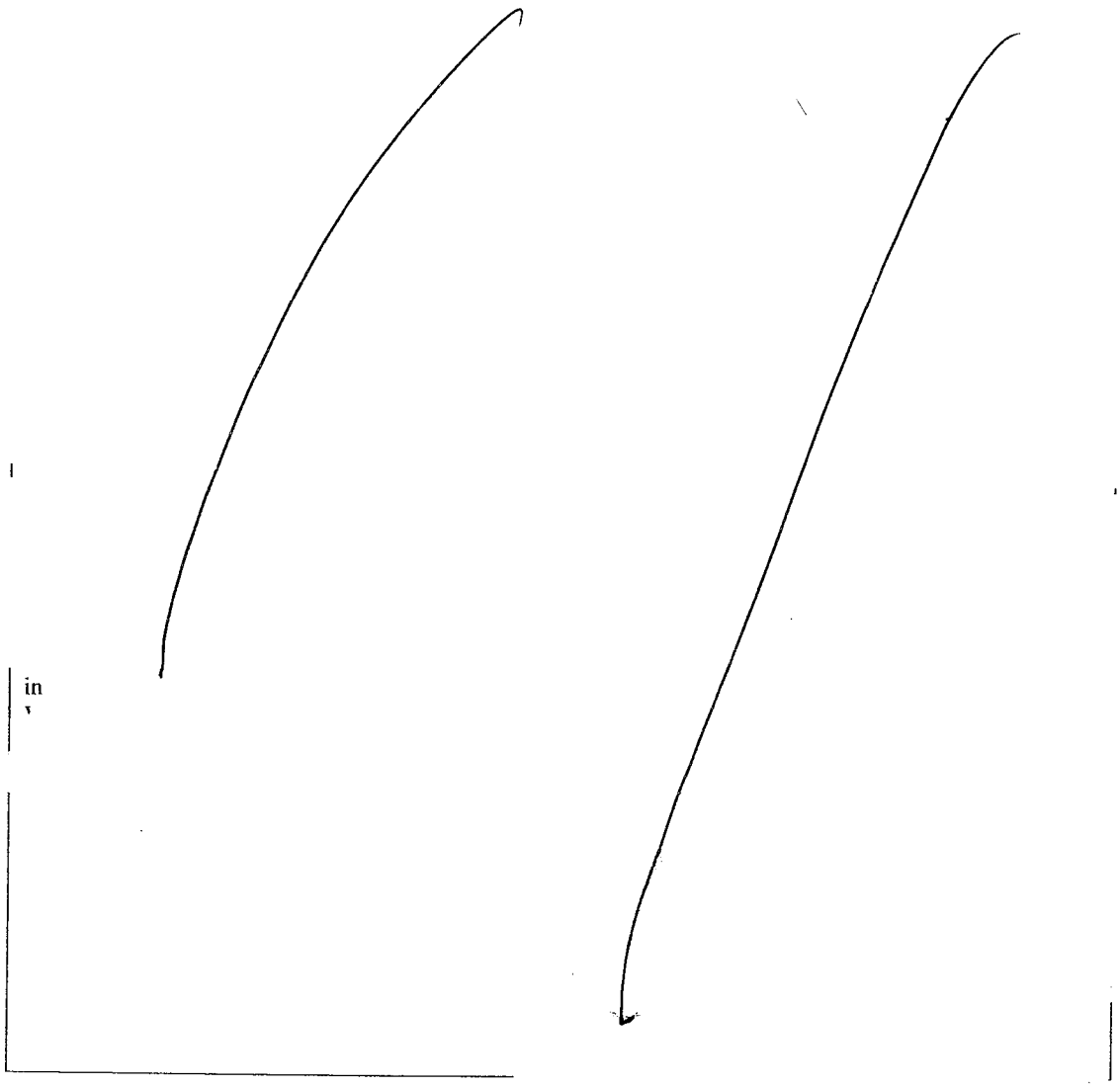


5 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



II. Introduction and Background

The nonclinical development program for the current NDA submission for Voltaren Gel (diclofenac sodium gel) with the Division (HFD-550 originally) began with the PIND 64,334 meeting in Feb 2003. The proposed indication at that time was

with a development program similar to Voltaren Emulgel (topical diclofenac diethylammonium gel), a nonprescription product available in many foreign countries.

The PIND discussion with the Division regarding the present diclofenac sodium gel product presented the problems and concerns of this pathway and

proposed indication. When the IND was submitted in Nov 2003, the proposed indication was changed to osteoarthritis.

Diclofenac has been approved in several products and formulations. Voltaren oral tablets (NDA 19-201), was approved first in 1988, and is currently indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and for acute or long-term use in the relief of the signs and symptoms of ankylosing spondylitis. The studies within NDA 19-201 provide the majority of nonclinical support for the topical formulation of NDA 22-122 under review. There are three other Voltaren products also marketed by this Sponsor and listed in the table "Approved Diclofenac Products" below. There are also two currently marketed topical diclofenac products from other Sponsors; neither is indicated for the treatment of osteoarthritis. One of these, Solaraze® (NDA 21-005), has a chronic indication and contains the same active pharmaceutical ingredient, diclofenac sodium, but at a higher concentration (3%) than the proposed diclofenac sodium (1%) product of NDA 22-122.

Approved Diclofenac Products

Product/ Company	Active Ingredient /Dosage Form	NDA	Year Approved	Indication
Voltaren® (Novartis)	diclofenac sodium enteric coated tablets	19-201	1988	➢ For relief of the signs and symptoms of osteoarthritis ➢ For relief of the signs and symptoms of rheumatoid arthritis ➢ For acute or long-term use in the relief of the signs and symptoms of ankylosing spondylitis
Voltaren Ophthalmic® (Novartis)	diclofenac sodium 0.1% solution/drops	20-037	1991	➢ For the treatment of postoperative inflammation in patients who have undergone cataract extraction ➢ For the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
Cataflam® (Novartis)	diclofenac potassium immediate release tablets	20-142	1993	➢ For treatment of primary dysmenorrhea ➢ For relief of mild to moderate pain ➢ For relief of the signs and symptoms of osteoarthritis ➢ For relief of the signs and symptoms of rheumatoid arthritis
Voltaren-XR® (Novartis)	diclofenac sodium extended-release tablets	20-254	1996	➢ For relief of the signs and symptoms of osteoarthritis ➢ For relief of the signs and symptoms of rheumatoid arthritis
TOPICAL (DERMAL) PRODUCTS				
Solaraze® (Bioglan Pharms Corp)	diclofenac sodium gel 3% (topical)	21-005	2000	➢ For treatment of actinic keratoses
Flector® (INST Biochem)	diclofenac epolamine, 1.3%, topical patch	21-234	2007	➢ For treatment of acute pain due to minor strains, sprains, and contusions.

FOREIGN TOPICAL PRODUCTS				
Voltaren® Emulgel™	Diclofenac diethylamine, 1.16%	-	-	➢ For the relief of pain, inflammation and swelling in: • Soft-tissue injuries: trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains, bruises and backache (sports injuries); • Localized forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy; ➢ For the relief of pain of non-serious arthritis of the knee or fingers. (localized forms of degenerative rheumatism, e.g. osteoarthritis of the peripheral joints and of the vertebral column).

The advantage of dermal dosing directly over the site of pain and inflammation, is the potential for achieving effective local concentrations of diclofenac while greatly reducing systemic concentrations of the drug and lessening the chance for gastrointestinal and cardiovascular adverse effects. While a nonclinical study demonstrated greater tissue concentrations directly under the site of application than at a more distal site, the clinical pharmacokinetic data (table below) demonstrated the striking disparity between systemic concentrations of diclofenac administered by topical application compared to oral tablets.

Pharmacokinetic Parameters and Comparison of Voltaren® to Oral Diclofenac Sodium Tablets After Repeated Administration		
Treatment	**C_{max} (ng/mL)** (Mean ± SD) % of Oral	**AUC_{0-24} (ng•h/mL)** (Mean ± SD) % of Oral
Topical Voltaren® Gel 4 x 4 g per day **(=160 mg diclofenac sodium per day)**	15.0 ± 7.33 0.633%	233 ± 128 5.79%
Topical Voltaren® Gel 4 x 12 g per day **(=480 mg diclofenac sodium per day)**	53.8 ± 32.0 2.21%	807 ± 478 19.7%
Oral Diclofenac sodium tablets p.o. 3 x 50 mg per day **(=150 mg diclofenac sodium per day)**	2270 ± 778	3890 ± 1710

For this product, the emphasis of the nonclinical program therefore has not been on toxicological findings from systemic effects, but rather dermal toxicology and phototoxicology such as cutaneous irritation and hypersensitivity responses. With the submission of the NDA, additional information concerning the drug product impurities and novel excipients of the formulation were provided that revealed potential deficiencies in the nonclinical drug development program. These are discussed in the Nonclinical Safety Issues Relevant to Clinical Use, section III C.

III. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The nonclinical support for the safety of Voltaren Gel relied mainly on studies originally submitted to support Voltaren (NDA 19-201), an oral tablet formulation of diclofenac sodium. Additional studies were submitted to support the topical route of administration and the safety of impurities/degradants and excipients. These included studies of absorption and pharmacokinetics, dermal and eye irritation, skin hypersensitivity, and dermal photosensitivity studies. With a few exceptions (indicated below when appropriate) they appear to be adequately conducted and interpreted. There were no significant toxicological concerns that arose from these studies.

Dermal and Eye Irritation and Dermal Sensitization Studies: Dermal irritation was minimal in acute studies in rabbits, expressed as slight erythema visible at 1 hour after a 4 hour semi-occlusive application, but not present 24 hours later. No corrosive effects or edema was observed. In a 4-week study in rabbits, with repeated daily dermal application of diclofenac, a transient erythemic response was observed but was absent or attenuated within 2 weeks of continuous application. Repeated dermal exposure to diclofenac gel was categorized as slightly irritating. Diclofenac applied to the rabbit eye was classified as non-irritating according the Sponsor's interpretation of their findings using European assessment criteria (possibly misinterpreted). However, the observations of early onset reddening of conjuctiva and sclera with swelling, although reversible, lead this reviewer to conclude that it is an irritant. Studies in guinea pig found no evidence for a sensitizing potential of diclofenac. The [redacted] excipient, carbomer [redacted], of Voltaren Gel, which replaced [redacted] of the European product Voltaren Emulgel, was also tested for dermal sensitization in guinea pigs. No skin reactions occurred upon contact challenge with [redacted] carbomer [redacted] two weeks after induction with a 5% intradermal solution.

Photosafety Studies: Photosenstivity studies conducted in guinea pigs demonstrated slight irritation in both UV-exposed and control skin sites, suggesting diclofenac was not photosensitive. Photosensitivity studies with diclofenac are difficult to judge, due to the fact that diclofenac absorbs UV wavelengths near the shorter wavelengths (290 nm) of the recommended testing spectrum (≥290-400 nm), and the intensity of these wavelengths is substantially less than longer wavelengths over the tested spectral range due to technical limitations of the solar simulated light equipment and filtering. Despite these limitations one can conclude that diclofenac was not photosensitizing, and that if photodegradants occurred, they did not induce signs of toxicity. Diclofenac is known to degrade upon exposure to sunlight, but it was not determined if photodegradants were formed on or in the skin in these studies. However, this determination is not conducted in standard photosafety testing, since a positive finding for toxicity implies the occurance of some toxic product.

Repeated Topical Dose Studies: The longest study conducted for this chronic indication was a 4-week dermal repeated dose study in rabbits. The Sponsor provided additional information pertaining to dermal toxicity when requested to provide support for a proposed 12-week duration clinical studies. This was not submitted to the NDA, but was submitted when requested after the midcycle review meeting. This was a 12-week dermal application study in rabbits that compared daily single application of Voltaren Emulgel (400 mg/kg/day at a concentration of 10 mg/cm^2) with placebo Emulgel formulation. For comparison, a human daily dose of Voltaren Gel would consist of 4 applications per day, not to exceed 320 mg of diclofenac per day over an estimated area of 400 to 800 cm^2 for each application, corresponding to 0.4 to 0.8 mg/cm^2 (or ~5.3 mg/kg). Skin reactions in the 12-week rabbit dermal toxicity study included erythema, edema and papules, some scabs, flaking and cracking of the epidermis and a reduction in hair growth. However, these occurred in both diclofenac and placebo groups, were reversible, and therefore was attributed to the daily application and removal of occlusive dressings. There were no deaths, no changes in body weight, food consumption, hematology, clinical biochemistry, urinalysis, ophthalmology, hearing, organ weights, gross and histopathology between treatment groups. There was one animal with an ulcerated gastric mucosa in the diclofenac treatment groups thought to be due to accidental removal of the occlusive dressing and ingestion of diclofenac or pieces of the dressing. There was no toxicokinetic data provided for this study.

Genetic, carcinogenetic, and reproductive toxicology: These studies were conducted previously for approval of Voltaren (NDA 19-201) and are summarized in the body of this review. No toxicological concerns arose from those studies.

A substantial portion of the nonclinical review concerns studies that characterized the genetic, dermal and systemic toxicology of diclofenac-derived impurities, and excipients of the drug product. Specific nonclinical issues of these compounds that relate to clinical use are discussed in the nonclinical safety issues section III C.

Impurities/Degradants: The Sponsor identified four impurities derived from either the synthesis of diclofenac or the degradation of diclofenac upon stability testing. Three impurities/degradants ( ) exceed the ICH recommended threshold for qualification in stability tests at the proposed 36 month shelf life. Three impurities also had structural alerts for potential genotoxicity since they . Collectively, these four impurities were only partially qualified in genotoxicity testing by mutation studies and by acute oral studies, but lacked clastogenic assessment and were not studied in a 3-month daily application dermal toxicology study. These studies are necessary for qualification of drug substance and product impurities and degradants as stated in guidances ICH Q3A and Q3B(R2), respectively.

There is one novel impurity, , not present in previous diclofenac formulations which also exceeds the qualification threshold at the end of stability and contains a structural alert for genotoxicity. For this impurity, both mutagenicity (bacterial reverse mutation assay) and clastogenicity (chromosomal aberration assay) testing were negative for genotoxicity. Since no long term dermal toxicology studies were conducted with the

Voltaren Gel containing this impurity nor was a 3-month bridging toxicity study performed with this specific compound, the compound is incompletely qualified and further studies would normally be requested. It is important to note that this compound is

Novel Excipients: The novel excipients included cocoyl caprylocaprate and perfume . Perfume comprises only) of the drug product and is composed of compounds. The Sponsor supplied appropriate toxicological information for some of these compounds, while others were determined by this reviewer (through database searches) to be of minimal toxicological consequence (potentially allergenic) at the concentrations applied topically. Since it comprises less than of the drug product, it is unnecessary to further characterize the perfume or its components, as this level represents the recommended regulatory (ICH Q3B(R2) threshold for conducting toxicologic qualification of an impurity, which unlike an excipient has no benefit in the formulation.

Cocoyl caprylocaprate comprises , of the drug product. Although cocoyl caprylocaprate is listed in the European Pharmacopoeia and was acceptable to Chemistry Reviewers as indicated at an EOP2 meeting of June 1, 2005, we lack toxicology information to support its safe use. Upon our request for this information after the midcycle meeting, we received DMF for this excipient from the

Cocoyl caprylocaprate (CAS 95912-86-0,) is the caprylic/capric acid ester of saturated fatty alcohol C_{12-18} derived from

B. Pharmacologic activity

Voltaren Gel 1% is a gel formulation that contains diclofenac sodium as its active ingredient. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that has been in widespread therapeutic use since first approved in 1988. Diclofenac has potent anti-inflammatory, anti-nociceptive, and anti-pyretic properties. Diclofenac inhibits the enzyme, cyclooxygenase (COX), an early component in the arachidonic acid cascade. By inhibiting COX, diclofenac prevents the formation of thromboxanes, prostaglandins, and prostacyclin. Diclofenac also inhibits the production of leukotrienes by decreasing arachidonic acid release and increasing its uptake. It is hypothesized this uptake is into triglycerides, thus limiting the availability of arachidonic acid entering the COX and lipoxygenase pathways. The Sponsor claims, based on their human studies, that diclofenac is approximately 20-fold more potent as an inhibitor of COX 2 compared to COX-1 isozymes. However, the COX-2/COX-1 potency for diclofenac in humans varies substantially among published studies. The lack of clinical relevance for the COX-2/COX-1 specificity of diclofenac is also evident from the substantial number of gastrointestinal adverse effects with diclofenac reported in the literature. The role of thromboxane, prostaglandin, prostacyclin, and leukotriene inhibition in the therapeutic efficacy of diclofenac is not completely understood.

C. **Nonclinical safety issues relevant to clinical use**

When the NDA was submitted, a number of potentially problematic issues were revealed because the Sponsor had not provided sufficient information. These related to the lack of toxicological characterization of diclofenac-related impurities, novel excipients, and photodegradants.

Diclofenac Impurities/Degradants

Four impurities were derived from either the synthesis of diclofenac or the degradation of diclofenac upon stability testing. Voltaren Gel contains the same active pharmaceutical ingredient, diclofenac sodium, that has been used in Voltaren and Voltaren-XR and contains the same synthesis impurities as these oral products since the drug substance is synthesized by the same manufacturing process. For approximately 20 years of marketing, three of these impurities have been ingested in the various Voltaren oral products. With reference to the table of the clinical pharmacokinetic data above, the systemic exposure (AUC) to these impurities from topical application is expected to be less than one fifth of that of oral Voltaren. As exposure to these impurities is expected to be substantially lower than current exposures in approved oral Voltaren products, unless there is some clinical signal that would warrant further toxicological investigation, this reviewer accepts the current deficiencies in the toxicological characterization of these impurities and no further toxicological characterization is recommended. However, in our information request to the Sponsor in June 2007, we requested additional toxicological information, if available. The Sponsor had not conducted additional tests

The novel impurity, — which exceeded the qualification threshold of — was incompletely evaluated in the present NDA submission, lacking characteristization of its potential dermal and systemic toxicity. Toward the end of the review process, Sept 18, 2007, the Sponsor was sent a request to accept the stability specification of NMT — for — since an examination of the proposed commercial batches on 36 month stability indicated degradant levels far below the Sponsor's initial proposed specifications. This was acceptable by the Sponsor (email of Sept 19, 2007) and with the lowered specification no further qualification studies are necessary for this compound.

Novel Excipient: Cocoyl Caprylocaprate

The concentration of this excipient in Voltaren Emugel is the same as in Voltaren Gel, providing approximately 20 years of foreign clinical experience with dermal application of this excipient. It is also present in many cosmetic products (aftershave lotions, bath oils, blushers, cleansing lotions, eye shadows and liners, hair conditioners, lipsticks, suntan preparations, etc) where it is used as an emollient. The concentration of this excipient in these various products was not able to be determined from available information, but its prevalence in and widespread use in various topical product, some of which are applied to large surface areas (sunscreens, etc.) or may be used long-term (cleansing lotions and other cosmetics) have not signaled any safety concerns and provides reasonable assurance of its short-term safety. Scientific support for the short-term safety of cocoyl caprylocaprate is supported by the , DMF .

There has been no determination of the carcinogenic potential of cocoyl caprylocaprate. In the NDA process, genetic toxicology studies to determine both mutagenic and clastogenic potential are usually conducted as a prelude to later carcinogenicity studies. The DMF .. The clinical experience, despite about 20 years of availability in foreign markets, is insufficient to characterize its carcinogenic potential. Furthermore, full qualification of this excipient which would also be necessary for inclusion in the Inactive Ingredient Database would require a dermal carcinogenicity

study. As a component of Voltaren Gel, a product that could be applied daily for a lifetime, **a dermal carcinogenicity study of should be conducted for cocoyl caprylocaprate to determine its carcinogenic potential.** Although there is no study of this compound's clastogenic potential, the recommended study would supercede the need for a genetic toxicology study clastogenicity. The issue of the acceptability of cocyl caprylocaprate was raised at the EOP2 meeting by the Sponsor, but we did not recognize at that time its incomplete toxicological characterization, thus the concern of carcinogenic potential was not previously raised with the Sponsor. Therefore, we recommend this to be conducted as a Phase 4 commitment.

Photodegradants and sun exposure of the treated sites

Voltaren Gel should **be labeled to recommend individuals avoid sun exposure of the treated areas**. It is known from CMC stability studies for container protection of Voltaren Gel that photodegradants of diclofenac readily developed with exposure to solar simulated light. Although all of the nonclinical photosafety studies of were negative, there is reason to suspect the exposure intensity at 290 nm was inadequate. As revealed in exposure intensity-wavelength graphs, it is common for wavelength near the spectral boundaries to have attenuated intensities. This is due to do the light source and filtering. It is important for diclofenac photosafety studies, because the 290 wavelength is near diclofenac's absorption maximum and is comprises the lower boundary of the recommended range for ultraviolet radiation photosafety testing. Furthermore, it is not known if diclofenac photodegradants that are formed by exposure to simulated solar light or sunlight were actually formed in these phototoxicology studies, because this comparison is not required in standard testing and rarely, if ever, conducted. Thus, there is sufficient reason to doubt the adequacy of the standard photosafety studies, as a appropriate determination of diclofenac safety during sun exposure.

The Sponsor is referencing Solaraze for the dermal carcinogenicity and photococarcinogenicity studies as a 505(b)(2) NDA. Solaraze is labeled to avoid sun exposure, but there was no reason to provided. The indication for Solaraze was for treatment of actinic keratosis in which patients should avoid the sun anyway. The photococarcinogenicity study conducted for Solaraze approval demonstrated an earlier development of ultraviolet radiation-induced tumors, however this seemed to be minimized in the labeling of that product, perhaps because it was labeled for patients to avoid the the sun. Photodegradants were also identified in toxicological studies for Solaraze, but these were not examined for toxicological effects, since labeling to avoid sunlight rendered additional toxicological studies unnecessary. However, for the osteoarthritic patient population, unlike those with actinic keratosis, there is no clinical reason to avoid sunlight. The areas treated with Voltaren Gel, if exposed to sunlight, might result in elevated amounts of uncharacterized photodegradants based on CMC stability studies. This can be mitigated by labeling to avoid sun exposure of the Voltaren Gel-treated skin surfaces.

Based on review of the pharmacology and toxicology of this NDA, the following are strongly recommended:

1) A Phase 4 dermal carcinogenicity study for the excipient cocoyl caprylocaprate.

2) Labeling to include language to avoid sun exposure of the Voltaren Gel treated areas.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	**22-122**
Review number:	1
Sequence /date/type of submission:	000/Dec 20, 2006/commercial 505(b)(2)
Information to sponsor:	No
Sponsor and/or agent:	**Novartis Consumer Health** Parsippany, New Jersey 07054-0622
Manufacturer for drug substance:	Novartis Pharma AG, Basle, Switzerland CFN # 9611204 (formerly known as Novartis Pharma Klybeck AG, CFN # 9692036)
Reviewer name:	L.S. Leshin
Division name:	Division of Anesthesia, Analgesic and Rheumatology Drug Products
HFD	170
Review completion date:	September 26, 2007

Drug:

Trade name:	**Voltaren® Gel**
Generic name:	Diclofenac Sodium Topical Gel, 1% Diclofenac Sodium
Code Names:	GP 45840 Zy-17727B NCH 927806 (Voltaren Emulgel, diclofenac diethylamine)

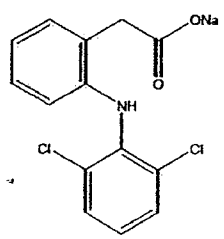
Chemical name:

2-[2,6-dichlorophenyl] amino] benzeneacetic acid, monosodium salt

Sodium [o-(2,6-dichloroanilino)phenyl]acetate

CAS registry number:	15307-86-5
Molecular formula:	318.13
Molecular weight:	$C_{14}H_{10}Cl_2NNaO_2$

Structure:



Related Code names within this review (See Appendix 1)

CGP 13294 = 3'-hydroxydiclofenac (metabolite)
CGP 14217 = 4'-5-dihydroxydiclofenac (metabolite)
GP 47766 = 4'-hydroxydiclofenac (metabolite)
GP 47852 = 5'-hydroxydiclofenac (metabolite)

/ impurity/degradation product
impurity/degradation product
/ impurity/degradation product
/ impurity/degradation product

Relevant INDs/NDAs/DMFs:

IND 64,334 (Diclofenac sodium topical gel, 1%)
NDA 19-201 (Voltaren®, diclofenac sodium, Novartis Pharmaceuticals Corporation, approved July 28, 1988)
NDA 20-142 (Cataflam®, diclofenac potassium, Novartis Pharmaceuticals Corporation, approved Nov 24, 1993)
NDA 20-254 (Voltaren-XR®, diclofenac sodium, Novartis Pharmaceuticals Corporation, approved March 8, 1996)
NDA 21-005 (Solaraze; diclofenac sodium topical gel 3%; approved Oct 16, 2000; Bioglan Pharmaceuticals Corp.)
DMF /
DMF /
DMF /

Drug class: Non-steroidal anti-inflammatory analgesic

Intended clinical population: joints amenable to treatment, such as the hands and knees

Route of administration: Topical

Clinical formulation: Diclofenac sodium topical gel 1% is a white, opaque emulsion-gel containing 1 g diclofenac sodium per 100 g of gel as active ingredient

Recommended Dosing Regimen

Lower Extremities including the knees, ankles and feet	Upper Extremities including the elbows, wrists and hands
4 g of the gel applied to the affected joint, four times daily, not to exceed 16 g daily per lower joint	2 g of the gel applied to the affected joint, four times daily, not to exceed 8 g daily per upper joint.
Maximum daily amount of the product to be used over all affected joints is 32 g which corresponds to 320 mg of diclofenac sodium per day. (Based on the clinical pharmacokinetic studies, the application area is estimated to be between 400 and 800 cm^2 for multiple sites dosing at this maximal dose.)	

Dose of Voltaren Gel and diclofenac sodium

Treatment Site	Compound	Dose/ Application	Area of Application[1]	Dose/ Application Site	Dose Frequency	Dose/Day
Knee Ankle Feet	Voltaren Gel	4 g/site	Knee ~400 cm^2	10 mg/cm^2	QID	16 g 40 mg/cm^2
	Diclofenac sodium	40 mg/site		0.1 mg/cm^2		160 mg 0.4 mg/cm^2
Elbow Wrist Hand	Voltaren Gel	2 g/site	Hand ~200 cm^2	10 mg/cm^2	QID	8 g 40 mg/cm^2
	Diclofenac sodium	20 mg/site		0.1 mg/cm^2		80 mg 0.4 mg /cm^2

[1] based on study VOSG-PN-113

Table 2-1 Drug product composition

Component [1]	Reference to quality standard	Function	% w/w
Diclofenac sodium *(Diclofenac sodium)*	USP/Ph. Eur.	Active ingredient	1.00
Isopropyl alcohol *(Isopropyl alcohol)*	USP/Ph. Eur.		
Propylene glycol *(Propylene glycol)*	USP/Ph. Eur.		
Cocoyl caprylocaprate	Ph. Eur.		
Mineral oil	USP/Ph. Eur.		
Polyoxyl 20 cetostearyl ether	NF/Ph. Eur.		
Carbomer Homopolymer Type C	NF/Ph. Eur.		
Strong ammonia solution	NF/Ph. Eur.		
Perfume	In-house standard		
Purified water *(Water, purified)*	USP/Ph. Eur.		

[1] Component names in italics are the names referenced in European Pharmacopoeia.

Table 4-1 Cross reference of adopted product names during development

Product name	Other adopted product names
Diclofenac sodium topical gel 1%	(diclofenac sodium topical gel) 1%
	(diclofenac sodium topical gel), 1%
	DSG 1%
	DSG
	Voltaren
	Voltaren 1% Emulgel
	Voltaren Emulgel 1%
	Diclofenac sodium gel 1% (w/w)
	Voltaren 10 mg/g Emulgel
	Voltaren sodium gel 1%
	Voltaren sodium gel
	Voltaren gel 1%
	Voltaren gel

Excipients

NCH 927806 1% is the code name for Voltaren Emulgel (10 mg/g). It was used in some nonclinical studies, and its composition is presented below.

Table 2-1 Voltaren® 1% Emulgel® composition

Components	% w/w
Diclofenac diethylamine	1.16
Isopropyl alcohol	
Propylene glycol	
Cocoyl caprylocaprate	
Mineral oil	
Polyoxyl 20 cetostearyl ether	
water	

Emulgel is the diclofenac diethylamine salt rather than the diclofenac sodium salt. In the product under review, diclofenac sodium is used instead of diclofenac diethylamine and the Carbomer Homopolymer Type C/ replaces the for the following benefits according to the Sponsor:

1) The active ingredient diclofenac sodium is a well established drug substance approved by the FDA for use in Voltaren® (diclofenac sodium) Enteric-coated Tablets (NDA No. 19-201) because it is proven as a safe and efficacious analgesic.
2) The easy-to-apply emulsion gel characteristics of the Voltaren® 1% Emugel® are conserved.
3) The drug product is free from diethylamine, an organic amine that may react with nitrous acid, nitrates, or an atmosphere with high nitrous oxide concentrations to form N-nitrosamines.

The early nonclinical studies were conducted with either diclofenac sodium or diclofenac diethylamine (diethylammonium) formulated in the Emugel vehicle. Later GLP studies conducted in the early 2000's were formulated in the Voltaren Gel vehicle.

In developing the Voltaren Gel vehicle, the Emugel was modified to [redacted] with carbomer homopolymer Type C ([redacted]) as [redacted], and diethylamine was replaced [redacted] These changes have potentially significant toxicological implication. The change in carbomer type is to one that theoretically [redacted] Evidence for this was not presented, nor referenced. However, this carbomer is currently used in cosmetics and other dermatological formulation and listed in the Agency's Inactive Ingredient Database for use at a concentration greater than contained in Voltaren Gel. The other change in the vehicle removed the organic amine that may react with nitrous acid, nitrates or atmospheric nitrous oxides to form N-nitrosamines, known carcinogens.

> ***Reviewer's Comments:*** Given these improvements in the vehicle and change to diclofenac sodium salt, it is unfortunate that the nonclinical studies used so many different codes and names for the study drug and/or vehicle. Despite the clarification provided in the Chemistry section of the submission (see table 4-1, above), it was often not clear from comparison with the certificates of analysis and previous drug codes which salt form or vehicle was actually used in the study. Fortunately, due to the general lack of toxicity noted in the nonclinical studies, and expected greater safety of Voltaren Gel compared to Voltaren Emulgel (but not assessed by comparison in nonclinical studies), the type of active drug salt and type of vehicle used were not considered problematic for the overall conclusions.

The excipients selected for the drug product, their concentration (in % w/w and in mg/g) and their characteristics relative to their functions are discussed below. All excipients comply with the respective USP and/or Ph. Eur. monographs except [redacted] which meets the Sponsor's in-house specification. Refer to the CMC review for additional chemistry information.

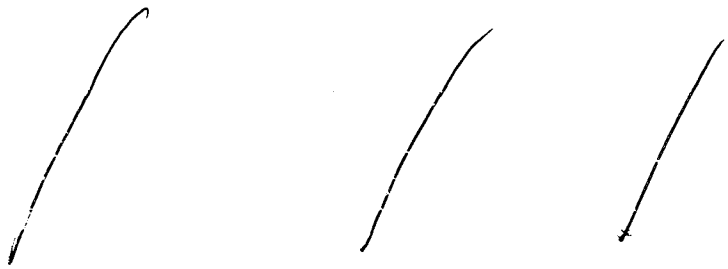
Diclofenac and Excipient Components

COMPONENTS	% w/w	DOSE/DAY maximum allowed for all joints (g)	EXCIPIENT APPROVAL[1]
Diclofenac sodium (1 g/100 g gel)	**1.0**	**0.32**	
Isopropyl alcohol			**Inactive Ingredient List** **Maximum: — in topical lotion**
Propylene glycol			**Inactive Ingredient List** **Maximum: — in topical gel**
Cocoyl caprylocaprate			**Novel Excipient**
Mineral oil (—)			**Inactive Ingredient List** **Maximum — in topical ointment**
Polyoxyl 20 cetostearyl ether —			Used in previous approved drugs at — NDA 22-013, clobetasol propionate foam NDA 21-978, desonide foam
Carbomer Homopolymer Type C (Carbomers)			**Inactive Ingredient List** **Maximum — in topical transdermal gel**
Strong ammonia solution —			
Perfume —			**Novel Excipient**
Purified water			
Total	**100 g**	**32 g**	

[1] maximum potency %

Both cocoyl caprylocaprate and perfume — are novel excipients. Cocoyl caprylocaprate was the only novel excipient comprising greater tha — /w) of the drug product, thus requiring toxicological characterization. Although it was listed in the European Pharmacopoeia, toxicology information was lacking. Upon our request for this information after the midcycle meeting, we received DMF —

Cocoyl caprylocaprate (CAS 95912-86-0, — ") is the caprylic/capric acid ester of saturated fatty alcohol C_{12-18} derived from —



The reviewer concurs with the above findings of those studies after review of the DMF. Its concentration in the product is — w/w), so it is not expected to harmful. However, the substance may build up within the dermis with repeated application, which could potentially reach local comedogenic concentrations. The calculated daily application would be — day

The concentration of this excipient in Voltaren Emugel is the same as in Voltaren Gel, providing approximately 20 years of clinical experience with dermal application of this excipient. However, in contrast to diclofenac and its related impurities, the carcinogenic potential of cocoyl caprylocaprate has not been studied and the 20 years of clinical experience is inadequate to characterize its carcinogenic potential. Furthermore, full qualification of this excipient which is needed for inclusion in the Inactive Ingredient Database requires dermal carcinogenicity study. Since Voltaren Gel will be applied daily for a lifetime, it is recommended that a dermal carcinogenicity study should be conducted for cocoyl caprylocaprate to determine it carcinogenic potential.

Impurities

are diclofenac related substances that have the potential of forming in the drug product. All are specified diclofenac degradation products in the drug product specifications.

- was typically present and controlled as an impurity in the drug substance.
- was not typically present in the drug substance and was not observed from manufacture or packaging of the drug product. They were observed in drug product manufactured — during stability.
- was formed by It was found during stability testing at levels at or below the reporting threshold of when the drug product was manufactured . It was also found above the reporting threshold when the drug product was manufactured when stored at 25 °C and 60% RH for 36 months. This compound did not form in the tablet formulation of Voltaren described in NDA 19-201 and is therefore a novel impurity found only in this topical product.

- One unknown impurity, with a retention time relative to diclofenac of — has been observed in the drug product studied on stability. At 36 months storage at 25 and 30 °C/60% RH and at 6 months storage at 40 °C/75% RH this unknown impurity has not exceeded the reporting threshold of —

No other significant impurities at or above the reporting threshold of — were observed in the drug product at release or after being stored for 36 months at 25°C and 30°C/60% RH and for 6 months at 40 °C/75% RH. Very small peaks, significantly below the reporting threshold of — were observed in the chromatograms, but did not increase with time or stress.

All degradation products observed above the reporting threshold of —, were included in the product specifications. — has not been observed at a level that exceeds the reporting threshold but was included in the product specifications to be consistent with the current Voltaren Tablet NDA 19-201. Refer to the CMC review for additional information.

Table 1-1 Specifications for diclofenac degradation products in finished product

Degradation product	Release limit	End of shelf-life limit
•	• nmt[1]	• nmt
•	• nmt	• nmt
•	• nmt	• nmt
•	• nmt	• nmt
• Individual unspecified, unidentified	• nmt	• nmt
• Total degradation products[2]	• nmt	• nmt

[1] nmt = not more than

[2] All impurities at a level greater than the reporting threshold are summed and reported as total impurities.

Degradants/Impurities of Drug Product (Reviewer's Table)

Compound	Acceptance Criteria % of drug product (Amount applied/day at maximal daily dose)[1]		Structural Alert for Genotoxicity (conclusion from genotoxicity assays)	Comment	Missing Information for Toxicologic Qualification*
	Release	36 months (proposed shelf life)			
—	NMT —	NMT —	No Not mutagenic; Not clastogenic	Exceeds qualification threshold: > — at 36 months[3]	**3-Month Dermal Toxicity**
—	NMT —	NMT —	Yes (Genotoxicity not tested)	Exceeds qualification threshold: > —/day at release and at 36 months[2] > —, at 36 months[3]	**Genotoxicity Assays** (Mutation and Clastogenicity) **3-Month Dermal Toxicity**
—	NMT —	NMT —	Yes Not mutagenic; (Clastogenicity not tested)	Exceeds qualification threshold: > —day at release and at 36 month[2]	**Genotoxicity Assay** (Clastogenicity); **3-Month Dermal Toxicity**
—	NMT —	NMT —	Yes Not mutagenic; Not clastogenic	Exceeds qualification threshold: > — at 36 month[3]	**3-Month Dermal Toxicity**

[1] intended maximal dose of diclofenac applied per day = 0.32 g (32 g of topical gel)

[2] structural alerts for genotoxic potential need to be limited to no greater than 1.5 µg/day (Guidances for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005)

[3] threshold for application of maximum daily dose of 0.32 g of diclofenac, is — µg) or — total daily dose (termed total daily "intake" in guidance), (Guidances for Industry: ICH Q3B(R2) Impurities in New Drug Products, July 2006).

* See Executive Summary for explanation of regulatory position on to not require full toxicologic qualification.

Reviewer's Comment: For the maximal dose of diclofenac applied per day = 0.32 g (from 32 g of topical gel) the qualification threshold for application of 0.32 g of diclofenac is — , or — otal daily intake (assumed to be same as total daily application if 100% absorbed). As indicated in the reviewers table below, all four impurities meet the release specifications, but — exceed the 36 month shelf-life stability specifications. Collectively, these four impurities were only partially qualified in genotoxicity testing by mutation studies and by acute oral studies, but lacked clastogenic assessment and were not studied in a 3-month daily application dermal toxicology study. The impurities were derived from either the synthesis of diclofenac or the degradation of diclofenac upon stability testing. Voltaren Gel contains the same active pharmaceutical ingredient, diclofenac sodium, that has been used in Voltaren and Voltaren-XR since it is synthesized by the same manufacturing process. For approximately 20 years of marketing, three of these impurities — have been ingested in the various Voltaren oral products. In addition, the systemic exposure (AUC) to these impurities from topical application is expected to be less than one fifth of that of oral Voltaren. Unless there is some clinical signal that would warrant further toxicological investigation, this reviewer accepts that the current deficiencies in the toxicological characterization of these impurities, do not warrant further studies. As exposure to these impurities is expected to be substantially lower than current exposures in approved oral Voltaren products, no further toxicological characterization is necessary.

In our information request to the Sponsor in June 2007, we requested additional toxicological information, if available. The Sponsor had not conducted additional tests, but did acknowledge our comment that guidance and requirements change over the years

The novel impurity, — which exceeded the qualification threshold of 0.2%, was incompletely qualified, lacking characteristization of its potential dermal and systemic toxicity. Toward the end of the review process, Sept 18, 2007, the Sponsor was sent a request to accept the stability qualification threshold of — for — , since an examination of clinical batch measurements indicated results far below the Sponsor's specifications. This was acceptable by the Sponsor (email of Sept 19, 2007) and no further qualification studies are necessary for this compound.

Photostability

The photostability data for the drug product indicated that without package protection the product is photosensitive. The gel darkened and separated and the diclofenac sodium degraded. However, the
and degradation product data for the product packaged in aluminum tubes that are impermeable to light, provided evidence that the product is adequately protected from light.

The exposure was controlled to insure the drug product was exposed to light providing an overall illumination of not less than 1.2 million-lux hours and an integrated near ultraviolet energy of not less than 200-watt hours/m^2. The total amount of exposure was determined using a calibrated radiometer/photometer (with a UVA detector and an probe).

> ***Reviewer's Comments:*** Various exposure parameters for the above photostability tests were not provided. The light source and its characteristics were also not provided. Because this product will be removed from its light protected tube and applied onto the skin, it will be readily exposed to sunlight and artificial light. The active component will then degrade as evidenced above. The photodegradants need to be identified and characterized for potential toxicity. The Sponsor did not indicate the wavelength absorption range for diclofenac. The Merck Index indicates that diclofenac has an absorption peak at 283 nm in methanol, and at 276 nm in phosphate buffer, pH 7.2. These wavelengths are usually outside the test range in phototoxicity testing (>290nm, testing for UVB effects) and possibly explain the consistent lack of effects noted in phototoxicity testing. However, the results here (at unknown wavelengths) and from other diclofenac topical products within the Division (with known wavelengths or direct sunlight exposure) indicate that photodegradants will form. They should be identified and tested for toxicology effects or the product should be labeled to avoid sun and strong light exposure.

Regulatory History

The nonclinical development program for Voltaren Gel (diclofenac sodium gel) with the Division (HFD-550 originally) began with the PreIND-64334 meeting in Feb 2003. The proposed indication at that time was to '

The Division explained the problems with indication When the IND was submitted in Nov 2003, an indication for osteoarthritis was proposed. The nonclinical studies provided safety coverage for the initial clinical pharmacokinetic, dermal sensitization and phototoxicity studies, but lacked safety coverage for studies longer than 4 weeks duration and thus were insufficient for the proposed 12 week efficacy studies. In response, the Sponsor

submitted information comparing nonclinical findings of diclofenac diethylammonium (now termed diclofenac diethylamine) with diclofenac sodium, submitted a 12-week rabbit dermal toxicology study with Voltaren Emulgel, and human data from studies with Voltaren Emulgel. It was decided that these studies provided sufficient information to justify the safety of the 12 week clinical studies without further nonclinical study. No additional toxicology studies including long-term dermal toxicology studies were performed for this NDA.

A End of phase 2 meeting held on June 19, 2004 and for CMC issues on June 1, 2005, and no specific nonclinical issues were addressed based on our knowledge at the time of Voltaren's long use and lack of specific details concerning excipients and impurities of the drug product. These became concerns during the review process, but were resolved by information later received from the Sponsor in response to our requests.

Voltaren oral tablets is currently indicated for relief of the signs and and symptoms of osteoarthritis and rheumatoid arthritis, and for acute or long-term use in the relief of the signs and symptoms of ankylosing spondylitis. There are three other Voltaren products also marketed by this Sponsor and listed in the table of Approved Diclofenac Products below. There are two currently marketed topical products, neither is indicated for the treatment of osteoarthritis. One of these, Solaraze® (NDA 21-005), has a chronic indication and contains the same active pharmaceutical ingredient, diclofenac sodium, but at a higher concentration (3%) than the proposed diclofenac sodium (1%) product of NDA 22-122. Refer to the table in section III.A. of the Executive Summary.

For (b)(2) applications:
Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-122 are owned by Novartis Consumer Health or are data for which Novartis Consumer Health has obtained a written right of reference. Any information or data necessary for approval of NDA 22-122 that Novartis Consumer Health does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Novartis Consumer Health does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-122.

Novartis Consumer Health will rely on the Agency's findings of safety from both dermal carcinogenicity and dermal photococarinogenicity studies for Solaraze™ (diclofenac sodium), 3% Gel, NDA 21-005, now marketed by Bradley Pharmaceuticals.

In addition Novartis Consumer Health will rely on the Agency's findings of safety from studies for Voltaren® (diclofenac sodium and diclofenac potassium) tablets (Novartis Pharmaceuticals; NDAs 19-201, 20-254 and 20-142) for which a letter of authorization is included within this application. As requested in the pre-NDA meeting, the nonclinical legacy documents from NDA 19-201 have been included in the application in Module 4.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Report number/ Location (eCTD = common technical document section number, electronic submission)	Title
ADME	
12-march-2002 eCTD 4.2.2.2.1	Memo: In vitro skin penetration of diclofenac from Voltaren® Emulgel® 1%, and the US Emulgel with Diclofenac Sodium
internal-report-03171 (dated 11.07.03) eCTD 4.2.2.2.2	Diclofenac sodium gel (Diclofenac Na 1%) – pH range [redacted] Comparison of the in vitro skin penetration rate.
internal-report-03201 (dated 06/08/2003) eCTD 4.2.2.2.3	Diclofenac sodium gel (diclofenac Na 1%) Voltaren Emulgel (diclofenac diethylamine 1.16%) – Viscosity: Comparison of the in vitro skin penetration rate – 06 August 2003.
N01-C-00299 eCTD 4.2.2.2.5	Plasma kinetic study and evaluation of anti-inflammatory activity using the hairless rat ultraviolet-induced erythema model of sunburn
B12-1977 eCTD 4.2.2.4.1	GP 45840: Influence of diclofenac-Na and various compounds on hepatic microsomal drug metabolizing enzyme systems in the rat in vivo.
B86-1982 eCTD 4.2.2.7.1	GP 45840: Binding of diclofenac-Na, flufenamic acid, phenylutazone and salicylic acid to serum proteins of healthy rats and rats with induced arthritis.
Genetic Toxicology	
v4405/02 eCTD 4.2.3.3.1.8	Photomutagenicity test in Zy-17727B active substance on induction of reverse mutations in bacteria.
v4402-02 eCTD 4.2.3.3.1.17	Photomutagenicity test with Zy-17727B active substance on formation of chromosomal aberrations in cultured Chinese hamster ovary cells.
v4402-14 eCTD 4.2.3.2.2.8	In vivo (bone marrow) chromosomal aberration test in rats treated with Zy-17727B active substance.
Local Tolerance	
Skin	
843178 eCTD 4.2.3.6.1	NCH 927806 1%: Primary skin irritation study in rabbits (4-hour semi-occlusive application).
843186 eCTD 4.2.3.6.2	NCH 927806 1%: 4-week repeated dose dermal toxicity study in the rabbit (semi-occlusive application).
843180 eCTD 4.2.3.6.3	NCH 927806 1%: Determination of phototoxicity in albino guinea pigs.
Eye	
843182 eCTD 4.2.3.6.4	NCH 927806 1%: Primary eye irritation study in rabbits.
Antigenicity	
Skin	
843179 eCTD 4.2.3.7.1.1	NCH 927806 1%: Contact Hypersensitivity in albino guinea pigs, maximization-test.
V4413-09	Sensitization study with NCH 927806 (1%) in guinea pigs

eCTD 4.2.3.7.1.2	(maximization test).
844802 eCTD 4.2.3.7.1.3	NCH 927806 1%: Contact hypersensitivity in albino guinea pigs, maximization-test.
Excipient	
845093 eCTD 4.2.3.7.1.7	Carbomer — Contact hypersensitivity in albino guinea pigs, maximization-test.
Photosensitivity	
843181 eCTD 4.2.3.7.1.4	NCH 927806 1%: Determination of photoallergenicity in albino guinea pigs (including information about allergenicity, photoirritation and irritation).
845817 eCTD 4.2.3.7.1.5	NCH 927806 1%: Determination of photoallergenicity in albino guinea pigs (including information about allergenicity, photoirritation and irritation).
PAC-PH-02-0247 eCTD 4.2.3.7.1.6	PAC-PH-02/0247: Assessment of photosensitization on the albino guinea pig.
Impurities, Qualification Studies	
63/50-D5140 eCTD 4.2.3.7.6.5	— Reverse mutation in four histidine-requiring strains of Salmonella typhimurium and two tryptophan-requiring strains of Escherichia coli.
63/51-D5140 eCTD 4.2.3.7.6.6	— nduction of chromosome aberrations in cultured human peripheral blood lymphocytes
63/52-D6144 eCTD 4.2.3.7.6.1	— Single dose oral toxicity study in the rat.
63-53-D6144 eCTD 4.2.3.7.1.8	— Skin sensitisation study in the guinea pig
88-6185 eCTD 4.2.3.7.6.2	— Acute oral toxicity study in rats.
936002 eCTD 4.2.3.7.6.7	— Salmonella and escherichia/livermicrosome test.
93-6004 eCTD 4.2.3.7.6.4	— ilot 14-day oral toxicity study in rats.
63/40-1052 eCTD 4.2.3.7.6.8	— Reverse mutation in five histidine-requiring strains of Salmonella typhimurium.
63/39-1052 eCTD 4.2.3.7.6.9	— Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the — technique.
063/037 eCTD 4.2.3.7.6.3	— Single dose oral toxicity study in the mouse (approximation of the minimum lethal dose level.)
063/038-D6144 eCTD 4.2.3.7.6.10	— Skin sensitization study in the guinea pig.

Studies not reviewed within this submission:

Most of the following studies were submitted to previous NDAs and were reviewed at those times.

Pharmacology	
Primary Pharmacodynamics	
34540 eCTD 4.2.1.1.1	November 20th 1972 – GP 45840: Pharmacological Investigations
[redacted] eCTD 4.2.1.1.2	Section III: Pharmacology – 12/4/70
Secondary Pharmacodynamics	
34540 eCTD 4.2.1.2.1	November 20th 1972 – GP 45840: Pharmacological Investigations
Safety Pharmacology	
Pharmacodynamic Drug Interactions	
Pharmacokinetics	
Analytical Methods and Validation Reports	
Absorption	
5-1972 eCTD 4.2.2.2.4	5/1972-GP 45840 – Pharmacokinetics and metabolism in animals (mouse, rat, dog, monkey)
Distribution	
B33-1975 eCTD 4.2.2.3.2	GP 45840: Comparison of organ and tissue concentrations in albino and pigmented rats with particular reference to the eye
B6-1979 eCTD 4.2.2.3.3	GP 45840: Binding to proteins in human serum and in serum of the rat, dog and monkey. Displacement interactions with salicylic acid, acetylsalicylic acid, phenylbutazone, prednisolone, tolbutamide, acenocoumarol and warfarin. Dialysability and reversibility of binding.
B86-1980 eCTD 4.2.2.3.4	GP 45 840: Placenta passage in pregnant mice and rats.
Metabolism	
Excretion	
B81-1979 eCTD 4.2.2.5.1	GP 45840: Passage of unchanged diclofenac into mother's milk of breast-feeding healthy women during treatment with 100 mg VOLTAREN per day for one week after delivery
Pharmacokinetic Drug Interaction	
Other Pharmacokinetic Studies	
Toxicology	
Single-Dose Toxicity	
22-sept-1977 eCTD 4.2.3.1.1	GP 45840 (Voltaren Na Salt) – acute toxicity studies (single administration).
0289-70L eCTD 4.2.3.1.2	Oral LD50 of GP 45840 in rhesus monkeys
Repeat-Dose Toxicity	
840321 eCTD 4.2.3.2.1	Final Report GP 45840 28 days range finding toxicity study in mice.
Rat	
FR-2020-0006 eCTD 4.2.3.2.2	Subacute and chronic toxicological studies of GP 45840 in rats 1-and 6-month oral administration.
6804080 eCTD 4.2.3.2.3	Preparation of GP 45840: Report on the 90 day toxicity study oral administration – Rat.
A-70-423, 774, 775, 776,	GP 45840: Subchronic toxicity – rat, oral (4 weeks).

A-70-415, A-70-423 eCTD 4.2.3.2.4	
428978 eCTD 4.2.3.2.5	GP 45840 (Voltaren): Palatability study with repetitive administration on adult rats.
444878 eCTD 4.2.3.2.6	GP 45840 (Voltaren): Palatability study with repetitive administration on juvenile rats.
4R03, 133-74-SL eCTD 4.2.3.2.7	28-day subcutaneous toxicity test in rats with compound GP 45840.
709178, 78R14, 29/79/SL eCTD 4.2.3.2.8	Voltaren (GP 45840): One-month daily subcutaneous injection study in rats.
798, A-70-425, 797 eCTD 4.2.3.2.9	GP 45840: Subchronic toxicity studies, rat, oral (15 weeks).
6907140, A70-427 eCTD 4.2.3.2.10	Subchronic Toxicity
Dog	
A-70-428-133 eCTD 4.2.3.2.11	A-70-428 133 – GP 45840: Subchronic toxicity – dog, oral (16 days).
A-70-429-135 eCTD 4.2.3.2.12	A-70-429, 135 – GP 45840: Subchronic toxicity – dog, oral (30 days).
A-70-430-136 eCTD 4.2.3.2.13	A-70-430, 136 – GP 45840: Subchronic toxicity – dog, oral (3 months).
6804161-A70-431 eCTD 4.2.3.2.14	6804161, A-70-431 – Preparation GP 45840: Report on the 90-day toxicity study, oral administration, beagle dog.
Monkey	
0121-68-L, A-70-386f eCTD 4.2.3.2.15	GP 45840: Dose-rangefinding study in rhesus monkeys.
151-72-SL eCTD 4.2.3.2.16	52-week oral toxicity study in baboons with compound GP 45840
Genetic Toxicology	
In vitro	
Diclofenac	
21 Jul 1977 eCTD 4.2.3.3.1.1	Salmonella/Mammalian-microsome mutagenicity test with GP 45840.
2 Mar 1978 eCTD 4.2.3.3.1.2	Salmonella/Mammalian-microsome mutagenicity test with GP 45840.
6 Jun 1978a eCTD 4.2.3.3.1.7	Mutagenicity test on Saccharomyces cerevisiae MP-1 in vitro with GP 45840.
6 Jun 1978b eCTD 4.2.3.3.1.9	Salmonella/Mammalian-microsome mutagenicity test with urine and bile concentrates from rats treated with GP 45840.
6 Jun 1978c eCTD 4.2.3.3.1.10	Salmonella/Mammalian-microsome mutagenicity test with urine and bile concentrates from baboons treated with GP 45840.
8 Jun 1978 eCTD 4.2.3.3.1.11	Salmonella/Mammalian-microsome mutagenicity test with urine and bile concentrates from human being treated with GP 45840.
31872077 eCTD 4.2.3.3.1.12	Point mutation assay with mouse lymphoma cells with GP 45840 (in vitro test for mutagenic properties in mammalian cells)
CGP 13294 (3'-hydroxydiclofenac, metabolite)	
1 Dec 1977a eCTD 4.2.3.3.1.3	Salmonella/Mammalian-microsome mutagenicity test with CGP 13294.
78-2307 eCTD 4.2.3.3.1.13	Point mutation assay with mouse lymphoma cells with CGP 13294.
CGP 14217 (4'-5-dihydroxydiclofenac, metabolite)	
1 Dec 1977b eCTD 4.2.3.3.1.4	Salmonella/Mammalian-microsome mutagenicity test with CGP 14217.
78-2308	Point mutation assay with mouse lymphoma cells with CGP 14217.

eCTD 4.2.3.3.1.14	
GP 47766 (4'-hydroxydiclofenac, metabolite)	
14 Dec 1977a eCTD 4.2.3.3.1.5	Salmonella/Mammalian-microsome mutagenicity test with GP 47766.
78-2309 eCTD 4.2.3.3.1.16	Point mutation assay with mouse lymphoma cells with GP 47766.
GP 47852 (5'-hydroxydiclofenac, metabolite)	
14 Dec 1977b eCTD 4.2.3.3.1.6	Salmonella/Mammalian-microsome mutagenicity test with GP 47852.
78-2310 eCTD 4.2.3.3.1.15	Point mutation assay with mouse lymphoma cells with GP 47852 (in vitro test for mutagenic properties in mammalian cells).
***In vivo* (including supportive toxicokinetics evalutations)**	
Diclofenac	
20 Mar 1973 eCTD 4.2.3.3.2.1	Chromosome studies on somatic cells – GP 45840, Chinese hamster (test for mutagenic effects on bone marrow cells).
31 May 1974 eCTD 4.2.3.3.2.2	Nucleus anomaly test on somatic interphase nuclei – GP 45840 (Voltaren®) – Chinese hamster (test for mutagenic effects on bone marrow cells).
40700677 eCTD 4.2.3.3.2.3	Nucleus anomaly test in somatic interphase nuclei, long-term study with GP 45840 (active substance of Voltaren®) – Chinese hamster – (test for mutagenic effects on bone marrow cells).
40690677 eCTD 4.2.3.3.2.4	Chromosome studies in somatic cells, long-term study with GP 45840 (active substance of Voltaren®) – Chinese hamster (test for mutagenic effects on bone marrow cells).
30170476 eCTD 4.2.3.3.2.5	Chromosome studies in male germinal epithelium - GP 45840 (active substance of Voltaren®) – mouse – (test for mutagenic effects on spermatogonia).
30180476 eCTD 4.2.3.3.2.6	Chromosome studies in male germinal epithelium - GP 45840 (active substance of Voltaren®) – mouse – (test for mutagenic effects on spermatocytes).
32710600 eCTD 4.2.3.3.2.7	Dominant lethal study – GP 45840 mouse (NMRI) (test for cytotoxic or mutagenic effects on male germinal cells).
2 Jun 1978 eCTD 4.2.3.2.2.9	Intrasanguine host-mediated assay with S. *typhimurium* with GP 45840
Carcinogenicity	
Oral Dosing	
Mouse	
GU 841110 Ciba-Geigy, Sept 1988 eCTD 4.2.3.4.1.1	24 months carcinogenicity study in mice.
Rat	
8-76 Ciba-Geigy, Sept 1976 (Pre-GLP) eCTD 4.2.3.4.1.3	GP 45840: 98 week oral administration to rats, Vol I and II
GU 785271 Ciba-Geigy, April, 1982 eCTD 4.2.3.4.1.2	GP 45840: active ingredient of Voltaren™, 24month carcinogenicity and chronic toxicity study in rats.
505(b)(2) Studies-- Solaraze NDA 21-005 **Dermal Dosing Carcinogenicity Study and** **Dermal Dosing Photococarcinogenicity Study**	

NDA 21-005 Solaraze (this was also submitted in Jan 1985 in support of NDA 19-201 for Voltaren Tablets; Ciba Geigy) Includes: **Study 5.3 (87000)** **Study 5.4 (808-002)**	Section III Single and Repeat Oral Toxicology Studies of the Pharmacology/Toxicology review for NDA 21-005 Solaraze Includes: 2-year Dermal Carcingenicity Study of Diclofenac Gel in the Albino Mouse A 12-Month Study to Determine the Influence of Diclofenac Topical Gel on Photocarcinogenesis in Hairless Mice
Reproductive and Developmental Toxicity	
Mice	
M-22 eCTD 4.2.3.5.2.1	Segment II reproductive study in mice.
70-3-4 eCTD 4.2.3.5.2.2	Mouse Segment II (test for teratogenic or embryotic effects).
18-Jul-1974 eCTD 4.2.3.5.2.3	Expertise on teratology of GP 45840
Rat	
1-Oct-1972a eCTD 4.2.3.5.1.1	1 Oct 1972a – Segment I reproductive study in rats.
30-Aug-1971-23-Sep-1971 eCTD 4.2.3.5.2.4	Segment II reproductive study in rats.
12-Sep-1972-6-Oct-1972 eCTD 4.2.3.5.2.5	Reproductive study in rats.
70-2-21 eCTD 4.2.3.5.2.6	Rat Segment II (test for teratogenic or embryotoxic effects).
28-apr-1977 eCTD 4.2.3.5.2.7	The effect of voltaren-ampoule solution (called "Voltaren" for short) on the pregnant rat and foetus after intramuscular administration.
791989 eCTD 4.2.3.5.2.8	Teratology study (segment II) in rats (subcutaneous administration).
Rabbit	
6-68-47-68 eCTD 4.2.3.5.2.9	Rabbit segment II (test for teratogenic or embryotoxic effects)
25-may-1976 eCTD 4.2.3.5.2.10	The effect of voltaren-ampoule solution Batch No. B011761 T (called "Voltaren" for short) on the pregnant rabbit and foetus after intramuscular administration
Postnatal development	
Rat	
1-Oct-1972b eCTD 4.2.3.5.3.1	Segment III reproductive study in rats

Literature References

These studies provided by the Sponsor were not formally reviewed, but some the information was incorporated into the review.

botta-1985.pdf Ciba-Geigy Ltd(Basle), Switzerland, report Nr. B91/1984, 31 January 1985	Botta L, (1985) GP 45840 G: Absorption, distribution and excretion after oral and topical application in guinea pigs. Percutaneous absorption in the rabbit.
chan-2001.pdf Hum Reprod16(11):2390-2393.	Chan LY, Chiu PY, Siu SS, Lau TK (2001) A study of diclofenac-induced teratogenicity during organogenesis using a whole rat embryo culture model.
cryer-1998.pdf Am J Med; 104:413-421.	Cryer B and Feldman M (1998) Cyclooxygenase-1 and cyclooxyenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs.
degen-1988.pdf Xenobiotica; 18(12):1449-1455.	Degen PH, Dieterle W, Schneider W, et al (1988) Pharmacokinetics of diclofenac and five metabolites after single doses in healthy volunteers and after repeated doses in patients.
faigle-1988.pdf Xenobiotica; 18(10):1191-1197.	Faigle JW, Böttcher I, Godbillon J, et al (1988) A newmetabolite of diclofenac sodium in human plasma.
hiramatsu-1990.pdf Arzneimittelforsching 40(10):1117-1124	Hiramatsu T, Akita S, Salamin PA and Maier R (1990) Assessment of Topical non-steroidal anti-inflammatory drugs in animal models.
krupp-1975.pdf Schweiz med Wschr; 105:646-652.	Krupp P, Exer B, Menassé R, et al (1975) Neue aspekte der entzündungshemmung durch nicht-steroide antiphlogistika: wirkung von Voltaren.
ku-1986.pdf Am J Med; 80 Suppl 4B:18-23.	Ku EC, Lee W, Kothari HV, et al (1986) Effect of diclofenac sodium on the arachidonic acid cascade.
kyuki-1983.pdf Japan J Pharmacol; 33:121-132.	Kyuki K, Shibuya T, Tsurumi K, et al (1983) Antiinflammatory effect of diclofenac sodium ointment (cream) in topical application.
leemann-1993.pdf Life Sciences; 52(1):29-34.	Leemann TD, Transon C and Dayer P (1993) Cytochrome P450TB (CYP2C): a major monooxygenase catalyzing diclofenac 4'-hydroxylation in human liver.
masubuchi-2001.pdf Drug Metab Dispos. 29(9):1190-1195	Masubuchi Y, Ose A, Horie T (2001) Mechanism based inactivation of CYP2C11 by diclofenac.
masubuchi-2002.pdf Drug Metab Dispos. 30(10):1143-8.	Masubuchi Y, Ose A, Horie T (2002) Diclofenac induced inactivation of CYP3A4 and its stimulation by quinidine.
menasse-1978.pdf Scand J Rheumatol; Suppl 22:5-16.	Menassé R, Hedwall PR, Kraetz J, et al (1978) Pharmacological properties of diclofenac sodium and its metabolites.
menassee-1974.pdf Toxicol Appl Pharmacol; 29:389-396	Menassé-Gdynia R and Krupp P (1974) Quantitative measurement of gastrointestinal bleeding in rats: the effect of nonsteroidal anti-inflammatory drugs.
oh-han-2006.pdf Pharmacol Res.53:75-79.	Oh YH, Han HK (2006) Pharmacokinetic interaction of tetracycline with non-steroidal anti-inflammatory drugs via organic anion transporters in rats.
riess-stierlin-1978.pdf Scand J Rheumatol; suppl 22:17-29.	Riess W and Stierlin H (1978) Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren.
scholer-1986.pdf Am J Med; 80 Suppl 4B:34-38.	Scholer DW, Ku EC, Boettcher I, et al (1986) Pharmacology of diclofenac sodium.

sioufi-1981.pdf In: Kåss E (ed) Voltaren®– new findings. Proceedings of an international symposium on Voltaren during the 15th international congress of rheumatology, June 22 1981, Paris. Hans Huber, Berne, 1982:19-30.	Sioufi A, Stierlin H, Schweizer A et al (1981) Recent findings concerning clinically relevant pharmacokinetics of diclofenac sodium.
stierlin-1979.pdf Xenobiotica; 9(10):611-621.	Stierlin H and Faigle JW (1979) Biotransformation of diclofenac sodium (Voltaren®) in animals and man. II. Quantitative determination of the unchanged drug and principal phenolic metabolites, in urine and bile.
tang-1999.pdf Drug Metab Dispos. 27(3):365-72.	Tang W, Stearns RA, Bandiera SM, Zhang Y, Raab-C, Braun MP, Dean DC, Pang J, Leung KH, Doss GA, Strauss JR, Kwei GY, Rushmore TH, Chiu SH, Baillie TA. (1999) Studies on cytochrome P-450-mediated bioactivation of diclofenac in rats and in human hepatocytes: identification of glutathione conjugated metabolites.
tang-2003.pdf Curr Drug Metab. 4(4):319-29.	Tang W (2003) The metabolism of diclofenac-- enzymology and toxicology perspectives.
todd-1988.pdf Drugs; 35:244-285.	Todd PA and Sorkin EM (1988) Diclofenac sodium: a reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. \
yan-2005.pdf Drug Metab Dispos. 33(6):706-13. \	Yan Z, Li J, Huebert N, Caldwell GW, Du Y, Zhong H (2005) Detection of a novel reactive metabolite of diclofenac: evidence for CYP2C9-mediated bioactivation via arene oxides.
yu-2005.pdf Drug Metab Dispos. 33(4):484-8.	Yu LJ, Chen Y, Deninno MP, O'Connell TN, Hop CE (2005) Identification of a novel glutathione adduct of diclofenac, 4'-hydroxy-2'-glutathion-deschlorodiclofenac, upon incubation with human liver microsomes.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Voltaren Gel 1% is a gel formulation that contains diclofenac sodium as its active ingredient. Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that has been in widespread therapeutic use for approximately 20 years. Diclofenac sodium inhibits the enzyme, cyclooxygenase (COX), a early component in the arachidonic acid cascade. By inhibiting COX, diclofenac prevents the formation of thromboxanes, prostaglandins, and prostacyclin. Diclofenac also inhibits the production of leukotrienes by decreasing arachidonic acid release and increasing its uptake. It is hypothesized this uptake is into triglycerides, thus limiting the availability of arachidonic acid entering the COX and lipoxygenase pathways. In human blood, diclofenac is approximately 20-fold more potent as an inhibitor of COX-2 compared to COX-1 isozymes, although this value varies substantially among published studies. Since clinical studies find a substantial number of gastrointestinal adverse effects with diclofenac, it is not considered a very specific COX-2 isozyme inhibitor, in disagreement with some statements by the Sponsor.

Diclofenac has potent anti-inflammatory, antinociceptive, and antipyretic properties demonstrated in numerous animal models administered orally, intravenously or intraperitoneally. Anti-inflammatory and antinociceptive effects were also demonstrated with topical application. Topical application of diclofenac sodium suppressed the inflammatory response in the adjuvant arthritis model and edema in the paw, skin and ear induced by different chemicals. Antipyretic activity was demonstrated in response to oral treatment using the rat yeast-induced fever model.

The anti-inflammatory, anti-nociceptive, and antipyretic actions of diclofenac are all dependent on the inhibition of COX. Diclofenac inhibition of 5-hydroxyeicosatetraenoic acid and leukotriene formation has been demonstrated with rat and human leukocytes. Macrophages and monocytes are about five time more susceptible than polymorphonuclear leukocytes to this inhibitory effect. It is hypothesized this uptake is into triglycerides, thus limiting the availability of arachidonic acid entering the COX and lipoxygenase pathways. The role of thromboxane, prostaglandin, prostacyclin, and leukotriene inhibition in the therapeutic efficacy of diclofenac is not completely understood.

Investigation of the hydroxylated metabolites demonstrated some activity in at least two of the metabolites but the potency was significantly less than that of the parent molecule and they probably do not contribute significantly to the therapeutic activity. Clinical pharmacokinetic trials showed that with this formulation and dosing schedule, the systemic exposure to the active drug remains considerably lower than the levels routinely achieved with oral therapy.

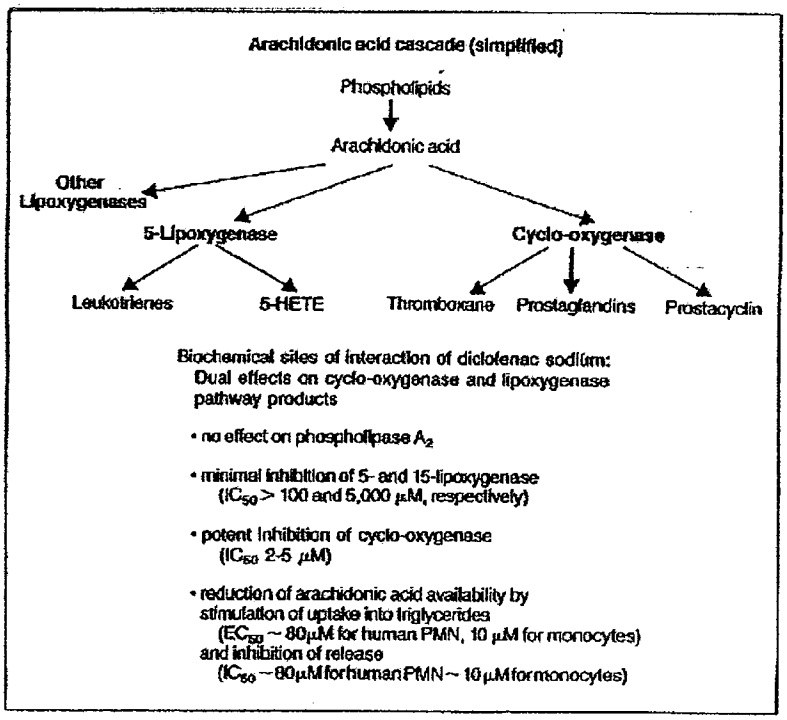


Figure 2-3: Biochemical sites of diclofenac sodium interaction

2.6.2.2 Primary pharmacodynamics

These studies were reviewed for NDA 19-201.
See Section 2.6.3 Pharmacology Tabulated Summary

Anti-inflammatory activity: Topical application

The anti-inflammatory activity of diclofenac was demonstrated following topical application. Kyuki et al (1983) formulated 1% diclofenac sodium in an ointment, cream gel, and in a series of creams containing 0.5-1.5% diclofenac sodium and applied them topically several different rat models of inflammation. The inhibition of edema was studied in carrageenan-induced skin edema, carrageenan-induced paw edema, croton oil induced edema in the ear, ultraviolet erythema, proliferation of the granulation tissue, adjuvant arthritis and pain to pressure stimulation. To determine the anti-inflammatory activity of diclofenac sodium in the adjuvant arthritis model in rats, inflammation was induced by injection of mycobacterium butyricum into the hind paws of 5 animals. The various formulations were next applied topically to the paws and the presence of edema was assessed. The diclofenac sodium cream was found to reduce the swelling (Table 5) and the effect was comparable to an indomethacin containing gel.

Table 5 Effects of cream containing diclofenac sodium (1%) on paw swelling in adjuvant arthritis model in rats (Kyuki et al, 1983)

Days	0	15	19	22
Primary inflammation				
% swelling of inoculated right paw (with diclofenac cream)*/ % swelling of right paw in animals in adjuvant control**	1.0	1.0	0.5	0.4
Secondary inflammation				
% swelling of uninoculated left paw (with diclofenac cream)*/ % swelling of left paw in animals in adjuvant control	1.0	1.0	0.8	0.67

Diclofenac sodium cream* The right hind paws of rats were inoculated with an emulsion of 0.6 mg mycobacterium butyricum. 100 mg gel was either applied to the inoculated paw or uninoculated paw daily for 7 days (from day 15 to day 22).

Adjuvant (ADA) control** The right hind paws of rats were inoculated with an emulsion of 0.6 mg mycobacterium butyricum.

A topical formulation very similar to the present, Voltaren® Emulgel™ containing 1.18% diclofenac diethylamine salt, is in use in many countries world-wide for the topical treatment of minor pains of muscles and joints. The present diclofenac sodium gel 1% differs very slightly from Voltaren® Emulgel™: its active ingredient is not diclofenac diethylamine salt, but the sodium salt. Similar absorption of diclofenac was observed in *in vitro* studies and in the clinical pharmacokinetic studies comparing DSG 1% with Voltaren® Emulgel™. Studies to determine the anti-inflammatory activity of topically applied gel containing diclofenac have been performed using the Voltaren® Emulgel™ in several animal models and reviewed in Hiramatsu et. al., 1990. Using the adjuvant arthritis test in rats, significant inhibition of swelling was observed upon topical application of 50 mg Voltaren® Emulgel™ (0.58 mgEq diclofenac-diethylamine) daily for 21 days from day 1 to day 21 following injection of adjuvant (Table 6).

Table 6 Adjuvant arthritis test in rats with Voltaren® Emulgel™

	Days	0	15	18	21	24	27	30	33	36
Size of uninoculated left paw of adjuvant treated animals/ Size of left paw of animals not treated with adjuvant	ADA control*	1.0	1.9	2.1	2.1	2.1	2.0	1.9	1.9	1.9
	Voltaren® Emulgel™ **	1.0	1.9	1.7	1.5	1.4	1.3	1.4	1.3	1.3
Paw size of Emulgel™ treated animals/Paw size of ADA control (%)		100	100	78	71	70	66	70	67	68

ADA control* The right hind paws of rats were inoculated with an emulsion of 0.6 mg mycobacterium butyricum.

Voltaren® Emulgel™** The right hind paws of rats were inoculated with an emulsion of 0.6 mg mycobacterium butyricum. 50 mg gel (0.5 mg eq diclofenac sodium) was applied to the inoculated paw daily for 21 days.

Activity of Diclofenac Metabolites

Menassé et al (1978) also reported on the pharmacological activity of four hydroxylated metabolites of diclofenac. The 4'-hydroxy derivative is the main product of biotransformation in humans and has a clear, dose-dependent, anti-edematous action in the kaolin rat paw test. It was six times more effective than aspirin in this respect but 30 times less active than diclofenac

sodium. The 3'-hydroxy derivative also has a clear inhibitory effect in this test but the 5-hydroxy metabolite and the 4',5-dihydroxy metabolite were ineffective. As with other NSAIDs this activity runs parallel with inhibition of prostaglandin synthesis *in vitro*.

The antinociceptive effects of the various metabolites were relatively weak, all four showing activity comparable with that of phenylbutazone in a rat acetic acid writhing test but only marginal effects in a mouse phenyl-benzoquinone writhing test. Only the 4'-hydroxy metabolite showed any significant antipyretic activity, again similar to that of phenylbutazone but much less effective than the parent molecule. The 3'-hydroxy 4'-methoxy indicated essentially no activity (Faigle et al, 1988).

2.6.2.3 Secondary pharmacodynamics

These studies were reviewed in previous NDAs.
See Section 2.6.3 Pharmacology Tabulated Summary

2.6.2.4 Safety pharmacology

These studies were reviewed for approval of NDA 19-201.
See Section 2.6.3 Pharmacology Tabulated Summary

2.6.2.5 Pharmacodynamic drug interactions

There were no pharmacodynamic drug interaction studies.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

PHARMACOLOGY SUMMARY

Report number/Title/Date	Type of Study Test system or protocol	Dose/ Route of administration	Findings
Primary Pharmacodynamics			
In vitro pharmacology			
Ku et al 1986 eCTD 4.3	Cell-free enzyme preparation	In vitro	Inhibition of cyclooxygenase
34540 11/20/1972 eCDTD 4.2..1.1.1	Antagonistic activity Isolated guinea pig ileum, jejunum, rat uterus	In vitro	Inhibition of contractions Diclofenac had no effect on contractions caused by acetylcholine or histamine in this system or those caused by bradykinin on a rat uterus preparation.
In vivo pharmacology, oral			
34540 11/20/72 eCDTD 4.2..1.1.1	Rat, carrageenan paw edema	1, 3 mg/kg Oral gavage	Anti-inflammatory activity
	Rat, anti cotton pellet granuloma	Oral gavage 0.3, 1, 2.5, 3.5	Anti-inflammatory activity
4/12/1970 eCDTD 4.2..1.1.2	Rat, aluminum silicate paw edema (normal and adrenalectomized male rats)	Oral gavage 1, 2.5, 5, 10, 10.5, 25, 50, 100, 200, 400	Anti-inflammatory activity
	Rat, albumin induced paw edema	Oral gavage 200	Anti-inflammatory activity
	Rat, albumin induced paw edema	Subcutaneous 100	Anti-inflammatory activity
	Rat, formalin inflammation	Oral gavage 200	Anti-inflammatory activity
	Rat, serotonin inflammation	Oral gavage 50, 200	Anti-inflammatory activity
	Rat, bradykinin inflammation	Oral gavage 50, 200	Anti-inflammatory activity
	Rat, 6-sulfanilamidoindazole (6SI) induced inflammation	Oral gavage 0.023, 0.045, 0.09, 0.18,	Anti-inflammatory activity

		0.375, 0.75, 1.5, 3.0	
	Rat, adjuvant arthritis	Oral gavage 0.25, 0.5, 1.3 daily for 14 days	Anti-inflammatory activity
In vivo pharmacology, topical			
Kyuki et al, 1983 eCDT 4.3	Rat, carrageenan edema, paw, skin	Topical 50 mg	Acute inflammation model: has anti-inflammatory activity
	Rat, croton oil ear edema	Topical 50 mg	Acute inflammation model: has anti-inflammatory activity
	Rat, paper disc granulation tissue	Topical 50 mg	Chronic inflammation model has anti-inflammatory activity
	Rat, adjuvant arthritis	Topical 100 mg for 7 days (15th day after adjuvant treatment)	Sub-acute inflammation model has anti-inflammatory activity

SECONDARY PHARMACODYNAMICS

Report number	Test system or protocol	Dose /Method of administration	Findings
Platelet aggregation inhibition			
34540 11/20/1972 eCTD 4.2..1.1.1	Rabbit and human plasma	In vitro	Platelet aggregation inhibition diclofenac was found to be a potent inhibitor of the secondary phase of platelet aggregation
Steroidal action			
Krupp et al 1975 eCTD 4.3	Rat, Injected with intraperitoneally with Na_2-$^{35}SO_4$	oral	uptake of ^{35}S into the skin and into sulfonated polysaccharides assessed for sulfonated glyco protein synthesis and metabolism No changes associated with diclofenac treatment
34540 11/20/1972 eCTD 4.2..1.1.1	Rat, kaolin-induced paw edema ± adrenalectomy	oral	Adrenalectomized rat did not alter diclofenac anti-inflammatory activity, Thus anti-inflammatory activity was not mediated by pituitary-adrenal axis activation

SAFETY STUDIES

Report number/ Location	Species/ strain Gender	Doses / Route	Findings
CNS			
34540 11/20/72 eCTD 4.2..1.1.1	Mouse/ NMRI Male, N= 4/dose	25, 50, 100 mg/kg oral	No distinct behavioral, neurological or autonomic signs.
Cardiovascular			
34540 11/20/72 eCTD 4.2..1.1.1	Guinea pig heart N= 4 preparations/dose	1, 10, 100 µg/mL in vitro	1 µg/mL: no effect 10 µg/mL: small increase in coronary blood flow and slightly reduced heart rate with a variable effect on myocardial contraction 100 µg/mL: cardiac arrest
	Dog/mixed breed (conscious) N= 2/dose (4 controls)	1, 3, 10 mg/kg Intravenous	Slight decrease in heart rate at 10 mg/kg. No effect on ECG, blood pressure.
	Cat, domestic (anaesthetized) N= 4 cats/dose	0.1 to 60 mg/kg Intravenous	0.3-10 mg/kg: slight transient increases in blood pressure 30 mg/kg: biphasic effects and bradycardia were seen in two cats 60 mg/kg: lethal to all four animals 0.3-1 mg/kg: increase in the pressure effects of adrenaline, the effects of noradrenaline and acetylcholine were not affected

<table>
<tr><td colspan="4">Respiratory</td></tr>
<tr><td>34540
11/20/72
eCTD 4.2..1.1.1</td><td>Cat, domestic
(anaesthetized)
N= 4 cats/dose</td><td>0.1 to 60 mg/kg
Intravenous</td><td>up to 10 mg/kg:
No effect on respiratory volume</td></tr>
<tr><td colspan="4">Gastrointestinal</td></tr>
<tr><td>Menassé-Gdynia and Krupp 1975
eCTD 4.3</td><td>Rat/Fischer
Male,
N= 6-12/dose</td><td>3, 10, 30 mg/kg
oral gavage</td><td>monitor ^{51}Cr labeled RBC
10 mg/kg: small increase in intestinal blood loss
30 mg/kg: significant blood loss</td></tr>
<tr><td>Menassé et al, 1978
eCTD 4.3</td><td colspan="3">the dose that would produce a blood loss of 150µL in a 72 hour period (gastrointestinal bleeding, GIB) for a range of compounds compared with the ED_{50} in the rat carrageenan paw edema test
Table 10 Anti-inflammatory effect, gastrointestinal bleeding (GIB) and tolerability ratios for various NSAIDs in rats
<table>
<tr><th>Compound</th><th>Carrageen paw edema, ED_{50}, mg/kg</th><th>Blood loss 150µL/72h, GIB, mg/kg</th><th>Ratio ED_{50}:GIB</th></tr>
<tr><td>Diclofenac sodium</td><td>2.1</td><td>17</td><td>8.1</td></tr>
<tr><td>Acetylsalicylic acid</td><td>900</td><td>240</td><td>0.3</td></tr>
<tr><td>Flufenamic acid</td><td>37</td><td>110</td><td>3.0</td></tr>
<tr><td>Ibuprofen</td><td>170</td><td>180</td><td>1.1</td></tr>
<tr><td>Indomethacin</td><td>5.2</td><td>5</td><td>1.0</td></tr>
<tr><td>Naproxen</td><td>20</td><td>48</td><td>1.0</td></tr>
<tr><td>Oxyphenbutazone</td><td>230</td><td>>300</td><td>-</td></tr>
<tr><td>Phenylbutazone</td><td>50</td><td>113</td><td>2.3</td></tr>
<tr><td>Sudoxicam</td><td>30</td><td>15</td><td>0.5</td></tr>
</table></td></tr>
<tr><td colspan="4">Renal</td></tr>
<tr><td>34540
11/20/72
eCTD 4.2..1.1.1</td><td>Rat/ SIV 50
Male,
N=5/dose</td><td>0.3, 1, 3, 10, 30 mg/kg
oral gavage

diclofenac compared with the known diruretic action of chlorthalidone (increases excretion of Na, K, Cl) in water loaded rats</td><td>0.3-1 mg/kg: reduced the excretion of electrolytes caused by chlorthalidone (5 mg/kg) with little effect on volume.
10, 30 mg/kg: diuretic effect of chlorthalidone abolished</td></tr>
<tr><td>Menassé et al, 1978
eCTD 4.3.13</td><td>Rat</td><td>Compared diclofenac with ibuprofen, indomethacin and phenylbutazone</td><td>All of these agents had qualitatively similar effects on sodium and chloride, partially antagonizing the effect of chlorthalidone.
None of the agents had a significant effect on potassium output
Effects on urine volume were seen with diclofenac, ibuprofen and phenylbutazone.
The doses required to produce these effects were generally in the upper range of the doses producing anti-inflammatory responses</td></tr>
</table>

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The systemic absorption, distribution, metabolism and excretion of diclofenac sodium were studied in different animal species submitted in NDA 19-201, and previously reviewed. They are summarized in the Tables of section 2.6.5 at the end of Pharmacokinetic section. Studies relevant to the topical application of diclofenac are summarized below.

ABSORPTION

Results from in vitro studies using hairless guinea pig skin also showed that skin penetration of diclofenac was similar for diclofenac sodium gel and Voltaren® Emulgel™. Similar absorption rates were obtained from diclofenac sodium gel formulations with pH ranging from [redacted]. The viscosity of the diclofenac sodium gel formulation [redacted] did not affect the penetration efficiency of diclofenac. These results indicate that, within this range of the product specifications, no significant influence on the absorption of diclofenac is to be expected.

There was one in vivo study in which plasma concentrations of diclofenac were determined in hairless rats after topical application of diclofenac diethylamine (Voltaren® Emulgel™) to skin sites of induced sunburn. Unfortunately this GLP study lacked descriptive clarity, had inconsistencies in data presentation, and most animals lost weight over the study duration. This made the determination of absorption and interpretation of the effect of sunburn problematic. It should also be noted that the 12-week repeated topical dose rabbit toxicology study performed with Voltaren Emulgel and requested to be submitted to this NDA lacked toxicokinetic data to enable a determination of absorption.

There was an unpublished study in the literature references section Botta (1985; Report B91/1984 from Ciba Geigy) in which the absorption of ^{14}C-diclofenac (GP 45840) in the Emugel™ formulation was studied after application to guinea pig and rabbit skin. For guinea pigs, 8% of the dose applied was absorbed when an occlusive bandage was also applied, and there was 5% absorption without the occlusive bandage. If the cornified layer of skin was scrapped away, the absorption was 10% of the applied dose. A single dose resulted in maximal blood radioacitivity concentrations at 6-8 hours after application. Steady state blood concentrations in guinea pigs were obtained after 3 days of twice daily applications. In rabbits, a pronounced gender effect was observed. In males, 16% and in females 40% of the applied dose was absorbed.

For comparison, the human clinical studies with topical treatment with Voltaren Gel 1% resulted in low systemic exposures to diclofenac. Typical use (treatment of 1 knee) resulted in only 6% of the AUC_{0-24} and 0.6% of the C_{max} of comparable oral diclofenac treatment (50 mg TID). Maximum use (treatment of 2 knees and 2 hands) resulted in 20% of the AUC_{0-24} and 2% of the C_{max} of the oral treatment.

DISTRIBUTION

To determine if diclofenac concentrations in the tissue compartments proximal to the site of topical application were higher than distal sites, Botta (1985, Report B91/1984 from Ciba Geigy) applied ^{14}C-diclofenac formulated in Emulgel™ to guinea pig doral skin twice daily for 6-days then measured radioactive tracer concentrations in plasma and two muscles, the musculus longissimus lumborum, underlying the site of application and a distant muscle, musculus gastrocnemius. In the three animals studied , the concentrations were about 4-fold higher in the proximal muscle than in the distant muscle, indicating establishment of a concentration gradient in tissues near the application site compared to more distal tissues. In control animals treated with oral diclofenac, there was no difference in the concentration between the muscles. In addition, topical application resulted in a proximal muscle concentration that was 50% of the plasma concentration whereas after oral application, only 10% was reached.

A clinical study by Davies and Anderson (1997) demonstrated that diclofenac penetrates and accumulate in the synovial cavity. Synovial diclofenac concentrations were increased and sustained for periods up to 12 h following multiple doses, with a ratio of synovial fluid to plasma concentration of ~5.

In both rats and mice, the tissue concentrations of ^{14}C-diclofenac remained below those in the blood for all organs investigated except the liver and kidney. Tissue concentrations in rats at 72 hours after intravenous treatment at 5 mg/kg were less than 0.1 µg/g except in the liver and kidney. With oral dosing (5 mg/kg to rats), 0.03-0.08 µg/g were found at 196 hours in these organs and no drug could be detected in any other organ or tissue. In structures of the eye and orbit there were no differences between the time concentration profiles between pigmented and albino rats. More extensive distribution studies after oral administration of diclofenac were reviewed for NDA 19-201

By equilibrium dialysis methodology, diclofenac was 99.2% bound to plasma proteins in rats and 99.6% bound in dogs, rhesus monkeys, baboons and humans.

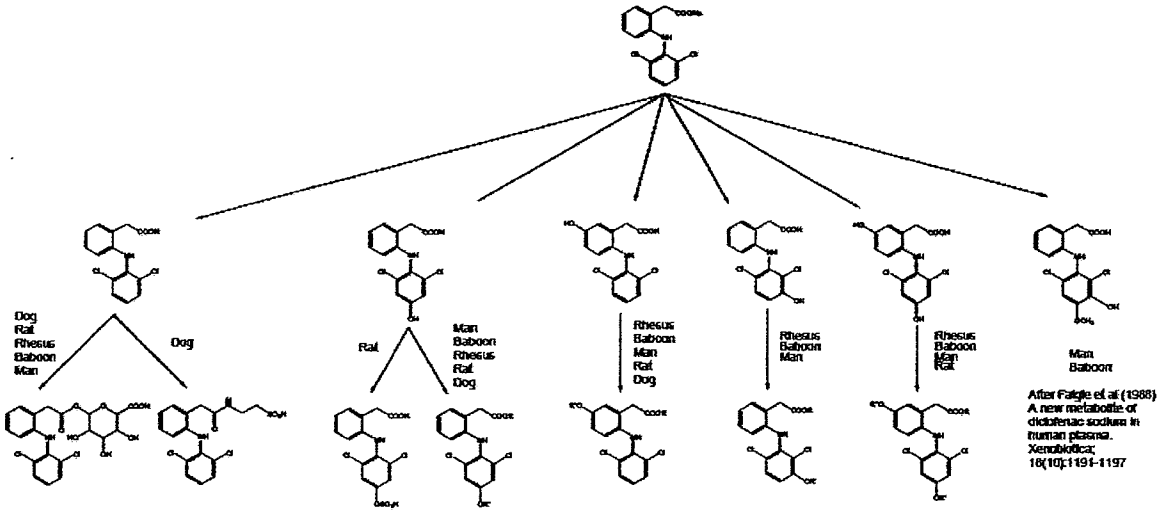
Distribution in Fetus

In pregnant mice, treated orally with 5 mg/kg ^{14}C-diclofenac, the concentration of radioactive substances in the fetus was less than in maternal blood up to 24 hours after treatment. Maximum radioactivity occurred at 3 hours in the fetal and between 3 and 6 hours in the dam. In autoradiograms taken at 12 hours, radioactivity was still apparent in the maternal liver, intestine, kidney and yolk sac epithelium but was only barely detectable in the fetus and amniotic fluid. In pregnant rats, treated orally with 5 mg/kg ^{14}C-diclofenac, maximum radioactivity occurred at 12 hours in the fetus and at 6 hours in the dam. The radioactivity measured at 24 hours in the fetus was similar to that in the dam. After reaching maximum values, the radioactivity was eliminated from the fetus at about the same rate as from the mother.

METABOLISM

Diclofenac is extensively metabolized in all species examined, and its biotransformation appears to be species specific. Other than by conjugation of the carboxyl group on the side chain, metabolism in rats and primates is primarily by hydroxylation of one or both of the two aromatic rings. The hydroxylated compounds formed occur mainly as conjugates which differ between species. Enterohepatic circulation is a significant feature of the pharmacokinetics of rats and dogs but not in primates. A possible metabolic pathway of diclofenac in humans is shown in Figure 5-1. These studies were reviewed previously for NDA 19-201.

Table 2.6.5.11.1. Metabolic scheme



Species are listed to reflect, in decending order, the importance of the pathway. R, R' and R" are not definitely identified ligands.
After Stierlin H, Faigle JW. Biotransformation of diclofenac sodium (Voltaren) in animals and in man. II Quantitative determination of the unchanged drug and principle metabolites, in urine and bile. Xenobiotica 1979; 9(10): 611-621.

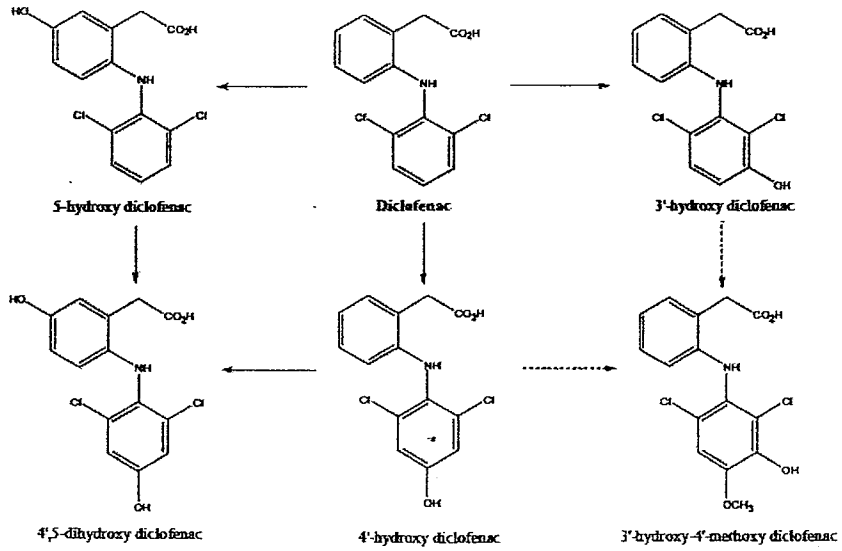


Figure 5-1: Proposed metabolic pathway for diclofenac in humans

The metabolism of diclofenac in the liver is mediated both by glucuronidation and cytochrome P450 (CYP) oxidative biotransformation. UGT2B7 (uridine-5'-diphosphoglucuronysl transferase isozyme2B7) is involved in glucuronidation of the carboxylic group of diclofenac. Diclofenac aromatic hydroxylation via CYP2C9 results in 5-hydroxy diclofenac, a major pathway and by a minor pathway via CYP2C8 producing 4-hydroxy diclofenac. These metabolites form glutathione (GSH) adducts. Three of them, 5-hydroxy-4-glutathione-S-yl diclofenac, 4'-hydroxy-3'-glutathione- S-yl diclofenac, and 5-hydroxy-6-glutathione-S-yl diclofenac were identified in *in vivo* in the bile of rats treated with diclofenac, and in vitro following incubation of rat liver microsomes and human hepatocytes with diclofenac. A fourth diclofenac GSH adduct, 4'hydroxy 2'glutathione diclofenac was recently identified in human liver microsomes. This GSH adduct appeared to be unique to humans and was not detected in monkey and rat liver microsomes. An additional significant metabolite in man and Old World monkeys, 3'-hydroxy-4'-methoxy diclofenac, has a long half-life and was not found in rodents or marmosets.

There are marked inter-species differences in biliary and renal excretion patterns. The metabolites of diclofenac identified in the different animal species and man are shown in the table below.

Table 2.6.5.11.1. Diclofenac conjugation

	Urine, %	Bile, %
Conjugates of diclofenac		
Rat	<5	30-40
Dog	5-10	80-90
Monkey	10-20	
Baboon	10-20	
Man	5-10	<5
Taurine conjugate		
Dog	20-30	
Conjugates of the 4'-hydroxy derivative		
Rat	20-30	10-20
Dog	<5	<5
Monkey	10-20	
Baboon	20-30	
Man	20-30	10-20
Conjugates of the 5-hydroxy derivative		
Rat	5-10	5-10
Dog	<5	<5
Monkey	20-30	
Baboon	10-20	
Man	5-10	5-10
Conjugates of the 3'-hydroxy derivative		
Monkey	5-10	
Baboon	5-10	
Man	<5	<5
Conjugates of the 4',5-dihydroxy derivative		
Rat	<5	<5
Monkey	5-10	
Baboon	5-10	
Man	5-10	<5

Glucuronide conjugates of the otherwise unchanged drug appear in the bile of rats and dogs. These readily revert to diclofenac-Na by alkaline hydrolysis and, in vivo, are subject to enterohepatic circulation. Neither these conjugates nor the unchanged drug are present in human bile. After: Reiss W, Stierlin H. Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren. Scand J Rheumatology 1978; suppl 22: 17-29.

In man, relatively little unchanged drug was detected either in the urine or bile. The principal metabolite is the 4'-hydroxy metabolite, accounting for about 40% of radioactivity in both urine and bile. Another significant human plasma metabolite of diclofenac is the 3'-hydroxy-4'-methoxy derivative, with a half-life of about 80 hours. This metabolite was also detected in baboon plasma but not in plasma from mice, rats or marmosets. The metabolite was found in

urine but only in minute amounts; the cumulative urinary excretion in humans over 96 hours accounted for 1.4% of an oral 100 mg dose.

Table 5-2 Comparison of plasma pharmacokinetics of diclofenac and its major metabolites in baboons and in man

Compound	Species	AUC_{0-96h} nmol/g.h	$AUC_{0-\infty}$ nmol/g.h	C_{max} nmol/g	t_{max} h	$t_{½}$ h
Unchanged diclofenac	Baboon	20.5	20.5	5.41	1	nc
	Man	7.38	7.38	11.03	0.33	1.1
4'-hydroxy metabolite	Baboon	5.14	5.14	0.23	1	nc
	Man	3.77	3.77	1.97	0.33	2.6
5-hydroxy metabolite	Baboon	4.86	4.86	0.31	1	nc
	Man	0.86	0.86	0.53	0.33	1.3
3'-hydroxy metabolite	Baboon	8.24	8.24	0.30	1	nc
	Man	2.33	2.33	0.50	0.33	1.4
4',5-dihydroxy metabolite	Baboon	0.00	0.00	0.00		
	Man	2.11	2.11	0.50	0.67	2.8
3'-hydroxy-4'-methoxy metabolite	Baboon	9.60	13.14	0.15	24	49
	Man	40.84	81.25	0.62	12	81

nc not calculated; these compounds were eliminated rapidly and were not detectable after 48h. The human dose was 100 mg, the baboon dose 5 mg/kg, both given orally.

The long half-life and slow elimination of the 3'-hydroxy-4'-methoxy metabolite results in relatively high exposures. However, it is inactive compared with diclofenac sodium when given orally to rats and mice and does not contribute significantly to the anti-inflammatory actions of diclofenac. It was 90% bioavailable in rats, judged from plasma concentrations following single oral and intravenous 10 mg/kg doses. Metabolite differences between oral and intravenous administration indicative of significant first pass effects ccurred in rats and dogs, but only differences between concentrations following oral and intravenous administration in rhesus monkeys.

The *in vitro* 4'-hydroxylation of diclofenac is catalyzed by the P450TB isozyme CYP2C9. In human liver microsomes. This P450TB isozyme CYP2C9 appears responsible for oxidation of polar acidic substances such as NSAIDs from different chemical classes. Treatment of rats with diclofenac sodium at 1 mg/kg for 4 days caused no significant alteration in the rate of microsomal O-demethylation, N-demethylation or C-hydroxylation or in the concentration of cytochrome P450. At higher doses (3, 6 and 10 mg/kg) there was a reversible dose-related suppression of all three enzymes and cytochrome P450. The suppression was attributed to depression of enzyme synthesis rather than any direct inhibition of enzyme activity.

EXCRETION

In a study of rats, dogs and rhesus monkeys, animals were treated orally or intravenously at 5 mg/kg, with ^{14}C-diclofenac sodium labeled on the α-carbon of the side chain. In rats 70-80% of the dose was recovered from urine and feces within 24 hours and 93-94% by 72 hours. Renal excretion accounted for 28% of the intravenous dose and 37% of the oral dose. In dogs, about 65% of the dose was recovered from urine and feces within 24 hours and 94-99% by 96 hours. Renal excretion accounted for 41.5% of the intravenous dose and 39.5% of the oral dose. In rhesus monkeys, about 80% of the dose was recovered from urine and feces within 24 hours and

92% by 72 hours. Following an oral dose 100% was recovered by 72 hours; 64% was collected within 24 hours from one animal but only 30% from a second monkey. Renal excretion accounted for 79.7% of the intravenous dose and 76.2% of the oral dose. In a similar human study using 50 mg doses, renal excretion exceeded biliary excretion and the total recovered within 96 hours accounted for 90% of the dose administered. There was no radioactivity in expired air collected over 24 hours.

In a study of lactating rats, 5 mg/kg of ^{14}C-diclofenac sodium was given orally. Radioactivity in the milk was always low, not more than 0.3 µg/mL. Unchanged drug accounted for 84% of radioactivity initially but was only 5% after 24 hours. The ratios of $AUC_{0\text{-}24h}$ values for milk to plasma were 0.2 for total radioactivity and 0.14 for unchanged drug.

There was no evidience for the claim by the Sponsor that enteroheptic circulation was involved in maintaining diclofenac in the body. In similarly treated bile duct cannulated rats, 77-91% of the diclofenac dose was recovered from the bile within 24 hours. Five minutes after an intravenous injection, 11% of the dose was recovered from the intestines and which increased to 89% at three hours. Although the Sponsor interpreted this as evidence of enteroheptaic circulation, it only inidcated that bile is an excretory route for diclofenac, whether diclofenac reuptake occurs in the gastrointestinal tract was not determined. Also, the form of labeled diclofenac may have changed during passage through the liver into the bile (conjugation, metabolism) such that it no longer absorbed by the gastrointerinal tract.
This does not preclude tha enterohepatic recycling does not occur, just that the evidence for it is lacking more definitive studies.

2.6.4.2 Methods of Analysis

Methods were reviewed in previous NDAs or within specific studies.

2.6.4.3 Absorption

Some studies were reviewed in previous NDAs.
See Section 2.6.5 Pharmacokinetic Tabulated Summary

Study title: **In vitro skin penetration of diclofenac from Voltaren® Emulgel® 1%, and the US Emulgel with Diclofenac Sodium**

Key study findings: There was no difference in the penetration rate of diclofenac sodium compared to diclofenac diethylamine (Voltaren Emulgel 1%) through guinea pig skin tested *in vitro* using Frantz cells.

Study no.: 12 March 2002, Memo
E-Location: CTD 4.2.2.2.1
Conducting laboratory and location: Preclinical Development, Novartis Consumer Health SA, Nyon, Switzerland
Date of study initiation: unknown, (report dated March 12, 2002)
GLP compliance: no

QA report: no

Drug, lot #, and % purity:

Voltaren Emulgel, Batch Nr WB182, Expiry date June 2004

Voltaren Emulgel USA, Diclofenac Na salt, Batch Nr. DPH-030 contains:

Diclofenac Na-salt instead of Diclofenac diethylamine salt,

Carbomer instead of

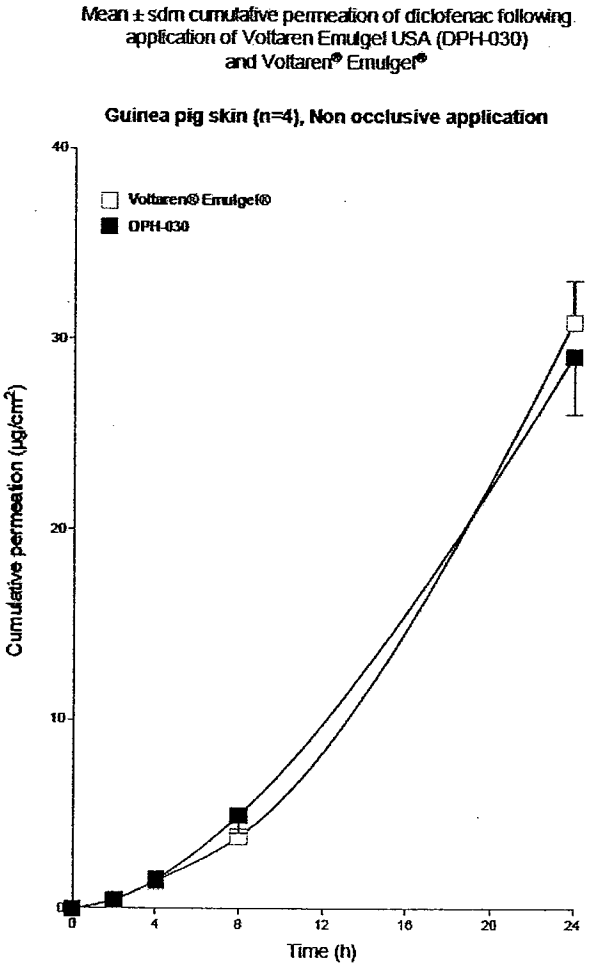
Ammonia

Methods

In vitro skin penetration studies were performed at 35°C in glass static diffusion cells (1.54 cm^2 area) using hairless Guinea pig skin. Skins were obtained from sacrificed animals, frozen on dry ice, and stored at -20°C. After thawing, the skins were mounted horizontally on the Franz cells, dermis side down. Following a pre-equilibration period, gels were applied to the skin surface to yield approximately 40 mg/cm^2, using a piston syringe. Samples of the receptor phase were collected at various time intervals: 0, 2, 4, 8 and 24 hours. The removed receptor volume (1 ml) was replenished with fresh receptor solution after each withdrawal. The quantities of diclofenac (expressed in terms of diclofenac-Na equivalent) permeating the skin were determined by a HPLC analysis of the collected fractions.

Results

At all time points: 2, 4, 8 and 24 hrs, there was no differences in the amounts of diclofenac sodium and diclofenac diethylamine that penetrated the skin (see figure below).



APPEARS THIS WAY
ON ORIGINAL

Study title: **Diclofenac sodium gel (Diclofenac Na 1%) – pH range — Comparison of the *in vitro* skin penetration rate**

Key study findings: The *in vitro* guinea pig skin penetration of diclofenac does not depend on the pH of the formulation in the range of — which are the specification limits for the product during shelf-life.

Study no.: Internal Report 03171
E-Location: CTD 4.2.2.2.2
Conducting laboratory and location: Novartis Consumer Health-OTC Nyon, Switzerland
Date of study initiation: unknown (Report dated Nov 7, 2003
GLP compliance: no
QA report: no
Drug, lot #, and % purity:

Four Diclofenac Sodium Gel with the following pH:

- — batch manufactured on 1 April 2003 in the pharmaceutical laboratory of Novartis Consumer Health-OTC, Nyon, Switzerland (packaged reference Nr. D00012R).
- —.: batch manufactured on 3 April 2003 in the pharmaceutical laboratory of Novartis Consumer Health-OTC, Nyon, Switzerland (packaged reference Nr. D00014R).
- — stability batches "DPH-030" manufactured on 2 March 2003 in the pharmaceutical laboratory of Novartis Consumer Health-OTC, Nyon, Switzerland. Sample stored at 5°C.
- — : clinical batch manufactured in Novartis Pharma, Wehr, Switzerland on 3 Feb 2003 (bulk ref. WD002V)

Method

In vitro skin penetration studies were performed at 35°C in glass static diffusion cells (1.54 cm^2 area) using hairless guinea pig skin. Skins were obtained from sacrificed animals, frozen on dry ice, and stored at -20°C. After thawing, the skins were mounted horizontally on the Franz cells, dermis side down. The receptor phase of phosphate buffered saline — contained within each diffusion cell (approximately 8 mL) was mixed using a magnetic stirring. After a pre-equilibration period, test products were applied to the skin surface to yield approximately 40 mg/cm^2 in the first series of experiments and 5 mg/cm^2 in the second series. Samples of the receptor phase were collected at various time intervals: 0, 2, 4, 8 and 24 hours. The removed receptor volume (1 mL) was replenished with fresh receptor solution after each withdrawal. The quantities of diclofenac (expressed in terms of diclofenac-Na equivalent) permeating the skin were determined by a HPLC analysis of the collected fractions. A total of 6 to 8 different measurements were made per formulation.

Results

When 40 mg/cm^2 skin was applied, an early effect of pH on the diclofenac skin penetration rate occurred. At the extremes of the pH range —, the skin penetration rate differed by a factor 2 after 4 hours, but only by a factor of 0.5 by 8 hours, with a higher skin penetration rates at lower pH. This is consistent with the theory that it is the neutral, acidic, form of the molecule

that penetrates the skin and not the ionized salt form. However, by 24 hours, there were no differences between groups in the cumulative diclofenac skin penetration rate. No difference was seen, at any time point, between the formulations with a pH of —

Table 1 Cumulative diclofenac skin penetration (40 mg/cm2)

Formulation	D0012R	D00014R	DPH-30	WD002V
Time (hours)	pH —	pH —	pH —	pH —
0	0	0	0	0
2	1.28 ± 0.21	1.02 ± 0.24	0.51 ± 0.10	0.50 ± 0.12
4	5.14 ± 0.52	4.31 ± 0.56	2.90 ± 0.26	2.69 ± 0.51
8	11.95 ± 1.20	10.06 ± 1.14	7.92 ± 0.57	7.48 ± 1.05
24	36.5 ± 1.25	37.33 ± 3.77	33.69 ± 2.32	35.50 ± 4.54

Cumulative diclofenac permeation ($\mu g/cm^2$)
Mean ± s.e.m

The quantity of product applied in the first series of experiments, 40 mg/cm^2, was considerably higher than the actual use of the product, 5 mg/cm^2 skin. The Sponsor hypothesized that the large quantity of applied product may have changed the natural pH of the skin and influenced the initial skin penetration rate of diclofenac. Therefore, a second series of experiments was conducted with these formulations in which the more physiological quantity of 5 mg/cm^2 skin was applied.

With application of 5 mg/cm^2, there was no significant effect of the pH of the diclofenac sodium gel was observed on the skin penetration rate. Therefore, under condition mimicking the human exposure, the skin penetration of diclofenac does not depend on the pH of the formulation in the range of — which are the specification limits for the product during shelf-life.

Table 2 Cumulative diclofenac skin penetration (5 mg/cm2)

Formulation	D0012R	D00014R	DPH-30	WD002V
Time (hours)	pH —	pH ⌣	pH —	pH ⌣
0	0	0	0	0
2	0 ± 0	0 ± 0	0.04 ± 0.04	0 ± 0
4	0.17 ± 0.08	0.20 ± 0.09	0.25 ± 0.13	0.26 ± 0.09
8	1.02 ± 0.22	1.08 ± 0.19	1.05 ± 0.33	1.40 ± 0.28
24	6.80 ± 1.10	6.69 ± 0.78	6.50 ± 1.14	7.99 ± 0.99

Cumulative diclofenac permeation ($\mu g/cm^2$)
Mean ± s.e.m

Study title: **Diclofenac sodium gel (diclofenac Na 1%) Voltaren Emulgel (diclofenac diethylamine 1.16%) – Viscosity: Comparison of the *in vitro* skin penetration rate**

Key study findings: There was no difference in the *in vitro* guinea pig skin penetration rate of two diclofenac sodium gel formulations differing in viscosity values, — Brookfield scale units. They were also similar to the penetration rate of Voltaren Emulgel, containing diclofenac diethylamine salt.

Reviewer Comment: The viscosity of Voltaren Emugel was not provided, limiting any ccomparative conclusions.

Study no.: Internal Report 03201
E-Location: CTD 4.2.2.2.3
Conducting laboratory and location: Novartis Consumer Health SA, Nyon, Switzerland
Date of study initiation: unknown (Report dated August 5, 2003)
GLP compliance: no
QA report: no ( )
Drug, lot #, and % purity:

- Voltaren Emulgel, bought in Switzerland (1.16% diclofenac diethylamine), Batch WB 182, expiry date 06.2004.
- Diclofenac Sodium Gel formulation Batch D00031R (viscosity — manufactured on the 19 June 2003 by Novartis Consumer Health, Lincoln, NE, USA.
- Diclofenac Sodium Gel formulation Batch D00032R (viscosity — manufactured on the 19 June 2003 by Novartis Consumer Health, Lincoln, NE, USA.

Methods
In vitro skin penetration studies were performed at 35°C in glass static diffusion cells (1.54 cm^2 area) using hairless guinea pig skin. Skins were obtained from sacrificed animals, frozen on dry ice, and stored at -20°C. After thawing, the skins were mounted horizontally on the Franz cells, dermis side down. The receptor phase of phosphate buffered saline (— within each diffusion cell was approximately 8 mL. Following a pre-equilibration period, gels were applied to the skin surface to yield approximately 5 mg/cm^2. The application mimicked the human exposure which is normally 1-5 mg/cm^2. Samples of the receptor phase were collected at 0, 2, 4, 8 and 24 hours. The removed receptor volume (1 mL) was replenished with fresh receptor solution after each withdrawal. The quantities of diclofenac (expressed in terms of diclofenac-Na equivalent) permeating the skin were determined by a HPLC analysis of the collected fractions. A total of 6 different measurements were made per formulation. The viscosity of these batches was determined by the method of Brookfield (RVT-C / 50 rpm / 25°C / 2 min).

Results
The quantity of diclofenac permeating the skin from the diclofenac sodium gel formulation did not vary with the viscosity at any time point up 24 hours. Under conditions mimicking human

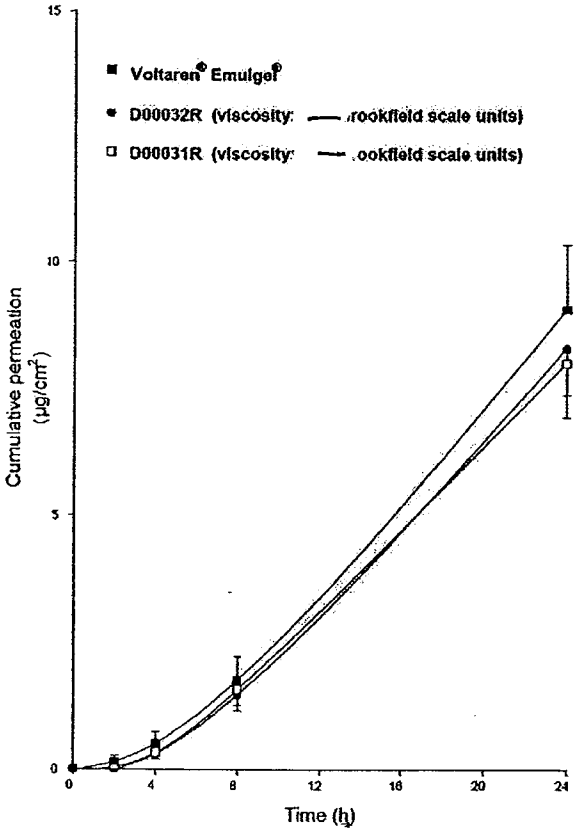
exposure, the skin penetration of diclofenac did not depend on the viscosity of the diclofenac sodium gel formulation in the range of — Brookfield scale units. Also, there was no significant difference in the diclofenac skin penetration rate between diclofenac sodium gel and the marketed product Voltaren Emulgel, which contains diclofenac diethylamine salt.

Table 1 Results of diclofenac skin permeation measurements

Cumulative permeation ($\mu g/cm^2$)	Voltaren Emulgel		D00031R (Viscosity —		D00032R (Viscosity —	
Time (h)	Mean	s.e.m	Mean	s.e.m	Mean	s.e.m
0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.15	0.13	0.05	0.03	0.01	0.01
4	0.51	0.23	0.33	0.13	0.30	0.11
8	1.76	0.46	1.57	0.31	1.47	0.32
24	9.06	1.29	8.00	1.07	8.29	0.92

Mean: average of results from 6 skin samples

s.e.m. : standard error of the mean



Study title: **Plasma kinetic study and evaluation of anti-inflammatory activity using the hairless rat ultraviolet-induced erythema model of sunburn**

Key study findings: Diclofenac diethylamine absorption through sunburned skin of hairless rats was slightly increased if applied at 30 minutes at the end of sunburn light exposure, but not if applied at 24 hours or longer after sunburn exposure.

Reviewer's comments: This GLP and QA study lacked descriptive clarity and had critical errors, making interpretation of the study problematic. Most animals lost weight over the few days of the study, including all 5 of the diclofenac treated non-sunburned control group. One animal treated with Voltaren Emulgel lost 90 g within 72 hours after treatment with diclofenac. This was not mentioned in study, the Sponsor indicated the weights were in an expected range for these animals. Furthermore there were inconsistencies mentioned for both the doses and concentrations of diclofenac. The C_{max} values were stated as being in the 0.5 to 0.8 pg/mL when actually they were in the 0.5 to 0.8 µg/mL range, if the table units are correct, or perhaps the table units 500 to 800 ng/mL are incorrect. This study will not be used to support the NDA.

Study no.: N01/C/00299
E-Location: CTD 4.2.2.2.5
Conducting laboratory and location: [redacted]
Date of study initiation: April 28, 1999
GLP compliance: yes
QA report: yes
Drug, lot #, and % purity:
Voltaren Emulgel, Batch OH8236, Purity unknown
(1.16% diclofenac diethylamine gel-emulsion (equivalent to 1.0% diclofenac sodium)

Method

Male hairless rats (N=5/group, 350-370 g body weight, 12-13 weeks of age) had four sites on the dorsolateral flanks of all animals irradiated with UV-B wavelengths at 5 MED (rninimum erythema dose; 1 MED corresponded to a radiant exposure of about 1,360 pW/cm^2 during a fixed period). The irradiated area (4 sites of 2.5 cm^2 each) was determined by twice the surface of the lamp head (***Reviewer:*** this is not explained). At 0.5, 24, 48 or 72 h after irradiation, rats were treated with a 24-h-occlusive topical application of diclofenac on the irradiated sites at 100 mg/cm^2 (***Reviewer:*** It is not clear based on Sponsor comments in the results if 100 mg refered to the gel or to diclofenac). The areas were occluded with 18-mm Finn Chambers. These animals were compared with treated non-irradiated animals. Erythema scores were obtained at 1, 4, and 24 hours after treatment. The percentage of protection was then calculated and compared. Diclofenac content in tail vein plasma was analyzed 0, 3, 8, 12, and 24 h after application of Voltaren Emulgel.

Results

There were no deaths and body weights were within the normal range. The mean erythema scores 1, 4 and 24 hours after treatment were similar for all groups. The sooner the application

of diclofenac after irradiation the lower the erthyma score. The results are summarized in the following table:

Mean Erythema Score (mean ± SD):

Evaluation time after Treatment (h)	No irradiation	Application time after 5MED irradiation			
		0.5 hour	24 hours	48 hours	72 hours
1	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.75 ± 0.72	1.90 ± 1.02
4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.95 ± 0.89	1.90 ± 1.02
24	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.22	0.75 ± 0.97	1.90 ± 1.02

In all animals, diclofenac was found in the plasma after application. The Cmax values were in the range of 0.5 to 0.8 µg/mL (500 to 800 ng/mL in the table below). [***Reviewer:*** The Sponsor's written text indicated pg/mL, then stated this amount was very low compared with the applied dose (250 mg of 1% diclofenac gel: 2.5 mg diclofenac/cm^2). Reviewer calculated this to be 10 mg/cm^2 if the 100 mg was diclofenac and not 100 mg of gel, (100 mg diclofenac/cm^2 x 2.5 cm^2 x 4 sites)]. Based on a total blood volume of approximately 15 mL, the Sponsor estimated the total plasma amount of diclofenac as 7.5 to 12 pg (***Reviewer:*** µg) which corresponded approximately to 1/200 to 1/300 of the applied dose (For non-irradiated skin this corresponds approximately to 1/250 of the applied dose (***Reviewer:*** depending on the amount applied which is unclear, this may be much greater than indicated here.)

Plasma Diclofenac Toxicokinetics

		AUC (24h) (h * ng/ml)	Cmax (ng/ml)	Tmax (h)
No irradiation		10 040 ±2 808	711.4 ± 309.9	24
Irradiation 5MED				
Time of treatment	0.5 h	14 021 ±2 770	813.5 ± 204.2	24
	24 h	8 086 ±2 571	494.5 ± 203.9	12
after irradiation	48 h	8 097 ±3 240	591.5 ± 322.5	8
	72 h	7 857 ±3 066	530.9 ± 220.1	24

The mean AUC was higher in animals treated 0.5 hour after irradiation than those not irradiated. C_{max} was higher in animals treated 0.5 hour after irradiation than those treated 24 hours after irradiation. The concentrations found in the plasma in animals treated 24, 48 and 72 hours after irradiation were lower than those obtained in non irradiated rats, and in anirnals treated 0.5 hour after irradiation. This early increase was relatively small (ratio: 1.4) and the Sponsor suggests it may not be clinically relevant and postulate the increase may be benificial since there would be a greater anti-inflammatory effect with increased penetration. An increase of the permeation just after irradiation would lead to an increase of diclofenac concentrations in plasma and then by a "physiological barrier" produced by the skin in response to the injury which reduces absorption resulting in reduced plasma diclofenac concentrations.

Reviewer: In the written pharmacokinetic summary, the following is written about this study which is inconsistent with the values presented in the above table, unless they are including all animals including sunburned animals,but it is not clear:

"The absorption of topically administered Voltaren® Emulgel™ containing 1.16% diclofenac diethylamine (equivalent to 1% diclofenac sodium) was investigated in rats. Plasma samples were obtained from all animals during the 24-hour treatment period. The AUC_{0-24h} was approximately 9620 h-ng/mL, Cmax was 628.4 ng/mL and median t_{max} was at 24 h, the last sample obtained. Absorption was initially rapid since the mean plasma concentration at 3 h (the first sample) was already more than 50% of the mean C_{max}. Approximately 30% of the topically applied dose of 10 mg/rat was absorption systemically."

Animal Weights

Group n°	Treatment	Irradiation	Time of treatment after irradiation	Animal n°	Weight (g) Start of the study	Weight (g) End of the study
1	Voltarene® Emulgel®	non irradiated	-	18	365	339
				4	361	334
				16	383	366
				22	337	315
				9	377	359
2	Voltarene® Emulgel®	5 MED	0.5 h	21	355	339
				13	346	376
				8	365	350
				12	382	371
				19	367	333
3	Voltarene® Emulgel®	5 MED	24 h	1	332	328
				6	348	337
				20	356	373
				25	349	336
				24	329	328
4	Voltarene® Emulgel®	5 MED	48 h	17	373	318
				23	332	355
				7	376	344
				10	333	251
				3	292	281
5	Voltarene® Emulgel®	5 MED	72 h	2	365	372
				11	375	383
				14	391	301
				5	337	372
				15	393	401

2.6.4.4 Distribution

These studies were reviewed in previous NDAs.
See Section 2.6.5 Pharmacokinetic Tabulated Summary

2.6.4.5 Metabolism

These studies were reviewed in previous NDAs.
See Section 2.6.5 Pharmacokinetic Tabulated Summary

2.6.4.6 Excretion

These studies were reviewed in previous NDAs.
See Section 2.6.5 Pharmacokinetic Tabulated Summary

2.6.4.7 Pharmacokinetic drug interactions

These studies were reviewed in previous NDAs.
See Section 2.6.5 Pharmacokinetic Tabulated Summary

2.6.4.8 Other Pharmacokinetic Studies

There were no nonclinical pharmacokinetic studies

2.6.4.9 Discussion and Conclusions

The current application is for a dermal preparation containing diclofenac sodium. No animal pharmacokinetic data were obtained with the proposed Voltaren® Gel 1% formulation. The results from *in vitro* studies and from a clinical pharmacokinetic study comparing the absorption of diclofenac from Voltaren® Gel 1% and Voltaren® Emulgel™ indicated that absorption of diclofenac from the two gels are very similar. Topical application of diclofenac diethylamine in animals produced higher drug concentrations in the tissue compartments beneath the site of application. These results indicated the possible absorption to target region underlying the site of application with the potential of low systemic concentrations of diclofenac. It was not determined if a depot of diclofenac developed at the site of topical application. Also studies to determine enhanced localization at joints were not determined in normal animals or animals with arthritis, either naturally occurring or experimentally induced.

2.6.4.10 Tables and figures to include comparative TK summary

Human PK parameters

Site and Area of Application	Dose/Site /Application	Dose/Day (QID)	Cmax (ng/mL)	AUC (ng-h/mL)
Study VOSG-PN-107				
1 Knee (400 cm^2)	4 g = 40 mg diclofenac = 0.1 mg diclofenac/cm^2	16 g = 160 mg diclofenac = 0.4 mg diclofenac/cm^2	After 7 days n=35 22.2 ± 33.3	After 7 days n=35 222 ± 140
Study VOSG-PN-113				
1 Knee (400 cm^2)	4 g = 40 mg diclofenac = 0.1 mg diclofenac/cm^2	16 g = 160 mg diclofenac 0.4 mg diclofenac/cm^2	After 7 days n=39 15.0 ± 7.3	After 7 days n=39 233 ± 128
2 Knees (800 cm^2) + 2 Hands (400 cm^2)	12 g = 120 mg diclofenac = 0.1 mg diclofenac/cm^2	48 g = 480 mg diclofenac = 0.4 mg diclofenac/cm^2	After 7 days n=39 53.8 ± 32.0	After 7 days n=39 807 ± 478
Voltaren (diclofenac sodium) tablets	50 mg	150 mg (TID)	After 7 days n=39 2270 ± 778	After 7 days n=39 3890 ± 1710

(Reference is made to NDA 19-201, from carcinogenicity studies)

Daily dietary dose (mg/kg)	Mice mean plasma levels (pmol/g)		Rats mean plasma levels (pmol/ml)		Study Number / Location (eCTD Section / Page)
	M	F	M	F	
0.1	28.6	22.2			GU 841110 Appendix D eCTD 4.2.3.4.1.1 / 270
0.25			54	98	GU 785271 Appendix F eCTD 4.2.3.4.1.2 / 98
0.3	48	66.3			GU 841110 Appendix D eCTD 4.2.3.4.1.1 / 270
0.5			153	219	GU 785271 Appendix F eCTD 4.2.3.4.1.2 / 98
1	180.3	347.7	236	312	GU 841110 Appendix D eCTD 4.2.3.4.1.1 / 270
2	315.9	499.8	300	408	GU 841110 Appendix D eCTD 4.2.3.4.1.1 / 270

Table 9 Pharmacokinetics Parameters in Four species after administration of diclofenac sodium (From Comprehensive summary: Pharmacology, NDA 19-201)

Species	Route	Dose (mg)	C_{max} (ng/ml)	T_{max} (minutes)	$T_{½}$ (hours)
Rat [a]	i.v.	5	13	5	4.5
Dog [a]	i.v.	5	34	10	3.5
	p.o.	5	13	60-120	
Monkey [a]	i.v.	5	40	10	2
	p.o.	5	3.6	120	
Mini-pig [b]	i.m.	1	4.2	20	3

[a] Radioactivity data
[b] Data obtained by gas chromatography

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Pharmacokinetic Studies

Report number/Title/ Date	Type of Study Test system or protocol	Method of administration Dose (mg/kg)	Findings
Absorption			
12-march-2002 eCTD 4.2.2.2.1 Pre GLP	In vitro dermal Abdominal skin of hairless Guinea pigs (area 1.54 cm^2)	40 mg/cm^2 Single dose; Diclofenac sodium gel 1% and, Voltaren® Emulgel™ (area 1.54 cm^2)	**In vitro skin penetration of diclofenac** from diclofenac diethylamine 1.16% diclofenac sodium 1%
-03171 (dated 11.07.03) eCTD 4.2.2.2.2 Pre GLP		5 and 40 mg/cm^2 Single dose; diclofenac sodium gel 1% pH	**In vitro skin penetration rate, effect of pH.** Diclofenac sodium pH range
-03201 (dated 06/08/2003) eCTD 4.2.2.2.3 Pre GLP		5 mg/cm^2 Single dose, diclofenac sodium gel 1% Brookfield scale Viscosity units	**In vitro skin penetration rate, effect of viscosity** diclofenac sodium diclofenac diethylamine)
N01-C-00299 eCTD 4.2.2.2.5 GLP: yes	Hairless rat, Topical, dermal	Single 24h Application Voltaren® Emulgel™ 100 mg/cm^2, on four 2.5 cm^2 sites	**Study Not Acceptable** **UV-induced erythema model of sunburn** Plasma kinetic anti-inflammatory activity
5-1972 eCTD 4.2.2.2.4 pre GLP	Mouse / BALBc x MIW Rat / Sprague-Dawley	10 mg/kg Oral, Single Dose diclofenac-Na 5 mg/kgIntravenous and oral	5/1972-GP 45840 – Pharmacokinetics and metabolism in animals (mouse, rat, dog, monkey)
B91/1984 eCTD 4.3; Botta 1985	Guinea pigs, Dunkin-Hartley Pirbright strain, 240-380 g	200, 400, 800 mg/kg GP 45840 (1.16% diclofenac-Emulgel), topical to dorsal skin area of 40 cm/kg, Single application (**Note:** expect similar uptake for increase dose, since mg/cm^2 would the same for all doses).	8% of dose was absorbed percutaneously when occlusive dressing was used, 200, 400 and 800 mg/kg dose corresponded to systemic uptake of 0.19 mg/kg, 0.38 mg/kg and 0.72 mg/kg respectively AUC 0 to 144 hours: 1.0, 3.3, 6.2 ug-h/g, respectively without occlusive dression 5% of dose was absorbed, Removal of cornified skin resulted in 10% of the dose absorbed Max blood radioactivity concentration occur at 6 to 8 hours after application of 200, 400 and 800 mg/kg ^{14}C-diclofenac were 51, 160, and 287 ng/g, respectively AUC 0 to 144 hours: 1.0, 3.3, 6.2 µg-h/g,

			respectively
		400 mg/kg ^{14}C-GP 45840 Emulgel, Repeated dose 2x/day (8 hrs apart) for 6 days Sp act in final formulation: 2.5 and 10 µCi/mg)	22% of the sum of all applied doses of ^{14}C-diclofenac absorbed Steady state concentration reached after 3 days was 500 ng/g Tissue concentrations: m. longissimus lumborum: 300 ng/g (under application site) m gastrocnemius: 89 ng/g
	rabbit, new Zealand white, wt 2.8-3.2 kg; male and female n=2/sex	400 mg/kg GP 45840 (1.16% diclofenac-Emulgel), topical to skin area of 40 cm/kg, (10 mg/cm^2), Single application, occlusive dressing	male: 16% of dose absorbed female: 40% of dose absorbed corresponds to systemic uptake of 0.74-1.86 mg/kg body weight
Distribution			
B33-1975 eCTD 4.2.2.3.2 pre GLP	Rat / albino RA25 Rat / black hooded Long Evans	5 mg/kg Intravenous Single dose	organ and tissue concentrations eye
B86-1982 eCTD 4.2.2.7.1	healthy rats and rats with induced arthritis.		**serum proteins binding of diclofenac** flufenamic acid phenylbutazone salicylic acid
B6-1979 eCTD 4.2.2.3.3 pre GLP	Serum (rat, dog, baboon, rhesus) In vitro	0.20, 1.85 µg/mL Single exposure	human serum proteins binding rat dog monkey. Displacement interactions with salicylic acid, acetylsalicylic acid, phenylbutazone, prednisolone, tolbutamide, acenocoumarol and warfarin. Dialysability and reversibility of binding.
B86-1980 eCTD 4.2.2.3.4 pre-GLP	Pregnant mouse / Tif:MAGf and Pregnant rat / Tif:RAIf	5 mg/kg Oral gavage Single dose	Placenta passage
B81-1979 eCTD 4.2.2.5.1	women	100 mg voltaren per day for one week after delivery	**Passage of unchanged diclofenac into mother's milk of breast-feeding healthy women**
Metabolism			
5/1972 eCTD 4.2.2.2.4 pre GLP	Rat / Sprague-Dawley Dog / beagle Rhesus monkey	5 mg/kg Intravenous and Oral Single dose	Rats: quantitative differences in the metabolite pattern following oral and intravenous administration, suggesting significant first pass effects in this species. Dogs: no differences were apparent Rhesus monkeys : only slight quantitative differences
B12-1977 eCTD 4.2.2.4.1	In vitro Rat liver	10^{-5}M	hepatic microsomal drug metabolizing enzyme in vivo

pre GLP	Microsomes In vivo Rat / Tif:RAIf	diclofenac sodium 1, 3, 6 or 10 mg/kg Oral gavage 4 days 1,	hepatic microsomal drug metabolizing enzymes At 3, 6 and 10 mg/kg: dose-related suppression in rate of microsomal O-demethylation, N-demethylation or C-hydroxylation and cytochrome P450; Was due to depression of enzyme synthesis rather than any direct inhibition of enzyme activity
Yu et al, 2005 Yan et al., 2005 eCTD 4.3	Human liver Microsomes		**diclofenac GSH adduct:** **4'hydroxy 2'glutathione diclofenac identified in human liver microsomes.** appeared to be unique to humans, not detected in monkey and rat liver microsomes
Excretion			
5/1972 eCTD 4.2.2.2.4 pre GLP	Rat / Sprague-Dawley Dog / beagle Rhesus monkey	5 mg/kg Intravenous and Oral Single dose	Species differences
Pharmacokinetic Drug Interactions			
Masabuchi et al 2001 eCTD 4.3	In vitro Rat liver microsomes		diclofenac could inactivate CYP2C11 in rat liver microsomes responsible for the 5-hydroxylation of diclofenac in rats
Masabuchi et al 2002 eCTD 4.3	In vitro Human liver microsomes		diclofenac could inactivate CYP3A4 in human liver microsomes responsible for the 5-hydroxylation of diclofenac in human,
Oh and Yan 2005 eCTD 4.3	rat		potential interaction between diclofenac and tetracycline: clearance of tetracycline was found to be reduced when rats were pre-treated with diclofenac 30 minutes prior to tetracycline administration. The systemic exposures (AUC) and t1/2 of tetracycline were increased.
B86/1982 eCTD 4.2.2.7.1 GLP: no	In vitro Rat serum	0.333, 0.999, 3.000 µg/mL Single exposure	plasma protein binding of healthy rats was compared with that in rats with induced arthritis no difference in the degree of binding of diclofenac between healthy and diseased animals

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The nonclinical studies for Voltaren Gel relied mainly on studies originally submitted to support Voltaren (NDA 19-201), an oral tablet formulation of diclofenac sodium. Genetic, carcinogenetic, and reproductive toxicological studies were conducted previously for approval of Voltaren (NDA 19-201) and were not reviewed here, but briefly summarized for the purposes of labeling. Additional studies were submitted to support the topical route of administration. Several of these studies were conducted in the 1970's and 1980's prior to GLP implementation, but were not submitted to NDA 19-201. Other more recently conducted GLP studies included dermal and eye irritation, skin hypersensitivity, and dermal photosensitivity studies. With a few exceptions (indicated below when appropriate) they appear to be adequately conducted and interpreted. There were **no approval-related toxicological concerns with the studies reviewed**. A number of potentially problematic issues were revealed because the Sponsor had not previously provided sufficient information. These related to the toxicology of diclofenac-related impurities, novel excipients, and photodegradants.

DICLOFENAC SYSTEMIC TOXICOLOGY

Single Dose Studies

Acute toxicity studies were previously conducted in mice, rats, guinea pigs, rabbits, dogs and monkeys for diclofenac sodium in NDA 19-201. Single dose experiments showed that the acute oral or intravenous LD50 in mice, rats and dogs is generally between 90 and 250 mg/kg. Rabbits appear somewhat more sensitive with an intravenous LD_{50} of around 60 mg/kg and monkeys considerably less sensitive with an oral LD_{50} around 3200 mg/kg. There were no obvious difference between the sexes. Acute signs of toxicity generally included dyspnea and recumbence in small laboratory animals and CNS and gastrointestinal effects in dogs and monkeys. Death following intravenous administration was usually attributed to respiratory or cardiac failure, while death following oral administration resulted from to gastrointestinal problems and peritonitis.

Repeat Dose Studies

Repeat dose oral gavage studies of up to six months duration in rats conducted in support of NDA 19-201 demonstrated a no observed adverse effect level (NOAEL) of 1 to 2 mg/kg/day. A similar result was obtained in a one month mouse study by dietary administration. At doses greater than 4 mg/kg/day, deaths were common and usually associated with mild anemia, neutrophilia, disturbance of plasma proteins, increased extramedullary hematopoiesis and, most prominently, ulceration of the gastrointestinal tract with accompanying peritonitis. This was commonly associated with hypertrophy or reactive hyperplasia of the mesenteric lymph nodes. In a one-year baboon study, five of 14 animals treated at 15 mg/kg/day had died by 8.5 months, even after this dosage was reduced to 10 mg/kg/day. Both constipation and diarrhea were

apparent and there was a high incidence of skin ulcers the severity of which was treatment-related. At the high dose only (where 13 of 14 animals died despite a dosage reduction) adrenal cortical hyperplasia was noted in several animals. Other changes seen in baboons were essentially similar to those in rats and the deaths were all associated with gastrointestinal changes. Gastrointestinal changes were also seen at the lowest dosages studied in baboons (5 mg/kg/day). Although the Sponsor attributed this to reflect an exacerbation of pre-existing conditions rather than a primary effect of treatment with diclofenac, they lacked sufficient evidence to completely rule out an effect of diclofenac.

GENETIC TOXICOLOGY

The potential genetic toxicology of diclofenac sodium has been studied in a numerous *in vitro* and *in vivo* studies for the original NDA 19-201. There were no positive results in either mutation or clastogenicity assays. These studies included bacteria reverse mutation (Ames) tests of diclofenac and its metabolites (by direct addition of urine and bile concentrates intially, then with the synthesized hydroxymetabolites of diclofenac), *in vitro* mouse lymphoma mutation studies of diclofenac sodium and its hydroxy-metabolites, *in vitro* chromosome aberration tests in Chinese hamster ovary cells and *in vivo* chromosome aberration tests in Chinese hamsters after both short-term treatment and repeated administration for 12 weeks, metaphase analyses of spermatogonia and spermatocytes following short term multiple dosings, dominant lethal study in mice, *in vivo* chromosome aberration study in bone marrow of rats, and *in vitro* photo-mutagenicity studies.

Photoclastogenic studies resulted in cytotoxicity, associated with a reduced mitotic index, at a very low concentration of diclofenac (25 µg/mL) and short period of UV radiation (with 16 minutes). This apparently was a threshold response as no chromosome aberrations were seen at lower doses of UV or at lower concentrations of diclofenac. The interpretation of this finding for genotoxicity induced by a combination of UV radiation and diclofenac is problematic without additional studies, perhaps using other test systems. However, as mentioned above, labeling to avoid sunlight would alleviate the need to further characterize this interaction.

CARCINOGENICITY

Oral (Dietary) Administration

One mouse and two rat carcinogenicity studies were conducted for NDA 19-201 with diclofenac powder mixed with the feed. The results of the carcinogenicity study with diclofenac sodium at doses of 0.1, 0.3, 1 and 2 mg/kg showed similar findings with regard to mortality and gastrointestinal irritation in mice and rats. No tumorigenic effect of diclofenac sodium was observed. Dose-related increases in mortality, especially among females, were observed at 1.0 and 2.0 mg/kg. Again, gastrointestinal ulceration and related complications were identified as the main causes for mortality. These complications included endocardial thrombosis with thrombo-embolism, hemosiderosis and extramedullary hemopoiesis in the spleen, and centrolobular necrosis in the liver. Using satellite animals, hematology indicated anemia with reticulocytosis and leukocytosis in animals treated at 1 or 2 mg/kg/day from Week 27 onwards. At the terminal examination one male receiving 0.3 mg/kg/day was anemic. Blood chemistry indicated changes in plasma proteins and alkaline phosphatase activity at the high dosage that