CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-122

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-122	Submission Date: 12/19/06
Submission Type; Code:	1S
Brand/Code Name:	Voltaren Topical Gel
Generic Name:	Diclofenac Na Topical Gel 1%
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	Novartis Consumer Health, Inc
Relevant IND(s):	64,334
Formulation; Strength(s):	1% diclofenac Na gel
Proposed Indication:	[redacted] joints amenable to [redacted] treatment, such as hands and knees
Proposed Dosage Regimen:	**Lower extremities, including the knees, ankles, and feet:** Apply the gel (4 g) to the affected joint, 4 times daily. Voltaren® should be gently massaged into the skin ensuring application to the entire affected joint. Do not use more than 16 g daily per lower joint. **Upper extremities including the elbows, wrists and hands:** Apply the gel (2 g) to the affected joint, 4 times daily. Voltaren® should be gently massaged into the skin ensuring application to the entire affected joint. Do not use more than 8 g daily per upper joint. Total usage should not exceed 32 g per day, over all affected joints.

Table of Contents

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology Evaluation II (OCP/DCP-II) has reviewed the Voltaren NDA submitted on 12/19/06.

From OCP perspective, the information contained in the Application is acceptable pending a satisfactory agreement can be reached with the Applicant regarding the Labeling for Voltaren.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

Novartis Consumer Health, Inc. has submitted NDA 22-122 for Voltaren topical 1% gel (1% diclofenac Na gel) for [redacted] joints amenable to [redacted] treatment, such as hands and knees. References were made to Solaraze™ (diclofenac sodium) 3% Gel NDA 21-005 (approved 10/16/00) for information and data pertaining to dermal carcinogenicity and photocodermal carcinogenicity, and to Novartis Pharmaceuticals NDA 19-201 (approved 7/28/88) for Voltaren® (diclofenac sodium) enteric-coated tablets [and, Voltaren-XR NDAs 20-254 (approved 3/8/96) and Cataflam NDA 20-142 (approved 11/24/93) as necessary].

With respect to the currently marketed topical products which contain diclofenac, Flector® Patch is the only topical product indicated for the topical analgesics, and is comprised of an adhesive material containing 1.3% diclofenac epolamine:

Drug Product	NDA #	Diclofenac amount	Indication
Solaraze™	21-005; Approved 10/16/00	diclofenac Na 3%	For the topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy. Solaraze Gel is applied to lesion areas twice daily.
Flector® Patch	NDA 21-234; approved 1/31/07	diclofenac epolamine 1.3% (180 mg diclofenac epolamine total amount)	For the topical treatment of acute pain due to minor strains, sprains, and contusions. The recommended dose of Flector® Patch is one (1) patch to the most painful area twice a day.

The Applicant conducted clinical safety and efficacy studies. The Applicant stated that data from two controlled clinical trials [VOSG-PN-310 (knee) and VOSG-PE-315 (hand)] provided replicate evidence of effectiveness of the drug for [redacted] compared to vehicle treatment. Additionally, a third study (VOSG-PN-304) was submitted as a supportive study and offered replicate evidence of efficacy in knee osteoarthritis, and a supportive uncontrolled long-term safety study (VOSG-PN-309) in knee osteoarthritis.

Two pharmacokinetic studies were completed, VOSG-PN-107 and VOSG-PE-113, using the to-be-marketed formulation. Since the drug is applied at the joints for the local treatment, the critical clinical pharmacology aspect of this NDA was to focus on the diclofenac systemic exposure.

Exposure-response relationship

The drug is applied at the joints for the local treatment. The joint fluids were not sampled for diclofenac concentration. Therefore, there is no exposure-response relationship for this product.

Single dosing

Pharmacokinetic parameters from a single dose study are not available. However, the single dose information is not critical for this product since the gel will be applied 'chronically' for OA indication.

Multiple dosing

There were two multiple-dose studies completed, VOSG-PN-107 and VOSG-PE-113. Study VOSG-PN-107 assessed diclofenac exposure due to heat application and exercise, and Study VOSG-PE-113 assessed the 'maximum-likely-use' scenario.

Study VOSG-PN-107:

This study was a steady-state, randomized, 3-period, 4-treatment crossover systemic bioavailability study of diclofenac comparing topical diclofenac sodium gel, 1%, to the same treatment plus heat application or exercise. Four (4) g of a diclofenac gel was applied 4 times daily for 7 days to one knee (400 cm^2), rubbed in for up to 1 minute until the gel had vanished. For heat treatment, moderate heat was applied to the knee for 15 minutes prior to each gel application. For exercise, first gel application of each day was

followed by 20-minutes of treadmill exercise. Pharmacokinetic parameters on Day 7 were compared. An analysis of variance (ANOVA) was performed on ln-transformed PK parameters to compare between groups.

The results indicated that there were some minor differences between treatment groups, e.g., point-estimates for Cmax and AUC for heat treatment group were lower by approximately 10 and 7.5%, respectively, compared with the reference treatment group. The data indicated that diclofenac exposure did not increase due to heat or exercise.

Study VOSG-PE-113:

This was a steady-state, randomized, open-label, 3-period, 3-treatment crossover systemic bioavailability study of diclofenac comparing topical diclofenac sodium gel, 1%, applied to one knee vs. two knees and two hands (maximum dose) and vs. oral diclofenac sodium tablets (50 mg enteric-coated) in normal healthy volunteers. Four (4) g of a diclofenac gel was applied 4 times daily for 7 days to one knee. Additionally, 12 g of a diclofenac gel was applied 4 times daily for 7 days to both knees (8 g) and hands (4 g). A 50-mg enteric-coated diclofenac tablet was taken orally 3 times daily for 7 days, as a reference.

Diclofenac Cmax and AUC exposure was compared after 12 g application on Days 1 and 7. On Day 7, the AUC increased approximately 3-fold compared to on Day 1.

Linearity

Study VOSG-PE-113 (see above for study design) assessed dose linearity from two gel doses, 4 g and 12 g, on Day 7. Diclofenac Cmax and AUC increased approximately 2.5-fold for both parameters for 12 g treatment compared with 4 g treatment, indicating that there is less-than-proportional increase in Cmax and AUC.

Relative bioavailability

Study VOSG-PE-113 (see above for study design) assessed a relative bioavailability of the 12 g gel, the maximum-likely-use scenario, against a 50-mg enteric-coated diclofenac tablet. On Day 7, diclofenac Cmax and AUC parameters were compared.

The diclofenac exposure from the gel, by comparing AUC exposure (without taking into account the dose administered), was approximately 20% compared to that of the 50-mg enteric-coated diclofenac tablet. The Cmax value from the gel was approximately 2% compared to that of the tablet.

The relative bioavailability of the Voltaren gel was calculated to be approximately 6.6%, compared to that of the oral IR tablet formulation (Voltaren 1% gel has 10 mg of diclofenac in 1 g of gel. The total daily amount of Voltaren gel applied was 48 g. This amounts to 480 mg of diclofenac applied topically daily. Similarly, the oral diclofenac daily intake was 150 mg.)

Steady state

Study VOSG-PN-107 (see above for study design) measured trough diclofenac concentrations each day for 7 days before the first gel application. The plasma profile showed inconclusive evidence if the 'true' steady-state was achieved by Day 7. Additional time-points at Days 8 and 9 may have provided conclusive evidence if the 'true' steady-state was achieved.

However, diclofenac plasma profile from Study VOSG-PE-113 indicated that steady-state may have been reached by Day 7. Both 4 and 12 g treatments showed that diclofenac concentrations 'leveled out' by Day 7.

Hepatic Impairment

Once diclofenac reaches the general circulation, diclofenac is metabolized primarily by conjugation or by hydroxylation of one or both of the benzene rings with subsequent conjugation. Diclofenac and its metabolites are excreted by urinary route.

Generally subjects with hepatic impairment may require reduced doses of diclofenac. For Voltaren gel, the diclofenac systemic exposure (without taking into account the dose administered) at maximum usage (two knees and two hands) was approximately 20% of that of the 50 mg diclofenac tablet. Therefore, the dose adjustment may not be necessary in subjects with hepatic impairment.

Elderly

Elderly subjects may have reduced liver or kidney functions and may require reduced doses of diclofenac. Additionally, it is possible that the morphology of elderly skin may be altered with aging and disease, causing increased diclofenac local and systemic concentrations. No pharmacokinetic studies were performed in this population. However, there were a substantial number of elderly subjects in the clinical efficacy and safety studies. There were no overall differences in effectiveness or safety were observed between elderly subjects and younger subjects. Therefore, the dose adjustment may not be necessary in elderly subjects.

Pediatric population

The Applicant requested a waiver for pediatric population. The Applicant indicated that there is no apparent reported incidence of osteoarthritis of the superficial joints in subjects below the age of 18 years, and stated that the Voltaren is not likely to be used in a substantial number of pediatric patients. The Applicant stated that the paucity of pediatric patients available would also make recruitment for the conduct of studies difficult or impossible.

Gender

No clinical pharmacology studies were conducted to assess gender differences. However, in Study VOSG-PE-113 a gender sub-analysis was performed by a visual inspection of the diclofenac plasma profiles. The visual inspection of the plasma profiles indicated that there were no differences observed between female and male subjects based on the Day 7 plasma profile.

External factors which influence diclofenac exposure

Diclofenac degrades if it is exposed to light which can decrease the diclofenac efficacy, by providing less diclofenac to be absorbed at the sight. There were no in vivo studies submitted to address the degradation and photo-degradant issues. As with other topical diclofenac products, the Voltaren gel photo-stability issues will be discussed in CMC review. Accordingly, the issues involving the photo-degradants and photo-toxicity will be addressed in the Pharmacology/Toxicology review.

Meanwhile, the photo-toxicity issue can be addressed in the Labeling by recommending subjects to avoid sun exposure after Voltaren Gel application.

Assay

Plasma and urine diclofenac and its metabolite, 4'-hydroxydiclofenac, were assayed in each sample using a validated LC/MSMS method with a limit of quantification (LOQ) of 0.5 ng/mL and 3 ng/mL, respectively.

Overall, the information submitted in this NDA is acceptable pending a mutual agreement can be reached with the Applicant with respect to Voltaren Labeling.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

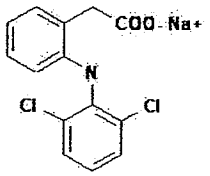
Voltaren topical gel 1% contains the active ingredient, diclofenac sodium, in an opaque, white gel base. The gel is applied topically.

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 (Carbomers)	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.

Diclofenac structure:



2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, the mechanism of action of diclofenac is not known, but may be related to prostaglandin synthetase inhibition as well as contribute to its efficacy in relieving pain associated with inflammation. NSAIDs act as inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 and cyclooxygenase-2 isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thomboxane from arachidonic acid. Prostaglandins act as messenger molecules in the process of inflammation.

Voltaren is indicated for ,oints amenable to treatment, such as the hands and knees in adults. Osteoarthritis (OA) is the most common form of joint disease, and is a chronic condition. OA is characterized by joint inflammation, degeneration and regeneration of articular cartilage and bone, causing joint pain, sometimes swelling, short duration stiffness after rest and limited mobility. The pathological changes often correlate poorly with clinical signs and symptoms. Pain can sometimes be substantial, especially in acute flare up periods. OA, particularly of knees

and hands, is widely recognized as one of the major causes of chronic disability in the adult population.

2.1.3 What are the proposed dosage and route of administration?

The Voltaren gel is applied topically. The following dosage is recommended for the lower and upper extremities:

Lower extremities, including the knees, ankles, and feet:

Apply the gel (4 g) to the affected joint, 4 times daily. Voltaren® should be gently massaged into the skin ensuring application to the entire affected joint. Do not use more than 16 g daily per lower joint.

Upper extremities including the elbows, wrists and hands:

Apply the gel (2 g) to the affected joint, 4 times daily. Voltaren® should be gently massaged into the skin ensuring application to the entire affected joint. Do not use more than 8 g daily per upper joint.

Total usage should not exceed 32 g per day, over all affected joints.

2.2 General Clinical Pharmacology

2.2.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (If yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes.

2.2.2 Exposure-response

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety and efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

The drug is applied at the joints for the local treatment. The joint fluids were not sampled for diclofenac concentration. Therefore, there is no exposure-response relationship for this product. The critical clinical pharmacology aspect of this NDA was to assess the diclofenac systemic exposure from the topical application of the gel.

2.2.2.2 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Single dose

Pharmacokinetic parameters from a single dose study are not available for Voltaren topical gel. However, the single dose information is not critical for this product since the gel will be applied 'chronically' for OA indication.

Multiple dose

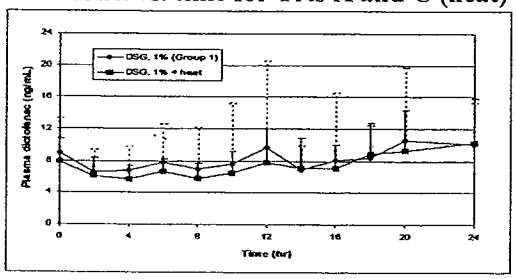
There were two multiple-dose studies, VOSG-PN-107 and VOSG-PE-113. Study VOSG-PN-107 assessed diclofenac exposure due to heat application and exercise, and Study VOSG-PE-113 assessed the 'maximum-likely-use' scenario.

Study VOSG-PN-107:

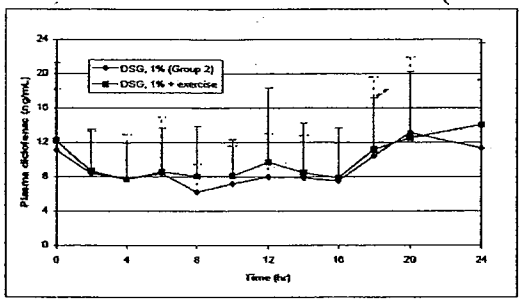
This study was a steady-state, randomized, 3-period, 4-treatment crossover systemic bioavailability study of diclofenac comparing topical diclofenac sodium gel, 1%, to the same treatment plus heat application or exercise. Four (4) g of a diclofenac gel was applied 4 times daily for 7 days to one knee (400 cm^2), rubbed in for up to 1 minute until the gel had vanished. Treatment A served as a reference arm. For Treatment C, moderate heat was applied to the knee for 15 minutes prior to each gel application. For Treatment D, first gel application of each day was followed by 20-minutes of treadmill exercise. Pharmacokinetic parameters on Day 7 were compared. An analysis of variance (ANOVA) was performed on ln-transformed PK parameters to compare between groups.

The results indicated that there were some minor differences between treatment groups, e.g., point-estimates for Cmax and AUC for heat treatment group were lower by approximately 10 and 7.5%, respectively, compared with the reference treatment group. The data indicated that diclofenac exposure did not increase due to heat or exercise.

Mean (SD) plasma diclofenac conc. vs. time for Trts A and C (heat) in Group 1 on Day 7



Mean (SD) plasma diclofenac conc. vs. time for Trts A and D (exercise) in Group 2 on Day 7



Descriptive statistics of diclofenac PK parameters in plasma (Mean ± SD)

Treatments	Cmax (ng/mL)	tmax (h)	AUC0-24 (ng•h/mL)
Group 1A# (N=18)	24.5 ± 42.0	19 (0-24)	218 ± 148
Group 2A* (N=17)	19.8 ± 21.5	18 (0-24)	226 ± 135
C (N=18)	13.3 ± 5.63	20 (0-24)	179 ± 63.2
D (N=17)	16.8 ± 10.1	18 (0-24)	234 ± 134

#: Reference for Group C (heat treatment)
*: Reference for Group D (exercise treatment)
A: diclofenac sodium gel; C: A + heat; D: A + exercise
Tmax: median (range)

Descriptive statistics of diclofenac and 4'-OH-diclofenac PK parameters in urine (Mean ± SD)

Treatment	Ae0-24 diclofenac (mg)	Ae0-24 4'-OH-diclofenac (mg)	Proportion excreted (% dose)
Group 1A# (N=18)	0.25 ± 0.17	0.49 ± 0.35	0.48 ± 0.34
Group 2A* (N=17)	0.27 ± 0.17	0.56 ± 0.37	0.54 ± 0.34
C (N=18)	0.23 ± 0.10	0.44 ± 0.20	0.44 ± 0.19
D (N=17)	0.26 ± 0.18	0.56 ± 0.42	0.53 ± 0.39

#: Reference for Group C (heat treatment)
*: Reference for Group D (exercise treatment)
A: diclofenac sodium gel; C: A + heat; D: A + exercise

Comparison of Treatments, A, C and D by ANOVA (95% confidence interval)

Least squares geometric mean ratios of Treatments C and D vs. Treatment A and associated 95% CIs shown below.

Comparison of diclofenac PK parameters in plasma (point estimate and 95% CI)

	Cmax (%)	AUC0-24 (%)
C/A (N=18)	90.0 (61.9-131)	92.5 (77.3-111)
D/A (N=16)	99.2 (74.6-132)	103 (87.8-120)

A: diclofenac sodium gel; C: A + heat; D: A + exercise

Comparison of diclofenac and 4'-OH-diclofenac PK parameters in urine (point estimate and 95% CI)

Treatment	Ae0-24 diclofenac (%)	Ae0-24 4'-OH-diclofenac (%)	Proportion excreted (%)
C/A (N=18)	105 (93.4-117)	102 (91.2-114)	103 (92.1-115)
D/A (N=16)	99.2 (83.0-119)	104 (92.6-116)	102 (89.4-115)

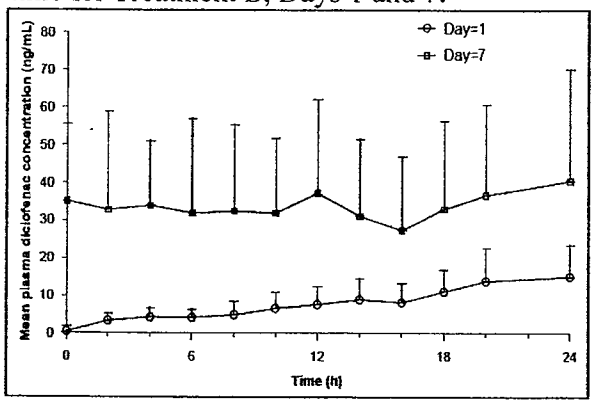
A: diclofenac sodium gel; C: A + heat; D: A + exercise

Study VOSG-PE-113:

This was a steady-state, randomized, open-label, 3-period, 3-treatment crossover systemic bioavailability study of diclofenac comparing topical diclofenac sodium gel, 1%, applied to one knee vs. two knees and two hands (maximum dose) and vs. oral diclofenac sodium tablets (50 mg enteric-coated) in normal healthy volunteers. Four (4) g of a diclofenac gel was applied 4 times daily for 7 days to one knee (Treatment A). Additionally, 12 g of a diclofenac gel was applied 4 times daily for 7 days to both knees (8 g) and hands (4 g) (Treatment B). A 50-mg enteric-coated diclofenac tablet was taken orally 3 times daily for 7 days, as a reference (Treatment C).

Diclofenac Cmax and AUC exposure was compared on Days 1 and 7 of Treatment B. On Day 7, the AUC increased approximately 3-fold compared to on Day 1.

Diclofenac conc. vs. time for Treatment B, Days 1 and 7:



Conversion of diclofenac plasma and urine parameters to least squares mean: Days 1 and 7 for Treatment B:

Treatment	Day	AUC0-24 (µg•h/mL)	Ae0-24 diclofenac (µg)	Ae0-24 4'-OH-diclofenac (µg)
B (N=39)	1	0.171 (0.148-0.198)	217 (184-256)	290 (246-341)
	7	0.714 (0.617-0.827)	617 (522-728)	1166 (990-1373)

Comparison of PK parameters on Days 1 and 7: ANOVA (point estimate and 95% CI):

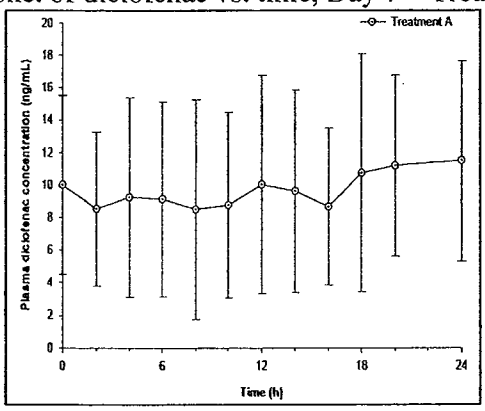
Treatment	Comparison	AUC0-24 (%)	Ae0-24 diclofenac (%)	Ae0-24 4'-OH-diclofenac (%)
B (N=39)	Day 7/Day 1	417 (367-474)	285 (248-327)	402 (350-462)

2.2.2.3 What information is available to assess linearity?

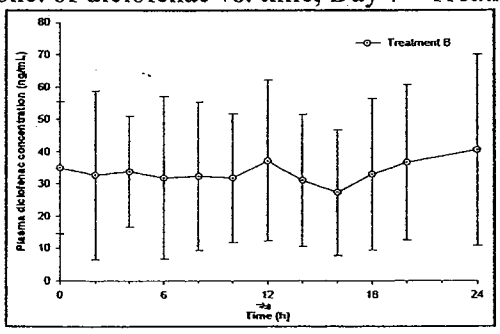
Study VOSG-PE-113 attempted to assess dose linearity from two gel doses, 4 g and 12 g, on Day 7. Four (4) g of a diclofenac gel was applied 4 times daily for 7 days to one knee (Treatment A), and 12 g of a diclofenac gel was applied 4 times daily for 7 days to both knees (8 g) and hands (4 g) (Treatment B). A 50-mg enteric-coated diclofenac tablet was taken orally 3 times daily for 7 days, as a reference (Treatment C).

Diclofenac Cmax and AUC increased approximately 2.5-fold for both parameters for 12 g treatment compared with 4 g treatment, indicating that there is less-than-proportional increase in Cmax and AUC.

Profile of avg. conc. of diclofenac vs. time, Day 7 – Treatment A, 4 g gel:



Profile of avg. conc. of diclofenac vs. time, Day 7 - Treatment B, 12 g gel:



Diclofenac plasma PK parameters on Day 7 for 4 g and 12 g gel: (n=39)

Treatment	Cmax (ng/mL)	tmax (h)	AUC0-24 (ng•h/mL)	Cmin (ng/mL)	Cav (ng/mL)
A	15.0 ± 7.33	14 (0-24)	233 ± 128	5.92 ± 3.65	9.70 ± 5.32
B	53.8 ± 32.0	10 (0-24)	807 ± 478	19.2 ± 12.1	33.6 ± 19.9
C	2270 ± 778	6.5 (1-14)	3890 ± 1710	5.70 ± 3.11	162 ± 71.2

Diclofenac urine PK parameters on Day 7 for 4 g and 12 g gel: (n=39)

Treatment	Ae0-24 diclofenac (µg)		Ae0-24 4'-OH-diclofenac (µg)	
	Day 1	Day 7	Day 1	Day 7
A	64.1 ± 64.1	265 ± 164	95.0 ± 85.5	539 ± 332
B	249 ± 118	672 ± 300	333 ± 160	1270 ± 602
C	-	10300 ± 3980	-	23400 ± 6280

Conversion of plasma PK parameters to least squares mean: Day 7 (n=39)

Treatment	Cmax (ng/mL)	AUC0-24 (ng•h/mL)
A	13.5 (11.7-15.6)	209 (183-240)
B	47.1 (40.8-54.3)	712 (621-816)
C	2130 (1850-2460)	3610 (3150-4140)

Conversion of urine PK parameters to least squares mean: Day 7 (n=39)

Treatment	Ae0-24 diclofenac (µg)	Ae0-24 4'-OH-diclofenac (µg)
A	226 (188-272)	467 (390-559)
B	617 (513-742)	1168 (976-1398)
C	9011 (7494-10835)	21150 (17631-25375)

Comparison of plasma PK on Day 7 using ANOVA (point estimate and 95% CI)

Comparison	Cmax (%)	AUC0-24 (%)
B/A	349 (302-403)	340 (294-394)

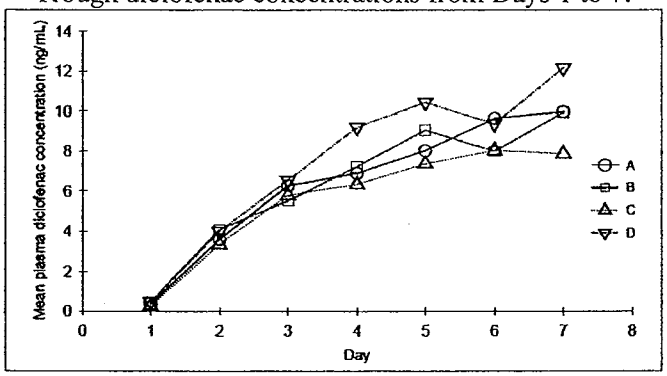
Comparison of urine PK on Day 7 using ANOVA (point estimate and 95% CI)

Comparison	Ae0-24 diclofenac (%)	Ae0-24 4'-OH-diclofenac (%)
B/A	273 (224-332)	250 (207-302)

2.2.2.4 How long does it take to reach steady-state?

Study VOSG-PN-107 measured trough diclofenac concentrations each day before the first gel application. The plasma profile showed inconclusive evidence if the 'true' steady-state was achieved by Day 7. Additional time-points at Days 8 and 9 may have provided conclusive evidence if the 'true' steady-state was achieved.

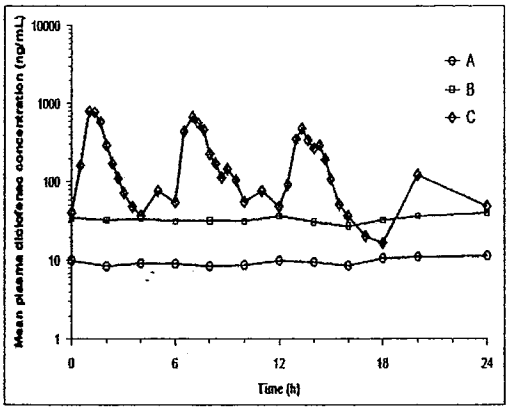
Trough diclofenac concentrations from Days 1 to 7:



A: diclofenac sodium gel; C: A + heat; D: A + exercise; Source:
B: *Voltaren® Emulgel™ - European product- diclofenacdiethylamine (DEA) gel;* this treatment arm was included in the study to compare against Treatment A

Diclofenac plasma profile from **Study VOSG-PE-113** also indicated that steady-state may have been reached by Day 7. Both 4 and 12 g treatments showed that diclofenac concentrations 'leveled out' on Day 7.

Profile of average concentrations of diclofenac versus time, day 7



A: 4 g on 1 knee; B: 12 g on 2 knees and 2 hands; C: diclofenac sodium 50-mg tablets

2.2.2.5 What is the relative bioavailability of the gel?

Study VOSG-PE-113 assessed a relative bioavailability of this gel against a 50-mg enteric-coated diclofenac tablet. Both treatments were taken either 4 (gel) or 3 (tablet) times daily for 7 days. On Day 7, diclofenac Cmax and AUC parameters were compared.

For the maximum-likely-use scenario, i.e., 12 g applied 4 times daily, the diclofenac Cmax and AUC exposure (without taking into account the dose administered) were approximately 2 and 20%, respectively, compared to that of the 50-mg enteric-coated diclofenac tablet.

Diclofenac plasma: Day 7

Treatment	Cmax (ng/mL)	AUC0-24 (ng•h/mL)
A (N=39)	15.0 ± 7.33	233 ± 128
B (N=39)	53.8 ± 32.0	807 ± 478
C (N=39)	2270 ± 778	3890 ± 1710

A: 4 g on 1 knee; B: 12 g on 2 knees and 2 hands; C: diclofenac sodium 50-mg tablets

Comparison of diclofenac plasma PK: Day 7

Comparison	Cmax (%)	AUC0-24 (%)
A/C (N=39)	0.633 (0.548-0.733)	5.79 (5.00-6.70)
B/C (N=39)	2.21 (1.91-2.56)	19.7 (17.0-22.8)

A: 4 g on 1 knee; B: 12 g on 2 knees and 2 hands; C: diclofenac sodium 50-mg tablets

Voltaren 1% gel has 10 mg of diclofenac in 1 g of gel. The total daily amount of Voltaren gel applied was 48 g. This amounts to 480 mg of diclofenac applied topically daily. Similarly the oral diclofenac daily intake was 150 mg.

Using the mass amount administered via the topical or oral routes, the relative bioavailability of the Voltaren gel was calculated to be approximately 6.5%, compared to that of the oral IR tablet formulation.

*Relative BA = [(807 ng.h/mL /3890 ng.h/mL) x (150 mg/480 mg)]

2.2.2.6 What are the characteristics of drug metabolism?

Once diclofenac reaches the general circulation, diclofenac is metabolized primarily by conjugation or by hydroxylation of one or both of the benzene rings with subsequent conjugation.

2.2.2.7 What are the characteristics of drug excretion?

Diclofenac and its metabolites are excreted by urinary route. As stated before, the dose adjustment may not be necessary in subjects with renal impairment.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Diclofenac is metabolized primarily by conjugation-glucuronidation or by hydroxylation of one or both of the benzene rings with subsequent conjugation. Diclofenac and its metabolites are excreted by urinary route. Generally subjects with hepatic and/or renal impairments, including elderly subjects who will have reduced liver or kidney functions, may require reduced doses of diclofenac.

For Voltaren gel, the diclofenac systemic exposure at maximum usage (two knees and two hands) was approximately 20% of that of the 50 mg diclofenac tablet. Therefore, the dose adjustment may not be necessary in subjects with hepatic and/or renal impairments.

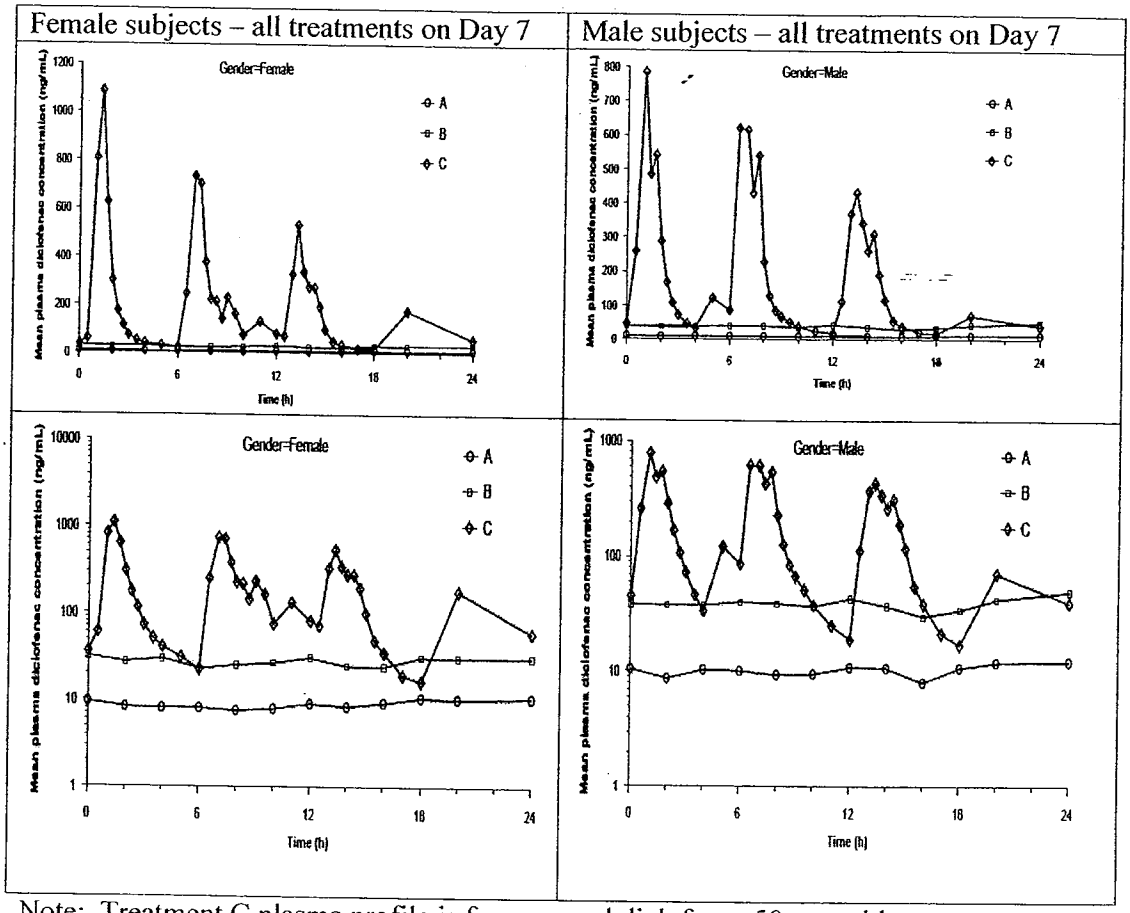
2.3.1.1 What is the status of pediatric studies and/or any pediatric plan for study?

The Applicant requested a waiver for pediatric population. The Applicant indicated that there is no apparent reported incidence of osteoarthritis of the superficial joints in subjects below the age of 18 years, and stated that the Voltaren is not likely to be used in a substantial number of pediatric patients. The Applicant stated that the paucity of pediatric patients available would also make recruitment for the conduct of studies difficult or impossible.

2.3.1.2 Gender

No clinical pharmacology studies were conducted to assess gender differences. However, in **Study VOSG-PE-113** a sub-analysis in gender was performed by a visual inspection of the diclofenac plasma profiles. The visual inspection of the plasma profiles indicated that there were no differences observed between female and male diclofenac concentrations on Day 7.

Comparison of profiles based on gender: 4 g (A) vs. 12 g (B) on Day 7:



Note: Treatment C plasma profile is from an oral diclofenac 50-mg tablet

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and what is the impact of any differences in exposure on pharmacodynamics?

Diclofenac degrades if it is exposed to light which can decrease the diclofenac efficacy. There were no in vivo studies submitted to address the degradation and photo-degradant issues. As with other topical diclofenac products, the Voltaren gel photo-stability issues will be discussed in CMC review. Accordingly, the issues involving the photo-degradants and photo-toxicity will be addressed in the Pharmacology/Toxicology review.

Meanwhile, the photo-toxicity issue can be addressed in the Labeling by recommending subjects to avoid sun exposure after Voltaren Gel application.

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Plasma and urine diclofenac and its metabolite, 4'-hydroxydiclofenac, were assayed in each sample using a validated LC/MSMS method with a limit of quantification (LOQ) of 0.5 ng/mL (plasma) and 3 ng/mL (urine).

For the standard curve generation, the following concentration levels were used for diclofenac in human plasma samples and for diclofenac and 4'-hydroxydiclofenac in human urine samples, respectively: 0.5, 2, 10, 20, 60, 100, 150, and 200 ng/mL, and 3, 6, 10, 20, 60, 200, 600, and 2000 ng/mL. The calibration curves were constructed daily. The parameters of the calibration line were obtained by linear least squares regression with a weighting factor of 1/C. The measurement error (%) computed for each calibration level was not allowed to fall outside of +20 % of the nominal value for the lowest level and +16 % for the other. The coefficient of determination had to be higher than 0.96, no more than two outliers could be discarded, and at least eight calibration levels had to be used unless duly documented. The LLOQ was 0.5 ng/mL for diclofenac in human plasma samples and 3 ng/mL for diclofenac and total 4'-hydroxydiclofenac in human urine samples.

The following quality control (QC) samples were prepared for diclofenac human plasma and diclofenac and 4'-hydroxydiclofenac urine samples, respectively: 1, 40, and 160 ng/mL, and 9, 40, and 1200 ng/mL.

The typical results for the standard curves of diclofenac in human plasma and urine are as follows:

Back-calculated concentrations (ng/mL) of diclofenac in human plasma:

	Cal at 0.500 ng/mL	Cal at 2.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 50.0 ng/mL	Cal at 100 ng/mL	Cal at 150 ng/mL	Cal at 200 ng/mL
Mean	0.505	1.89	9.33	18.7	50.9	101	152	214
S.D.	0.0271	0.0961	0.379	0.666	1.59	3.69	5.84	8.05
CV %	5.37	5.08	4.06	3.56	3.12	3.65	3.84	3.76
RE %	1.00	-5.50	-6.70	-6.50	1.80	1.00	1.33	7.00

* Deactivated, not used for calculations

Back-calculated concentrations (ng/mL) of diclofenae in human urine:

	Cal at 3.00 ng/mL	Cal at 6.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 60.0 ng/mL	Cal at 200 ng/mL	Cal at 600 ng/mL	Cal at 2000 ng/mL
Mean	2.99	6.03	10.00	20.3	61.02	208	612	1907
S.D.	0.0784	0.136	0.5310	0.794	1.564	5.56	18.3	66.1
CV %	2.62	2.26	5.31	3.91	2.56	2.67	3.00	3.47
RE %	-0.33	0.55	0.00	1.40	1.70	4.20	2.03	-4.65

* Deactivated, not used for calculations

Back-calculated concentrations (ng/mL) of 4'-hydroxydiclofenac in human urine:

	Cal at 3.00 ng/mL	Cal at 6.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 60.0 ng/mL	Cal at 200 ng/mL	Cal at 600 ng/mL	Cal at 2000 ng/mL
Mean	2.98	6.14	9.81	20.5	60.9	208	609	1897
S.D.	0.125	0.287	0.514	1.06	1.46	6.72	19.8	102
CV %	4.20	4.66	5.24	5.16	2.40	3.23	3.25	5.36
RE %	-0.60	2.40	-1.88	2.65	1.43	4.00	1.57	-5.15

* out of criteria, not used for calculations

The typical results for the QC samples of diclofenac in human plasma and urine are as follows:

Diclofenac in human plasma:

Curve number	QC at 1 ng/mL	QC at 40 ng/mL	QC at 160 ng/mL
Mean	0.969	40.9	178
SD	0.117	2.94	14
CV %	12.07	7.19	7.87

Diclofenac in human urine:

Curve number	QC at 9 ng/mL	QC at 40 ng/mL	QC at 1200 ng/mL
Mean	9.42	42.7	1157
SD	0.412	1.52	38.8
CV %	4.37	3.55	3.36

4'-hydroxydiclofenac in human urine:

Curve number	QC at 9 ng/mL	QC at 40 ng/mL	QC at 1200 ng/mL
Mean	8.96	39.8	1120
SD	0.861	5.04	81.9
CV %	9.61	12.66	7.31

3 Detailed Labeling Recommendations

10 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

4.2 Individual Study Review

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Study VOSG-PN-107

Title: A Steady-State, Randomized, 3-Period, 4-Treatment Crossover Systemic Bioavailability Study of Diclofenac Comparing Topical Diclofenac Sodium Gel, 1%, to the Same Treatment Plus Heat Application or Exercise, and to Topical Diclofenac Diethylamine Gel, 1.16%

Objectives:

- To determine the relative bioavailability of diclofenac following repeated applications of diclofenac sodium gel (DSG), 1% and diclofenac diethylamine gel (DDG), 1.16% (i.e., 4 g of gel over 400 cm^2 (one knee), qid for 7 days);
- To determine the effects of moderate exercise or applied heat on the systemic absorption of diclofenac following application of DSG, 1% (10 mg/cm^2, i.e., 4 g of gel over 400 cm^2 (one knee), qid for 7 days).

Study Design:

1. A single-center, randomized, open-label, multiple-dose, double 3-way crossover design,
2. 2 washout periods of 14 days each.
3. Subjects were at least 50 years, half of them at least 60 years of age, and the ratio male:female was 1:2.
4. 3 treatment periods of 7 days each, separated by 14-day washout periods. During each treatment period, trough blood samples were collected once a day from Day 1 to Day 7 and subsequently every 2 h through 24 h on Day 7 (except 22 h postdose); 24-h urine was collected on Day 7.
5. Plasma or urine diclofenac was assayed from each sample using a validated LC/MSMS method.
6. **4 g of a diclofenac gel was applied 4 times daily to one knee (400 cm^2)**, rubbed in for up to 1 minute until the gel had vanished. All subjects were scheduled to receive Treatment A (Diclofenac Sodium Gel, 1%, without heat or exercise), Treatment B (Diclofenac DEA Gel, 1.16%, without heat or exercise), and either Treatment C (Diclofenac Sodium Gel, 1%, application of moderate heat for 15 minutes prior to each gel application) or Treatment D (Diclofenac Sodium Gel, 1%, first application of each day was followed by 20-minutes of treadmill exercise).

← Screening period →	← Treatment period →				
Screening	Period 1	Washout 1	Period 2	Washout 2	Period 3
Within 21 days from Day 1	Days 1-7	Days 8-21	Days 22-28	Days 29-42	Days 43-49
Visit 1	Visits 2-8		Visits 9-15		Visits 16-22
Note: Length of washout described in study protocol as "at least 7 days".					

7. For all treatments, there were two groups which Group 1 will be administered Treatments A, B and C, and the other Group 2 will be administered Treatments A, B, and D. Within the group, treatments were crossed over:

Sequence No.	Period 1	Period 2	Period 3
Crossover 1 (A, B, C)			
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C
Crossover 2 (A, B, D)			
7	A	B	D
8	B	D	A
9	D	A	B
10	A	D	B
11	D	B	A
12	B	A	D

Note: Crossover 1 is Group 1-'heat' group ; and Crossover 2 is Group 2 – 'exercise' group.

8. Subject disposition for each group

	ABC Arm	ABD Arm
Total no. of subjects - n(%)		
Randomized	18 (100)	18 (100)
Exposed	18 (100)	18 (100)
Completed	18 (100)	16 (88.9)

9. Health status - by standard physical examination, and the measurement of blood pressure, heart rate, ECG and blood hematology and chemistry levels

Treatments: Treatments were to be applied at 7 AM, 12 AM, 5 PM and 10 PM.

1. Treatment A - DSG, 1%; control
2. *Treatment B - DDG, 1.16% (Voltaren® Emulgel™ - European product diethylamine gel*); control

3. Treatment C - DSG, 1%, with each application each day preceded by moderate heat for 15 minutes to the site of application;
4. Treatment D - DSG, 1%, with the first application each day followed by 20 minutes of moderate exercise on a treadmill.

Inclusion criteria:

1. Aged greater than or equal to 50, with 50% of subjects at least 60 years of age,
2. Male or female, in a ratio male:female of 1:2,
3. Having a body mass index (BMI) between 18 and 30 kg/m^2,
4. In good physical and mental health status, based on medical history and physical examination,
5. Having blood pressure and heart rate (supine and standing) within the normal ranges, or considered as normal by the investigator,
6. Having a normal ECG,
7. Having laboratory parameters within the normal ranges of the testing laboratory (the Investigator could include a volunteer having values outside the accepted range if, in his opinion, these values were not clinically relevant),
8. Having signed an informed consent form prior to initiation of any trial procedure, (for women of childbearing potential) using a known, effective means of contraception for at least 5 weeks before, during, and 1 month after the end of the trial,
9. (for women) presenting a negative pregnancy test at screening and having signed a pregnancy waiver form,
10. Being sufficiently cooperative and reliable, in the opinion of the Investigator, to adhere to protocol requirements.

Exclusion criteria:

1. Treated with systemic or local diclofenac within 2 weeks of study Day 1,
2. Requiring treatment with any topical or systemic medication during the study period other than hormone replacement therapy (HRT) and contraceptives,
3. Any active concomitant cardiac, gastrointestinal, renal, hepatic, coagulation, or any other clinically relevant disorder that could compromise the subject's welfare or confound the study results, known hypersensitivity of the skin,
4. Skin lesions, wounds or excessive pilosity at the application site,
5. History of drug addiction (positive drug screen) or excessive use of alcohol (weekly intake in excess of 28 units alcohol; one unit alcohol equals a glass of beer, a glass of wine or a measure of spirits), or heavy tobacco smoking (more than 15 cigarettes/day), or psychological or other emotional problems that were likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements,
6. History of allergy to diclofenac or related drugs (e.g., nsaids including aspirin), or to any other ingredient of the study medications, or clinically relevant allergic reactions of any origin,

7. Participated in another clinical trial or donated blood within 30 days of study Day 1, or previous participation in this trial,
8. Positive HIV1 or HIV2 serology,
9. Positive results from the hepatitis serology, indicative of acute or chronic hepatitis B or hepatitis C,
10. Unsuitable veins for repeated venipuncture,
11. Pregnant or in ongoing lactation.

Pharmacokinetics:

1. Blood samples during each treatment period:
    a. On Days 1 to 6, immediately prior to the morning dose;
    b. On Day 7, immediately prior to the morning dose and then every 2 h through 24 h, except after 22 h;
2. Urine samples during each treatment period:
    a. On Day 1, one sample prior to the morning dose;
    b. On Day 7, all fractions between first dose and 24 h later.
3. Plasma and urine diclofenac were assayed in each sample using a validated LC/MSMS method with a limit of quantification (LOQ) of 0.5 ng/mL (plasma) and 3 ng/mL (urine).

Analysis: Diclofenac in plasma at steady state (i.e. last day of application of each period) and derived PK parameters (Cmax, tmax, Cmin, AUC0-24, PTF), Ae0-24 for free diclofenac and 4'-OH-diclofenac in urine during the last day of each period.

Safety: Monitoring and recording of all adverse events (AEs), and pre- and post-study monitoring of vital signs and physical condition.

Statistical methods: Descriptive statistics on subject disposition, baseline characteristics and extent of exposure.

Summary statistics for all PK parameters by treatment: Comparison of Treatment B vs A, C vs A, and D vs A, using ANOVA on ln-transformed continuous parameters (Cmax, Cmin, AUC0-24, PTF, Ae), including the factors sequence, subject, period, and treatment yielding 90% confidence interval on test/reference ratios; Wilcoxon signed rank test for tmax.

Results:

1. Demographics

	Group 1 – (ABC arm)	Group 2 – (ABD arm)
	(N=18)	(N=18)
Sex - n (%)		
Male	6 (33.3)	6 (33.3)
Female	12 (66.7)	12 (66.7)
Race - n (%)		
Caucasian	18 (100)	18 (100)
Mean age (yr)	61.6	61.9
SD	7.2	8.6
Range	50.2-78.7	52.3-78.5
Mean weight (kg)	68.6	64.1
SD	8.4	12.9
Range	57.4-90.5	47.5-92.4
Mean height (cm)	165.8	162.0
SD	8.1	7.5
Range	155.0-183.0	148.0-176.5
Mean BMI (kg/m2)	24.9	24.2
SD	2.4	3.2
Range	21.0-29.1	19.5-29.7

The gel was usually applied to the right knee, with 4 exceptions: subject 15 because of a fall, subject 16 because of a wound on the right knee, subject 32 during period 3 because of an AE, and subject 33 because of braces on the right leg. Steady-state was not reached by Day 7, therefore, Cmin and PTF were not presented in the body of the present report.

2. Assay

Plasma and urine diclofenac were assayed in each sample using a validated LC/MSMS method with a limit of quantification (LOQ) of 0.5 ng/mL (plasma) and 3 ng/mL (urine). (DETERMINATION OF DICLOFENAC IN LITHIUM HEPARIMISED HUMAN PLASMA SAMPLES AND OF DICLOFENAC AND TOTAL 4'-HYDROXYDICLOFENAC IN HUMAN URINE SAMPLES COLLECTED DURING NOVARTIS CONSUWIER HEALTH S.A. STUDY NO. VOSG-PN-107)

Calibration curves

a. The concentration levels were: 0.5, 2, 10, 20, 60, 100, 150, and 200 ng/mL for diclofenac in human plasma samples and 3, 6, 10, 20, 60, 200, 600, and 2000 ng/mL for diclofenac and 4'-hydroxydiclofenac in human urine samples.
b. Calibration curves were constructed daily.

c. The parameters of the calibration line were obtained by linear least squares regression with a weighting factor of 1/C.
d. The measurement error (%) computed for each calibration level was not allowed to fall outside of +20 % of the nominal value for the lowest level and +16 % for the other.
e. The coefficient of determination had to be higher than 0.96, no more than two outliers could be discarded, and at least eight calibration levels had to be used unless duly documented.
f. The LLOQ was 0.5 ng/mL for diclofenac in human plasma samples and 3 ng/mL for diclofenac and total 4'-hydroxydiclofenac in human urine samples.

Quality control samples

a. 1, 40, and 160 ng/mL for diclofenac in human plasma samples
b. 9, 40, and 1200 ng/mL for diclofenac and 4'-hydroxydiclofenac in human urine samples
c. In order to be acceptable, any series of study samples had to be bracketed by valid QC samples (three before and three after). No more than two out of six QCs {and not both at the same concentration) could fall outside of +/_15 % of the nominal value for all levels.

Quality control samples of diclofenac in human plasma

Curve Number	QC at 1.00 ng/mL	QC at 40.0 ng/mL	QC at 160 ng/mL
Mean	0.969	40.9	178
S.D.	0.117	2.94	14.0
CV %	12.07	7.19	7.87
RE %	-3.10	2.25	11.25

* : Rejected because of poor chromatography, not used for calculations
# : Out of acceptance criteria (> 15 %), used for calculations

Quality control samples of diclofenac in human urine

Curve Number	QC at 9.00 ng/mL	QC at 40.0 ng/mL	QC at 1200 ng/mL
Mean	9.42	42.7	1157
S.D.	0.412	1.52	38.8
CV %	4.37	3.55	3.36
RE %	4.62	6.63	-3.58

Quality control samples of 4'-hydroxydiclofenac in human urine

Curve Number	QC at 9.00 ng/mL	QC at 40.0 ng/mL	QC at 1200 ng/mL
Mean	8.96	39.8	1120
S.D.	0.861	5.04	81.9
CV %	9.61	12.66	7.31
RE %	-0.46	-0.48	-6.67

#: Out of acceptance criteria (> 15 %), used for calculations

Back-calculated concentrations (nglmL) of diclofenac in human plasma

	Cal at 0.500 ng/mL	Cal at 2.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 50.0 ng/mL	Cal at 100 ng/mL	Cal at 150 ng/mL	Cal at 200 ng/mL
Mean	0.505	1.89	9.33	18.7	50.9	101	152	214
S.D.	0.0271	0.0961	0.379	0.666	1.59	3.69	5.84	8.05
CV %	5.37	5.08	4.06	3.56	3.12	3.65	3.84	3.76
RE %	1.00	-5.50	-6.70	-6.50	1.80	1.00	1.33	7.00

* Deactivated, not used for calculations

Back-calculated concentrations (nglmL) of diclofenae in human urine

	Cal at 3.00 ng/mL	Cal at 6.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 60.0 ng/mL	Cal at 200 ng/mL	Cal at 600 ng/mL	Cal at 2000 ng/mL
Mean	2.99	6.03	10.00	20.3	61.02	208	612	1907
S.D.	0.0784	0.136	0.5310	0.794	1.564	5.56	18.3	66.1
CV %	2.62	2.26	5.31	3.91	2.56	2.67	3.00	3.47
RE %	-0.33	0.55	0.00	1.40	1.70	4.20	2.03	-4.65

* Deactivated, not used for calculations

Back-calculated concentrations (nglmL) of 4'-hydroxydiclofenac in human urine

	Cal at 3.00 ng/mL	Cal at 6.00 ng/mL	Cal at 10.0 ng/mL	Cal at 20.0 ng/mL	Cal at 60.0 ng/mL	Cal at 200 ng/mL	Cal at 600 ng/mL	Cal at 2000 ng/mL
Mean	2.98	6.14	9.81	20.5	60.9	208	609	1897
S.D.	0.125	0.287	0.514	1.06	1.46	6.72	19.8	102
CV %	4.20	4.66	5.24	5.16	2.40	3.23	3.25	5.36
RE %	-0.60	2.40	-1.88	2.65	1.43	4.00	1.57	-5.15

* out of criteria, not used for calculations

3. Safety: Adverse events are summarized in the table below:

	DS Gel (A)	Diclofenac DEA Gel (B)	DS Gel + heat (C)	DS Gel + exercise (D)	A+C+D
	n (%)	n (%)	n (%)	n (%)	n (%)
total no. of subjects	36 (100)	36 (100)	18 (100)	17 (100)	36 (100)
no. with AEs	14 (39)	12 (33)	3 (17)	5 (29)	18 (50)
no. with suspected-related AEs	7 (19)	3 (8)	0 (0)	3 (18)	10 (28)
no. with moderate AEa	1 (3)	2 (6)	0 (0)	0 (0)	1 (3)
no. with local intolerance	5 (14)	3 (8)	0 (0)	2 (12)	7 (19)

- One adverse event led to the withdrawal of a subject: a moderate contact dermatitis on the application site, suspected to be related to the study drug, which occurred after application of diclofenac DEA gel and again after application of diclofenac sodium gel.
- Most suspected-related AEs related to local intolerance, which was observed in eight subjects (22%), after application of both diclofenac sodium and diclofenac DEA gels; most common events were application site dryness, application site reaction, and contact dermatitis.
- At discharge, abnormal vital signs were measured in 8 subjects. All these abnormalities were retested within normal limits or deemed not clinically relevant by the investigator. Physical examination performed at the end of the study did not reveal any abnormality except for the contact dermatitis that led to the subject withdrawal.

4. Plasma profiles

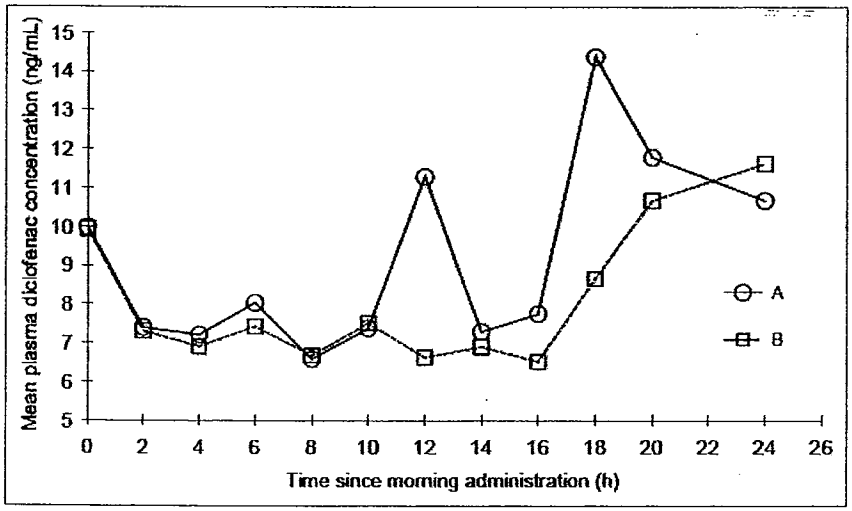
Comments:

a. In the plasma samples from two subjects, the diclofenac concentrations were high; Subject 21 had a plasma diclofenac concentration of — ng/mL on Day 7, 18 h post morning dose of Treatment A. The previous value was — ng/mL 16 h postdose and the next value was — ng/mL 20 h postdose.
b. Subject 31 had a plasma diclofenac concentration of — ng/mL on Day 7, 12 h post morning dose of Treatment A. The previous value was — ng/mL 10 h postdose and the next value was — ng/mL 14 h postdose.
c. It is not clear if steady-state was achieved by Day 7
d. The profile of the first 3 doses on day 7 followed a wave-like pattern in which there is a dropoff in concentration, which then reversed, reaching a peak 6 h after each dose. After the final dose, there was no dropoff, and the concentration remained high through 24h.
e. The wave-like pattern was less obvious in the profiles of the individual subjects, but the increase during the night was present in most subjects. The profiles of the different treatments were generally quite similar within subjects. The average

concentrations during Day 7 were similar in treatments A, B, and D. Concentrations achieved with Treatment C were minimally lower than with Treatment A.

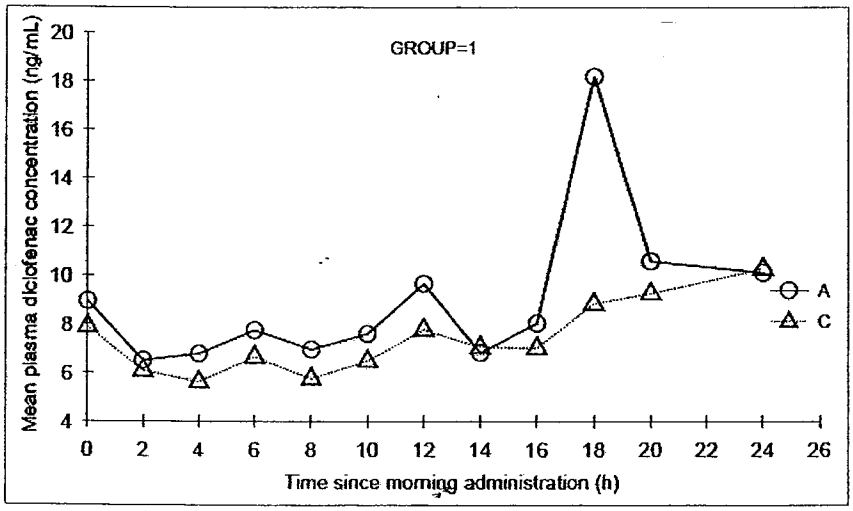
Profiles from using all data points:

Overall Profile of ave conc of diclofenac vs time, Day 7
Trt A vs Trt B – Combined all subjects



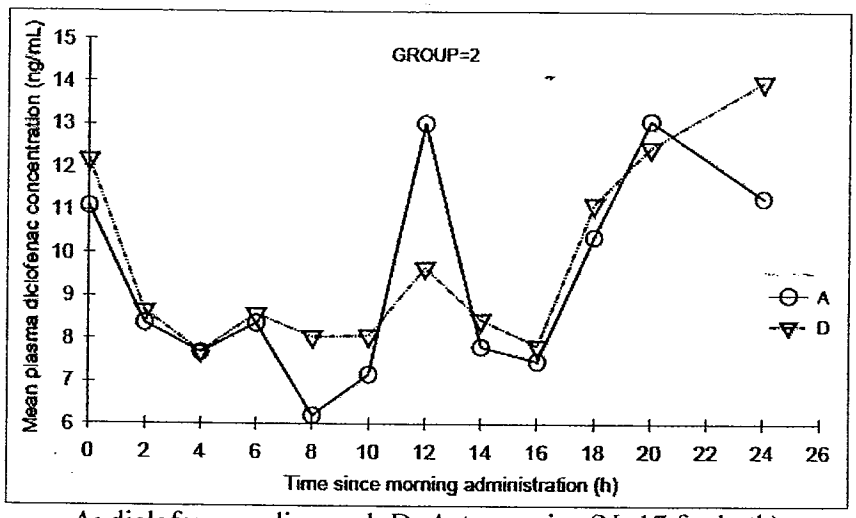
A: diclofenac sodium gel; B: diclofenac DEA gel (N=35)
Include original data points for Subject 21 (18-h value) and Subject 31 (12-h value).

Profile of ave conc of diclofenac versus time, Day 7 - Trt A vs Trt C in Group 1 only



A: diclofenac sodium gel; C: A + heat (N=18 for both)

Profile of ave conc of diclofenac vs time, Day 7 – Trt A vs Trt D in Group 2 only

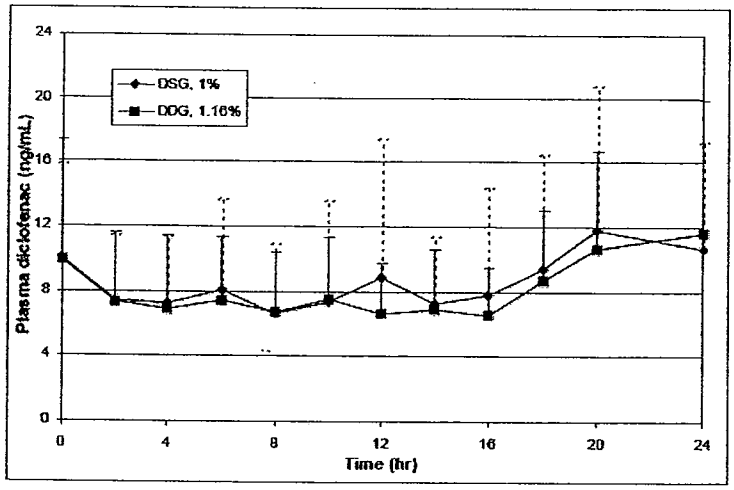


A: diclofenac sodium gel; D: A + exercise (N=17 for both)

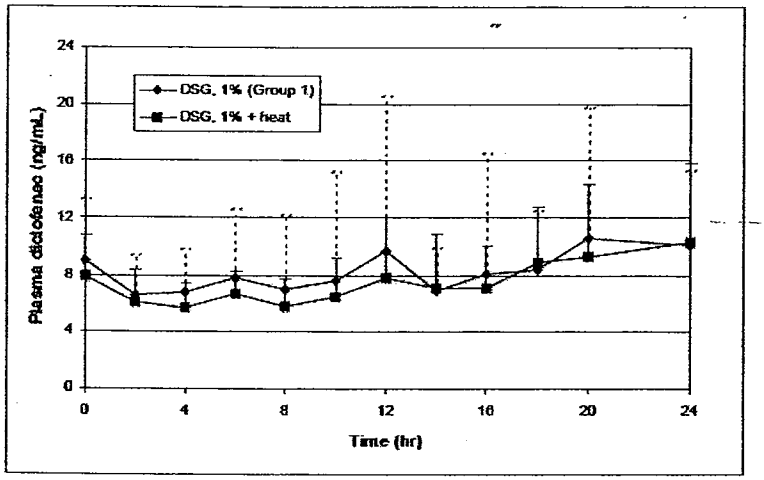
Profiles without the 2 'outlier' concentration timepoints (See above Comments # a and b)

The following profiles excluded the 2 'outlier' concentration points from Subject 21 (18-h value) and Subject 31 (12-h value).

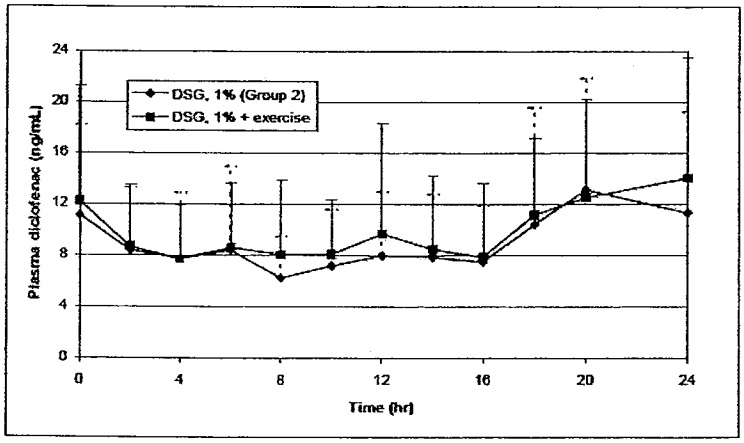
Day 7 Mean (+SD) plasma diclofenac conc (ng/mL) vs. time (hr) for all subjects who received Trts A and B



Day 7 Mean (+SD) plasma diclofenac conc (ng/mL) vs. time (hr) for Trts A and C (heat) in Group 1



Day 7 Mean (+SD) plasma diclofenac conc (ng/mL) vs. time (hr) for Trts A and D (exercise) in Group 2



5. PK parameters:

Descriptive statistics of PK parameters in plasma (Mean ± SD, except for tmax: median (range)

Treatment	Cmax (ng/mL)	tmax (h)	AUC0-24 (ng•h/mL)
A (N=35)	22.2 ± 33.3	18 (0-24)	222 ± 140
A (N=35)*	15.7 ± 11.9	18 (0-24)	207 ± 117
B (N=35)	14.0 ± 8.86	20 (0-24)	194 ± 95.9
C (N=18)	13.3 ± 5.63	20 (0-24)	179 ± 63.2
D (N=17)	16.8 ± 10.1	18 (0-24)	234 ± 134
A# from Group 1 only (N=18)	24.5 ± 42.0	19 (0-24)	218 ± 148
A# from Group 2 only (N=17)	19.8 ± 21.5	18 (0-24)	226 ± 135

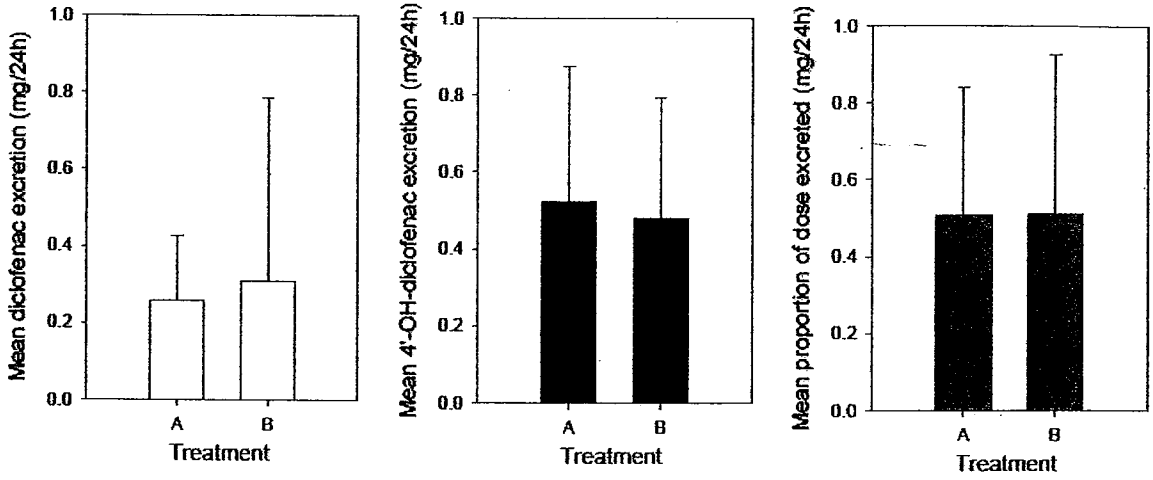
*: Without the 2 'outlier' concentrations from Subjects 21 and 31
#: Group 1 – Trts A, B, and C; Group 2 – Trts A, B, and D.

Descriptive statistics of PK parameters in urine

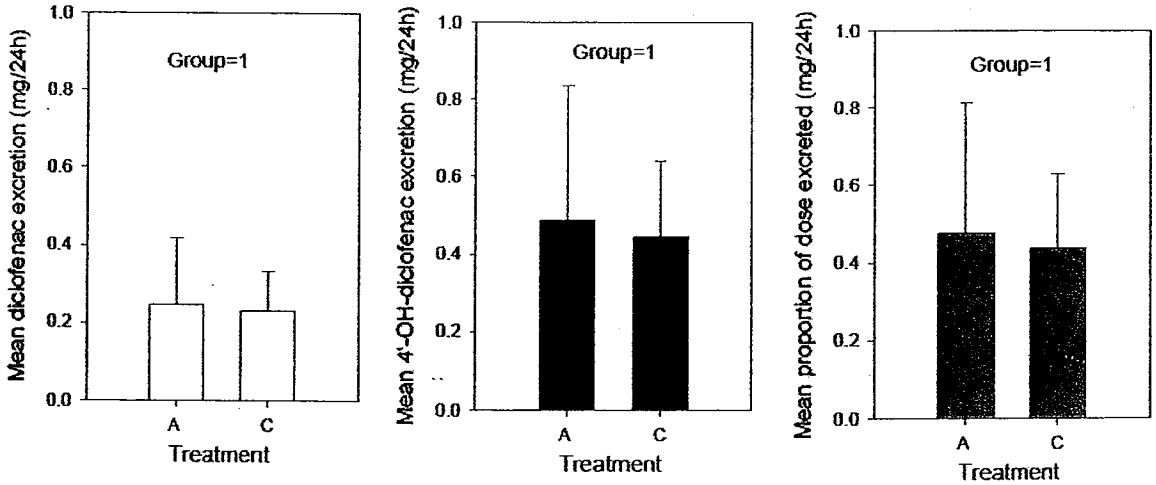
Treatment	Ae0-24 diclofenac (mg)	Ae0-24 4'-OH-diclofenac (mg)	Proportion excreted (% dose)
A (N=35)	0.26 ± 0.17	0.52 ± 0.35	0.51 ± 0.34
B (N=35)	0.31 ± 0.48	0.48 ± 0.32	0.51 ± 0.42
C (N=18)	0.23 ± 0.10	0.44 ± 0.20	0.44 ± 0.19
D (N=17)	0.26 ± 0.18	0.56 ± 0.42	0.53 ± 0.39
A from Group 1 only (N=18)	0.25 ± 0.17	0.49 ± 0.35	0.48 ± 0.34
A from Group 2 only (N=17)	0.27 ± 0.17	0.56 ± 0.37	0.54 ± 0.34

A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise
Groups 1 and 2 include subjects who were assigned to sequences with Treatments C and D, respectively; Mean ± SD

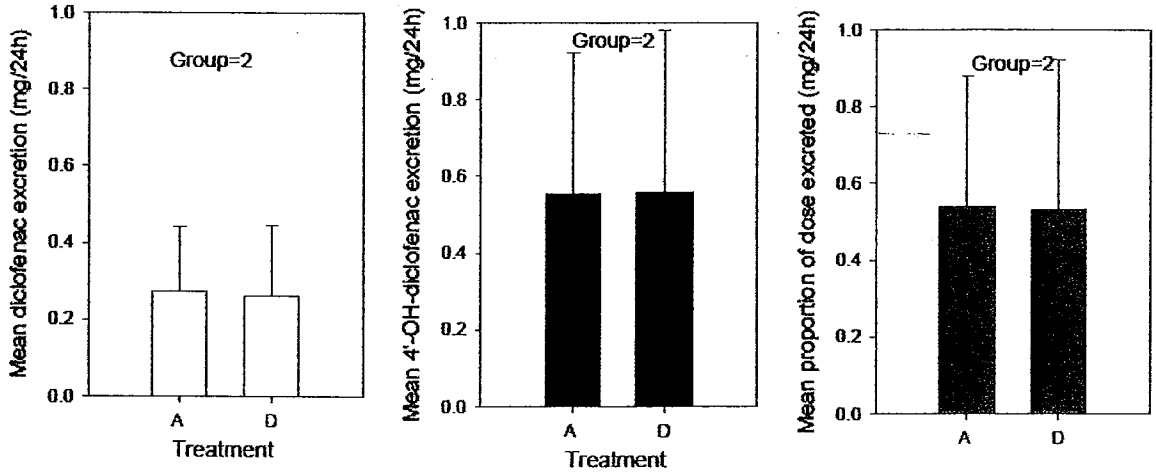
Average 24-h urinary excretion of diclofenac and 4'-OH-diclofenac, and proportion of diclofenac amount excreted in urine for treatments A and B
A: diclofenac sodium gel; B: diclofenac DEA gel
(Values are arithmetic means; error bars are SD; N=35.)



Average 24-h urinary excretion of diclofenac and 4'-OH-diclofenac, and proportion of diclofenac amount excreted in urine for treatments A and C in Group 1
Group 1 includes subjects who were assigned to sequences with Treatment C
A: diclofenac sodium gel; C: A + heat;
(Values are arithmetic means, error bars are SD; N=18.)



Average 24-h urinary excretion of diclofenac and 4'-OH-diclofenac, and proportion of diclofenac amount excreted in urine for treatments A and D in Group 2
Group 2 includes subjects who were assigned to sequences with Treatment D
A: diclofenac sodium gel; D: A + exercise;
(Values are arithmetic means, error bars are SD; N=17)



Comparison between treatments

Parameters from treatments were compared using the least squares mean and ANOVA.

Conversion to least squares means of diclofenac PK parameters in plasma

	Cmax	AUC0-24
Treatment	(ng/mL)	(ng•h/mL)
A (N=34)	13.8 (10.6-18.0)	187 (153-229)
B (N=34)	11.8 (9.04-15.3)	170 (139-208)
C (N=18)	12.2 (8.40-17.8)	169 (132-218)
D (N=16)	13.9 (9.37-20.5)	196 (142-271)
A Group 1 (N=18)	13.6 (9.33-19.8)	183 (142-235)
A Group 2 (N=16)	14.0 (9.44-20.7)	191 (139-264)

A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise
Groups 1 and 2 include subjects assigned to sequences with Treatments C and D, respectively; Least squares geometric mean (95% confidence interval) derived from ANOVA

Conversion to least squares means of diclofenac and 4'-OH-diclofenac PK parameters in urine

	Ae0-24 diclofenac	Ae0-24 4'-OH-diclofenac	Proportion excreted
Treatment	(mg)	(mg)	(% dose)
A (N=34)	0.21 (0.17-0.27)	0.43 (0.34-0.53)	0.42 (0.33-0.53)
B (N=34)	0.21 (0.16-0.27)	0.40 (0.32-0.49)	0.40 (0.32-0.51)
C (N=18)	0.21 (0.16-0.28)	0.41 (0.32-0.53)	0.40 (0.31-0.52)
D (N=16)	0.23 (0.17-0.30)	0.48 (0.36-0.64)	0.46 (0.35-0.61)
A from Group 1 only (N=18)	0.20 (0.16-0.27)	0.40 (0.31-0.52)	0.39 (0.31-0.51)
A from Group 2 only (N=16)	0.23 (0.17-0.30)	0.47 (0.35-0.62)	0.45 (0.34-0.60)

A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise
Groups 1 and 2 include subjects assigned to sequences with Treatments C and D, respectively; Least squares geometric mean (95% confidence interval) derived from ANOVA

Least squares geometric mean ratios of Treatments B, C and D vs. Treatment A and associated 90% CIs shown below.

Comparison of diclofenac PK parameters in plasma

	Cmax	AUC0-24
Comparison	(%)	(%)
B/A (N=34)	85.3 (69.3-105)	90.7 (82.7-99.5)
C/A (N=18)	90.0 (61.9-131)	92.5 (77.3-111)
D/A (N=16)	99.2 (74.6-132)	103 (87.8-120)

A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise

Comparison of diclofenac and 4'-OH-diclofenac PK parameters in urine

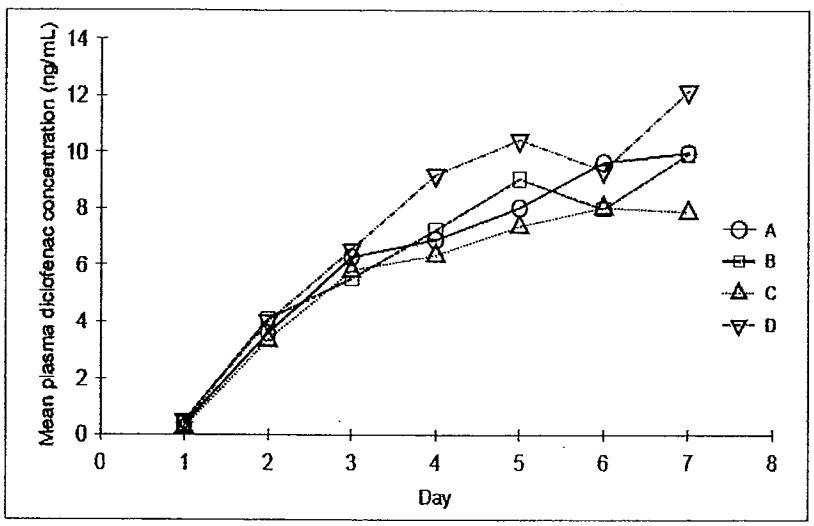
	Ae0-24 diclofenac	Ae0-24 4'-OH-diclofenac	Proportion excreted
Treatment	(%)	(%)	(%)
B/A (N=34)	97.0 (79.8-118)	93.2 (84.6-103)	96.6 (83.0-112)
C/A (N=18)	105 (93.4-117)	102 (91.2-114)	103 (92.1-115)
D/A (N=16)	99.2 (83.0-119)	104 (92.6-116)	102 (89.4-115)

A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise

Although ANOVA indicated that the treatment groups are different, diclofenac exposure did not increase due to heat and exercise, which is the main concern.

6. Steady-state

It is difficult to tell if the true steady-state was achieved by Day 7, by looking at the increased diclofenac concentration from Day 6 to 7.



Values are arithmetic means, N=36 for A and B, N=18 for C; N=17 for D; A: diclofenac sodium gel; B: diclofenac DEA gel; C: A + heat; D: A + exercise; Source:

Conclusions

No clinically relevant difference in systemic exposure was observed when heat or exercise was applied concomitantly to the diclofenac sodium gel treatment.

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Study VOSG-PE-113

Title: A Steady-State, Randomized, Open-Label, 3-Period, 3-Treatment Crossover Systemic Bioavailability Study of Diclofenac Comparing Topical Diclofenac Sodium Gel, 1%, Applied to One Knee vs. Two Knees and Two Hands (Maximum Dose) and vs. Oral Diclofenac Sodium Tablets (50 mg Enteric-coated) in Normal Healthy Volunteers

Objectives:

- To compare the systemic BA of diclofenac of repeated applications of DSG, 1%, qid, to one knee, 2 knees and 2 hands (maximum exposure), and repeated oral dosing of diclofenac sodium 50 mg tablets, tid.
- To compare accumulation of diclofenac in urine only from day 1 to day 7;

• To assess the effects of the different treatments on platelet aggregation and on COX1 and COX2 in blood as reflected by plasma thromboxane (TXB2) and prostaglandin E_2 (PGE2), respectively;

Study design:

Screening period	←——— **Treatment period** ———→					**Follow-up period[1]**
Screening	Period 1	Washout 1	Period 2	Washout 2	Period 3	Follow-up
Within 21 days from study day 1	Study days 1-7	Study days 8-21	Study days 22-28	Study days 29-42	Study days 43-49	Study days 70, 77, 84

[1] Only for subjects having received topical treatment during period 3

Treatment sequences

Sequence No.	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

Inclusion/Exclusion criteria:

Healthy volunteers ≥ 50 years old, with a BMI between 18 and 30 kg/m². At least 50% of subjects had to be ≥ 60 years old and 50% - 70% of them had to be female.

Treatments:

Treatment A - DSG, 1%, 10 mg/cm^2 applied to one knee (~400 cm^2 i.e., 4 g), qid for 7 days, (exposure 16 g of gel/day over 400 cm2);

Treatment B - DSG, 1%, 10 mg/cm^2 applied to both knees (~800 cm^2 i.e., 8 g) and to both hands (~400 cm^2 i.e., 4 g), qid for 7 days, (exposure 48 g of gel/day over 1200 cm^2);

Treatment C – diclofenac sodium 50 mg enteric coated tablets taken orally tid for 7 days, (exposure 150 mg of diclofenac/day);

Topical treatments were to be applied at 7 AM, 12 AM, 5 PM and 10 PM; the oral tablets were to be taken at 7 AM, 1 PM and 7 PM.

Pharmacokinetic analysis and sampling:

Blood samples:

• on days 1, 2 (except for treatment B) and days 5 through 7: prior to the morning dose;
• on day 1 (treatment B) and day 7 (treatments A and B): every 2 h through 24 h post-dose (except at 22 h);
• on day 7 (treatment C): at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 6.5, 7, 7.33, 7.67, 8, 8.33, 8.67, 9, 9.5, 10, 11, 12, 12.5, 13, 13.33, 13.67, 14, 14.33, 14.67, 15, 15.5, 16, 17, 18, 20, and 24 h post-dose;
• on days 28, 35, and 42 (for subjects treated with treatment A or B during period 3): in the morning.

Urine samples:

• on day 1, one sample prior to the morning dose;
• on day 1 (treatments A and B) and day 7 (all treatments), all voided urine for 24 h after first dose.

Diclofenac in plasma and diclofenac and 4'-OH metabolite in urine were assayed using a validated LC/MSMS method with a lower limit of quantification (LLOQ) of 0.5 ng/mL for plasma and 3 ng/mL, for urine.

PK analysis:

• concentration profile of diclofenac in plasma and derived AUC0-24 on day 1 of treatment B,
• concentration profile of diclofenac in plasma at steady state (i.e. last day of application of each period) and derived PK parameters (Cmax, tmax, Cmin, AUC0-24, AUC0-tmax, Cav, PT F) on day 7 for each treatment,
• Ae0-24 for diclofenac and 4'-OH-diclofenac on day 1 (treatments A and B only) and on day 7,
• T_{BLOQ}, T5%Cmax and t½z derived from diclofenac concentrations on days 28, 35 and 42 in subjects under treatment A or B during period 3.

Results:

1. Demographics

	All subjects (N=40)
Sex - n (%)	
Male	20 (50.0)
Female	20 (50.0)
Race - n (%)	
Caucasian	40 (100)
Mean age (yr)	59.9
SD	5.7
Range	50-74
Mean weight (kg)	74.2
SD	12.3
Range	52-103
Mean height (cm)	169.7
SD	9.3
Range	147-187
Mean BMI (kg/m^2)	25.6
SD	2.7
Range	20.4-33.0

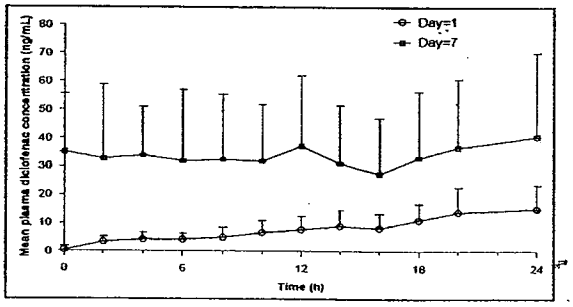
Three populations were defined: all randomized, safety, and PK (see Section 6.1.1, Populations). All 40 subjects were included in the first 2 populations (see Post-text table 7.3-1). Subject 132 was excluded from the PK population, but not from the safety population. Because she discontinued the study before day 7 of the first period, this subject contributed safety data but not PK data for treatment C (see Post-text table 7.3-2). Thus 39 of 40 subjects contributed PK and safety information for treatments A and B and 39 of 40 subjects contributed PK data for treatment C (see Post-text table 7.3-1).

Three subjects having received a topical treatment during period 3 did not agree to be included in the follow-up part of the study (see Section 6.1.1, Populations): subjects 108 and 137 (sequence B-C-A) and subject 130 (Sequence C-A-B). Those subjects did not contribute PK data for days 28, 35 and 42 of the last period, but had discharge assessments made on day 8 of the last period. A total of 22 subjects were included in the follow-up part of the study (11 having received treatment A and 11 having received treatment B during period 3).

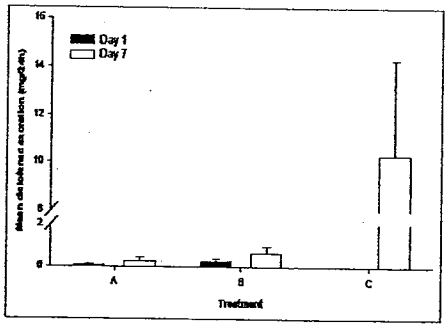
2. Plasma Profiles:

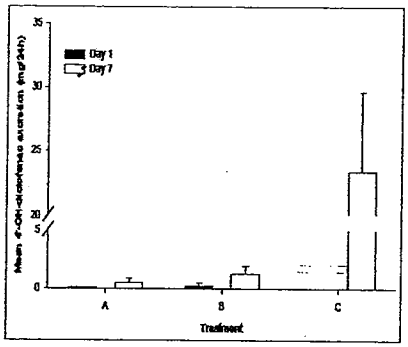
a. Day 1 vs. Day 7 comparison of Treatment B

Trt B: overall profile of avg. conc. of diclofenac vs. time, Day 1 and Day 7

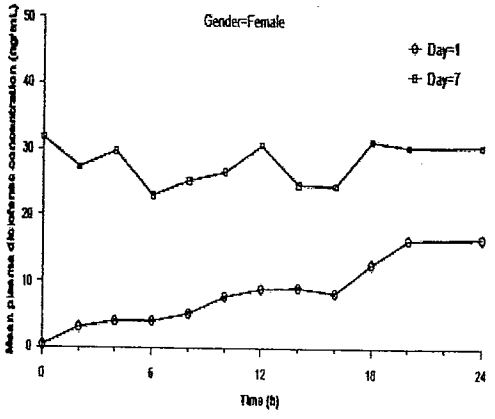
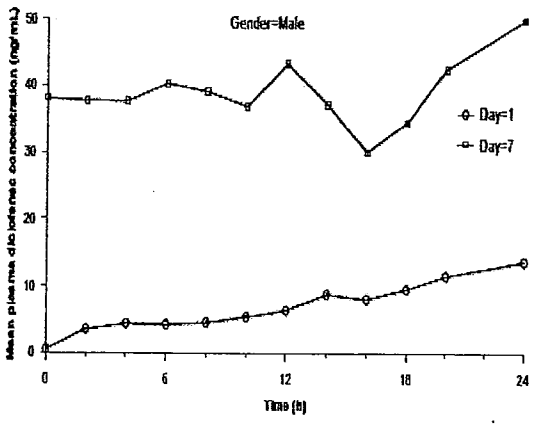


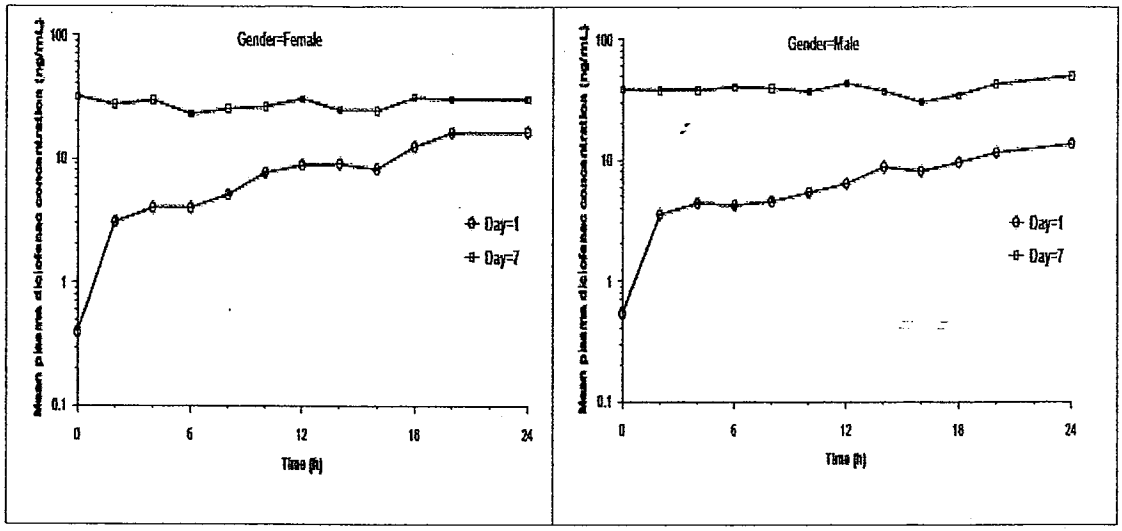
Average 24-h urinary excretion rate of diclofenac (left) and 4'-OH-diclofenac



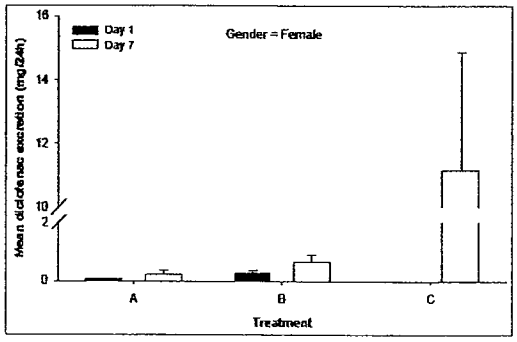


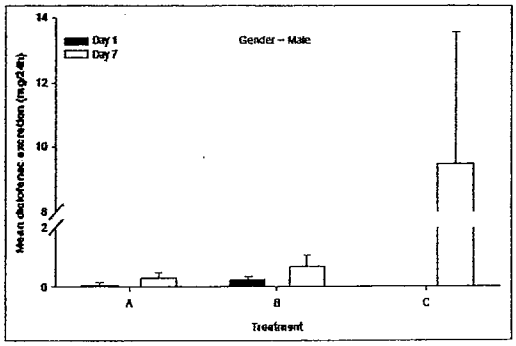
Comparison by gender:

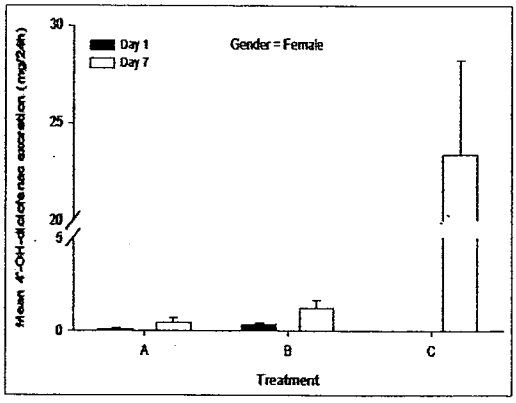
Female subjects Treatment B	Male subjects Treatment B
	

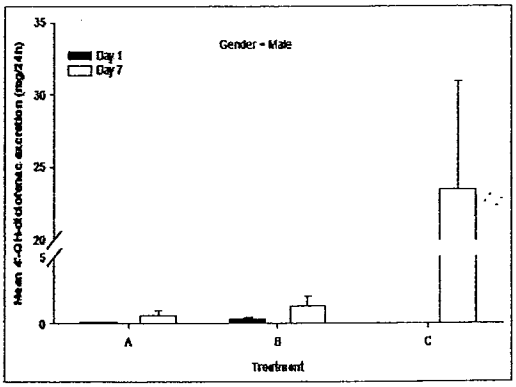


Average 24-h urinary excretion rate of diclofenac (top) and 4'-OH-diclofenac, by gender



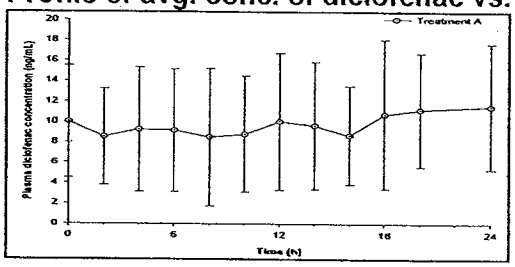




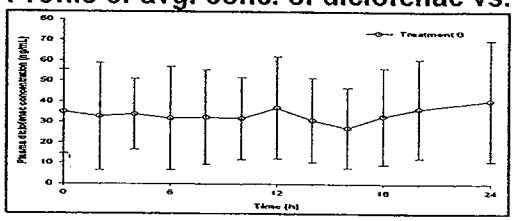


b. Plasma profiles from Day 7: **By individual Treatments**

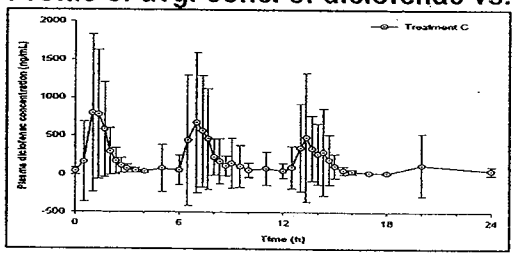
Profile of avg. conc. of diclofenac vs. time, Day 7 - Trt A



Profile of avg. conc. of diclofenac vs. time, Day 7 - Trt B



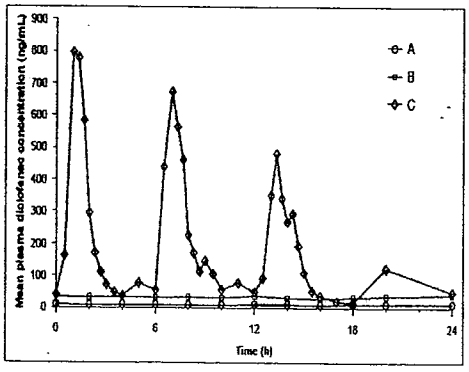
Profile of avg. conc. of diclofenac vs. time, Day 7 - Trt C

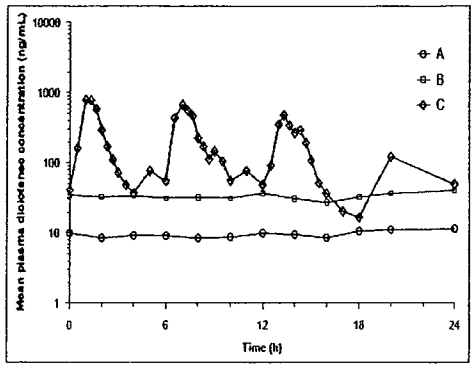


All treatments:

Profile of average concentrations of diclofenac versus time, day 7

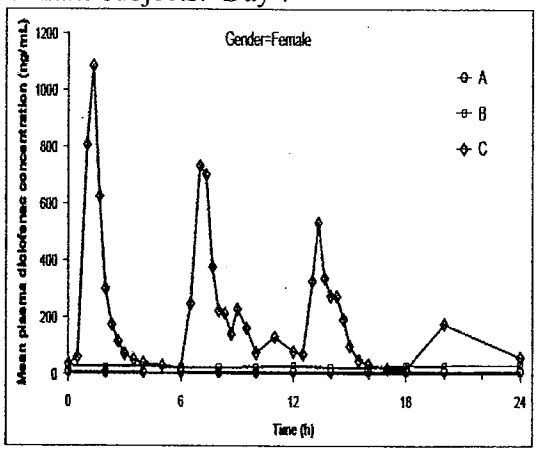
(A: diclofenac sodium topical gel 1% on 1 knee; B: diclofenac sodium topical gel 1% on 2 knees and 2 hands; C: diclofenac sodium tablets; Mean ± SD, except for t_{max}: median (range)

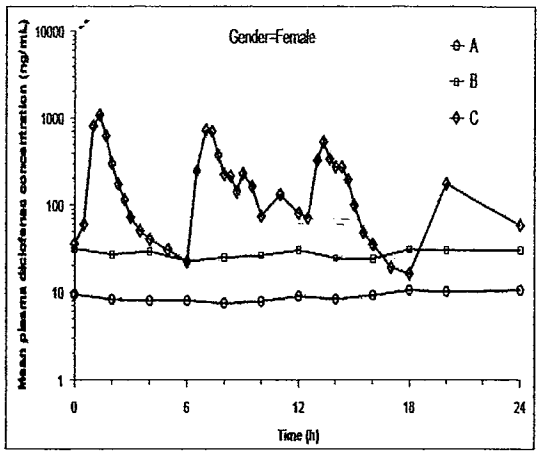




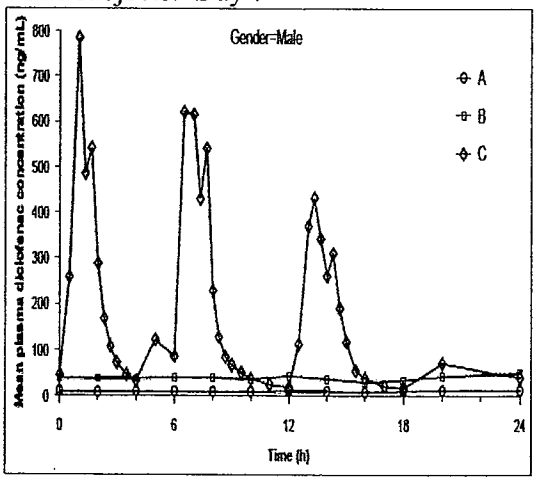
Comparison of profiles based on gender: Day 7

Female subjects: Day 7





Male subjects: Day 7



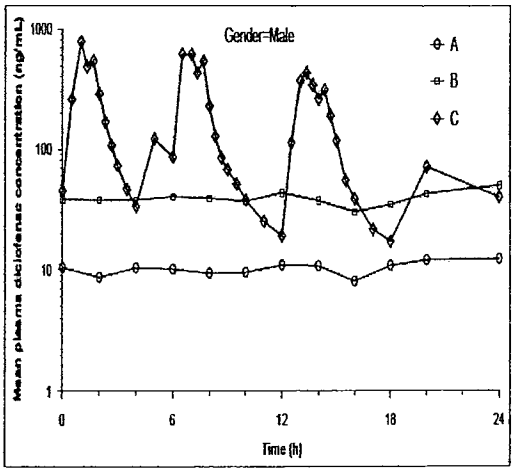
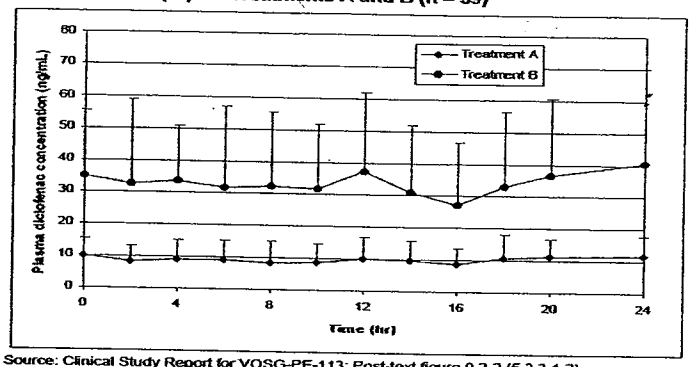
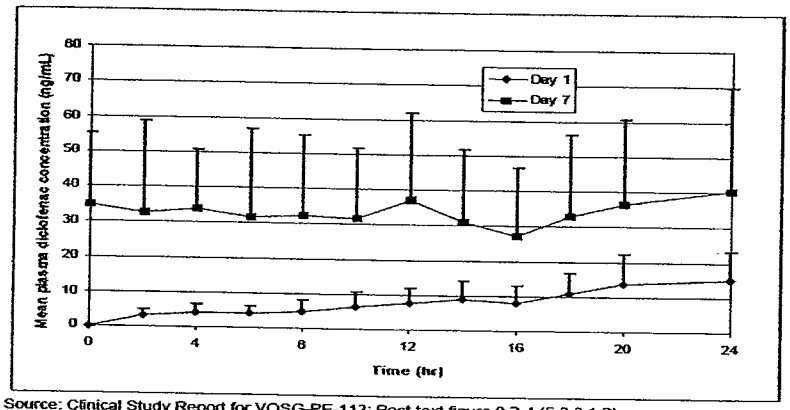


Figure 2-4 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatments A and B (n = 39)



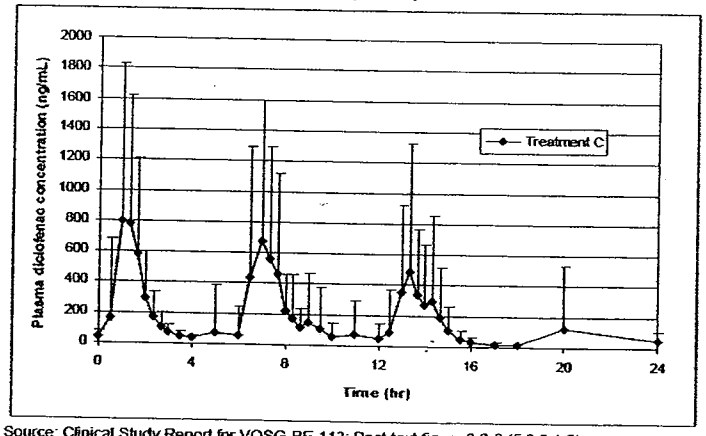
Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-2 (5.3.3.1.2)

Figure 2-6 Day 1 and Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatment B (n = 39)



Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-4 (5.3.3.1.2)

Figure 2-5 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatment C (n = 39)



Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-2 (5.3.3.1.2)

PK parameters:

Least squares means of PK parameters on days 1 and 7

Treatment	Day	AUC0-24 (µg•h/mL)	Ae0-24 diclofenac (µg)	Ae0-24 4'-OH-diclofenac (µg)
A (N=39)	1	--	46 (37-57)	70 (56-87)
	7		226 (181-283)	467 (376-580)
B (N=39)	1	0.171 (0.148-0.198)	217 (184-256)	290 (246-341)
	7	0.714 (0.617-0.827)	617 (522-728)	1166 (990-1373)

Comparison of PK parameters on day 7 vs day 1

Treatment	Comparison	AUC0-24 (%)	Ae0-24 diclofenac (%)	Ae0-24 4'-OH-diclofenac (%)
A (N=39)	day 7/day 1	-	493 (417-581)	666 (561-790)
B (N=39)	day 7/day 1	417 (367-474)	285 (248-327)	402 (350-462)

Plasma: Day 7

Treatment	Cmax (ng/mL)	tmax (h)	AUC0-24 (ng•h/mL)	AUC0-tmax (ng•h/mL)	Cmin (ng/mL)	Cav (ng/mL)	PTF (%)
A (N=39)	15.0 ± 7.33	14 (0-24)	233 ± 128	9.63 ± 5.20	5.92 ± 3.65	9.70 ± 5.32	95.6 ± 40.4
B (N=39)	53.8 ± 32.0	10 (0-24)	807 ± 478	34.4 ± 20.9	19.2 ± 12.1	33.6 ± 19.9	106 ± 51.6
C (N=39)	2270 ± 778	6.5 (1-14)	3890 ± 1710	292 ± 358	5.70 ± 3.11	162 ± 71.2	1516 ± 615

Urine:

Treatment	Ae0-24 diclofenac (µg)		Ae0-24 4'-OH-diclofenac (µg)	
	Day 1	Day 7	Day 1	Day 7
A (N=39)	64.1 ± 64.1	265 ± 164	95.0 ± 85.5	539 ± 332
B (N=39)	249 ± 118	672 ± 300	333 ± 160	1270 ± 602
C (N=39)	-	10300 ± 3980	-	23400 ± 6280[a]

N=39

Comparison between treatments

Parameters from treatments were compared using the least squares mean and ANOVA.

Least squares mean of **plasma** PK parameters on Day 7

Treatment	Cmax (ng/mL)	AUC0-24 (ng•h/mL)	AUC0-tmax (ng•h/mL)
A (N=39)	13.5 (11.7-15.6)	209 (183-240)	8.38 (5.98-11.7)
B (N=39)	47.1 (40.8-54.3)	712 (621-816)	29.8 (21.3-41.8)
C (N=39)	2130 (1850-2460)	3610 (3150-4140)	95.8 (68.3-134)

Comparison of plasma PK on Day 7

Comparison	Cmax (%)	AUC0-24 (%)	AUC0-tmax (%)
B/A (N=39)	349 (302-403)	340 (294-394)	NC
A/C (N=39)	0.633 (0.548-0.733)	5.79 (5.00-6.70)	8.75 (5.99-12.8)
B/C (N=39)	2.21 (1.91-2.56)	19.7 (17.0-22.8)	31.1 (21.3-45.5)

Least squares mean of **urine** PK parameters on Day 7

Treatment	Ae0-24 diclofenac (µg)	Ae0-24 4'-OH-diclofenac (µg)
A (N=39)	226 (188-272)	467 (390-559)
B (N=39)	617 (513-742)	1168 (976-1398)
C (N=39)	9011 (7494-10835)	21150 (17631-25375)[a]

N=38

Comparison

Comparison	Ae0-24 diclofenac (%)	Ae0-24 4'-OH-diclofenac (%)
B/A (N=39)	273 (224-332)	250 (207-302)
A/C (N=39)	2.51 (2.06-3.06)	2.21 (1.82-2.68)[a]
B/C (N=39)	6.85 (5.63-8.34)	5.52 (4.56-6.69)[a]

N=38

Pharmacodynamics:

Oral diclofenac treatment
Inhibited platelet aggregation
TXB2 (indicative of COX1 inhibition) by at least 30%
PGE2 (indicative of COX2 inhibition) by 100%.

Platelet aggregation did not appear to be inhibited by either of the topical treatments.

Treatment A (typical topical dose: one knee)
Did not appear to reduce the plasma concentration of TXB2
Appeared to produce a reduction of approximately 50% in PGE2.

Treatment B (maximal topical dose: two knees and two hands)
Appeared to produce a reduction of TXB2 by at least 30%
Appeared to produce a reduction of PGE2 by 90%

Safety

Table 4-2 Number (%) of subjects with most frequent AEs by preferred term - for terms with frequency > 1 event for any treatment. Study VOSG-PE-113

	DSG 4 g to one knee QID x 7 days	DSG 4 g to each knee 2 g to each hand QID x 7 days	oral diclofenac 50 mg TID x 7 days
	n (%)	n (%)	n (%)
Subjects Studied			
Total no. of subjects	39 (100)	39 (100)	40 (100)
Total no. with an AE	14 (36)	18 (46)	12 (30)
Preferred term			
Headache	6 (15)	0 (0)	2 (5)
Nasopharyngitis	2 (5)	4 (10)	1 (3)
Influenza-like illness	2 (5)	2 (5)	0 (0)
Gastroenteritis	1 (3)	1 (3)	2 (5)
Back pain	0 (0)	2 (5)	0 (0)
Dry mouth	0 (0)	0 (0)	2 (5)
Loose stools	0 (0)	0 (0)	2 (5)

Source: Clinical Study Report for VOSG-PE-113; Post-text table 10.1-1 (5.3.3.1.2)

Conclusions

There was a treated area-proportionality for the systemic exposure to diclofenac following treatment with Diclofenac Sodium Topical Gel, 1%, 10 mg/cm^2 of gel per application, four times a day for one week.

Exposure to diclofenac following treatment with the gel topical treatments was one to two orders of magnitude lower than the exposure following Diclofenac Sodium enteric-coated 50-mg tablets taken orally t.i.d. for one week.

Diclofenac accumulated from day 1 to day 7 by a ratio of about 400% in plasma and a ratio of about 300 to 400% in urine for treatment B, and by a ratio of about 500 to 650% in urine for treatment A. Concentrations were BLOQ in all subjects 28 days after the last day of treatment A application, and in all but one subject 35 days after the last day of treatment B application.

Oral diclofenac treatment significantly inhibited platelet aggregation, COX1 and COX2. The two topical treatments did not affect platelet aggregation but affected COX1 and COX2, to a lesser extent than the oral treatment and in proportion to the treated skin area.

All treatments were well tolerated. Incidence of events judged at least possibly related to the study drug was similar for all treatments. Ten percent of subjects experienced mild local tolerability disorders after treatment with diclofenac sodium topical gel, while 8% experienced mild gastrointestinal disorders after treatment with diclofenac tablets.

Special Safety Trials

Table 1-2 Summary of special safety trials

Study No.	Study objective, population	Subjects enrolled / completed	Treatment duration	Dosage of topical diclofenac	Type of control
VOSG-PN-108 (USA)	Study of the skin cumulative irritation potential of diclofenac sodium gel, 1%, when applied topically to normal, healthy volunteers (21-day cumulative irritation test)	42/36	21 days	15 x 200 µL	Active and vehicle
VOSG-PN-111 (USA)	Study of the skin sensitization potential of diclofenac sodium gel, 1%, when applied topically to healthy volunteers	260/233	3 weeks	9 x 200 µL	Active and vehicle
VOSG-PE-112 (UK)	Assessment of photo-toxicity potential of Diclofenac Sodium Topical Gel, 1%, after single cutaneous application and UV exposure in healthy volunteers	35/35	1 day	3 x 200 µL	Active and vehicle

Source: VOSG-PN-108 (5.3.4.1.1), VOSG-PN-111 (5.3.4.1.2), VOSG-PE-112 (5.3.4.1.3), Module 5.2, Tabular Listing of all Clinical Studies

Summary:

VOSG-PN-108:

"The cumulative irritation effect of DSG, 1%, applied occlusively on the skin over 21 days was minimal when compared to that of SLS, and only slightly higher than that of the blank patch."

VOSG-PN-111:

"No evidence of sensitization potential."

VOSG-PN-112:

"No evidence for any phototoxicity potential."

4.3 Consult Review (including Pharmacometric Reivews) – Not applicable

4.4 Cover Sheet and OCPB Filing/Review Form

New Drug Application Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	**22-122**	Brand Name	-	
OCP Division	II	**Generic Name**	**Diclofenac Na topical Gel 1%**	
Medical Division	HFD-170	Drug Class	Analgesic	
OCPB Reviewer	David Lee	Indication(s)		
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Topical Gel	
		Dosing Regimen	Single dose	
Date of Submission	12/19/06	Route of Administration	Percutaneous	
Estimated Due Date of OCP Review	-	Sponsor	Novartis Consumer Health, Inc.	
Medical Division Due Date	10/15/07	Priority Classification	Standard	
PDUFA Due Date	10/19/07			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
Single dose:	X			
Multiple dose:	X	2		Duration 7 days with WO of 14 days
Dose proportionality	X			
Patients-				
Single dose:				
Multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				Full Waiver – "No incidence in ped. population"
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	X	3		Skin special 'safety' study
Phase 1:				
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			Oral Voltaren enteric-coated tablet; Topical Voltaren Emulgel 1.16%
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total number of studies		5	2	
Filability and QBR comments				
	"X" if yes	Comments Related IND: 164,334		

Application filable ?	X	Yes. As a 505(b)(2) application, the Applicant submitted relative BA, multiple dose and dose proportionality (looking at the maximum likely dosing scheme) information.

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

/s/

David Lee
9/12/2007 10:19:55 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/12/2007 10:26:28 AM
BIOPHARMACEUTICS

New Drug Application Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	**22-122**	Brand Name	-
OCP Division	II	**Generic Name**	**Diclofenac Na topical Gel 1%**
Medical Division	HFD-170	Drug Class	Analgesic
OCPB Reviewer	David Lee	Indication(s)	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Topical Gel
		Dosing Regimen	Single dose
Date of Submission	12/19/06	Route of Administration	Percutaneous
Estimated Due Date of OCP Review	-	Sponsor	Novartis Consumer Health, Inc.
Medical Division Due Date	10/15/07	Priority Classification	Standard
PDUFA Due Date	10/19/07		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
Single dose:	X			
Multiple dose:	X	2		Duration 7 days with WO of 14 days
Dose proportionality	X			
Patients-				
Single dose:				
Multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				Full Waiver – "No incidence in ped. population"
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	X	3		Skin special 'safety' study
Phase 1:				
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			Oral Voltaren enteric-coated tablet; Topical Voltaren Emulgel 1.16%
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total number of studies		5		

Filability and QBR comments		
	"X" if yes	Comments Related IND: I64,334
Application filable ?	X	Yes. As a 505(b)(2) application, the Applicant submitted relative BA, multiple dose and dose proportionality (looking at the maximum likely dosing scheme) information.

Clinical Pharmacology summary presented by the Applicant:

Study VOSG-PN-107

Objectives:

• to determine the relative bioavailability of diclofenac following repeated cutaneous applications of DSG, 1% and DDG, 1.16% (i.e., 4 g of gel over 400 cm^2 (one knee), qid for 7 days);
• to determine the effects of moderate exercise or applied heat on the systemic absorption of diclofenac following application of DSG, 1% (10 mg/cm^2, i.e., 4 g of gel over 400 cm^2 (one knee), qid for 7 days).

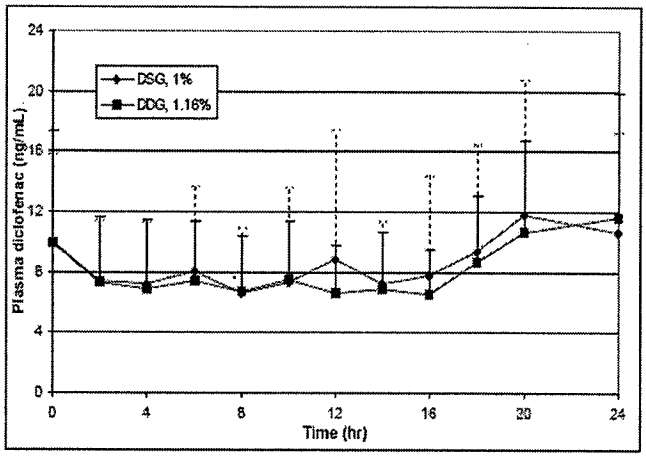
Treatments:

- Treatment A - DSG, 1%;
- *Treatment B - DDG, 1.16% (Voltaren® Emulgel™)*;
- Treatment C - DSG, 1%, with each application each day preceded by moderate heat for 15 minutes to the site of application;
- Treatment D - DSG, 1%, with the first application each day followed by 20 minutes of moderate exercise on a treadmill.

Treatments were to be applied at 7 AM, 12 AM, 5 PM and 10 PM.

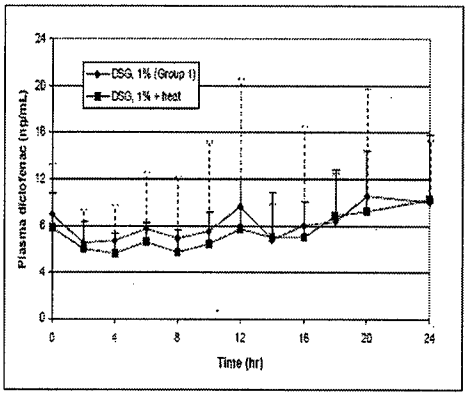
Plasma profiles:

Figure 2-1 **Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatments A and B**



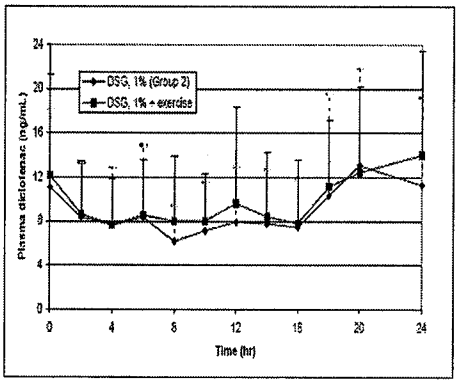
n = 35 both treatments

Figure 2-2 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatments A (DSG, 1%)and C (DSG, 1% + heat) in Group 1



n = 18 for both groups

Figure 2-3 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatments A (DSG 1%) and D (DSG, 1% + exercise) in Group 2



n = 17 for both groups

PK parameters:

Table 2-1 Day 7 C_{max}, t_{max} and AUC_{0-24} by treatment

	Treatment	C_{max}* (ng/mL)	t_{max}** (hr)	AUC_{0-24}* (ng•h/mL)
A	DSG, 1% (n = 35)	22.2 ± 33.3	18 (0 - 24)	222 ± 140
A§	DSG, 1% (n = 35)	15.7 ± 11.9	18 (0 - 24)	207 ± 117
B	DDG, 1.16% (n = 35)	14.0 ± 8.86	20 (0 - 24)	194 ± 95.9
C	DSG, 1% + heat (n = 18)	13.3 ± 5.63	20 (0 - 24)	179 ± 63.2
D	DSG, 1% + exercise (n = 17)	16.8 ± 10.1	18 (0 - 24)	234 ± 134

*(Mean ± SD); **Median (Range); §This group omits 2 outlying concentrations.

Table 2-3 Day 7 24-hour urinary excretion of diclofenac and 4'-OH-diclofenac (Mean ± SD)

	Treatment	Ae_{0-24} diclofenac (mg)	Ae_{0-24} 4'-OH-diclofenac (mg)	Proportion of applied dose excreted (%)
A	DSG, 1% (n = 35)	0.26 ± 0.17	0.52 ± 0.35	0.51 ± 0.34
B	DDG, 1.16% (n = 35)	0.31 ± 0.48	0.48 ± 0.32	0.51 ± 0.42
C	DSG, 1% + heat (n = 18)	0.23 ± 0.10	0.44 ± 0.20	0.44 ± 0.19
D	DSG, 1% + exercise (n = 17)	0.26 ± 0.18	0.56 ± 0.42	0.53 ± 0.39

Source: Clinical Study Report for VOSG-PN-107; Post-text table 9.2-7 to Post-text table 9.2-9 (5.3.3.1.1)

Study VOSG-PE-113

Objectives:

• To compare the systemic BA of diclofenac of repeated applications of DSG, 1%, qid, to one knee, 2 knees and 2 hands (maximum exposure), and repeated oral dosing of diclofenac sodium 50 mg tablets, tid.

• To compare accumulation of diclofenac in urine only from day 1 to day 7;

• To assess the effects of the different treatments on platelet aggregation and on COX1 and COX2 in blood as reflected by plasma thromboxane (TXB_2) and prostaglandin E_2 (PGE_2), respectively;

Treatments:

- Treatment A - DSG, 1%, 10 mg/cm^2 applied to one knee (~400 cm^2 i.e., 4 g), qid for 7 days, (exposure 16 g of gel/day over 400 cm2);

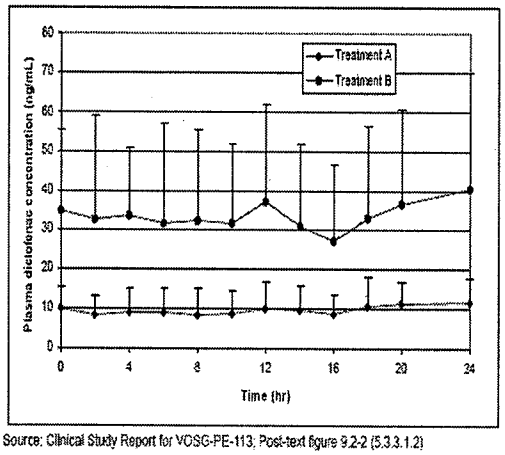
- Treatment B - DSG, 1%, 10 mg/cm^2 applied to both knees (~800 cm^2 i.e., 8 g) and to both hands (~400 cm^2 i.e., 4 g), qid for 7 days, (exposure 48 g of gel/day over 1200 cm^2);

- Treatment C – diclofenac sodium 50 mg enteric coated tablets taken orally tid for 7 days, (exposure 150 mg of diclofenac/day);

Topical treatments were to be applied at 7 AM, 12 AM, 5 PM and 10 PM; the oral tablets were to be taken at 7 AM, 1 PM and 7 PM.

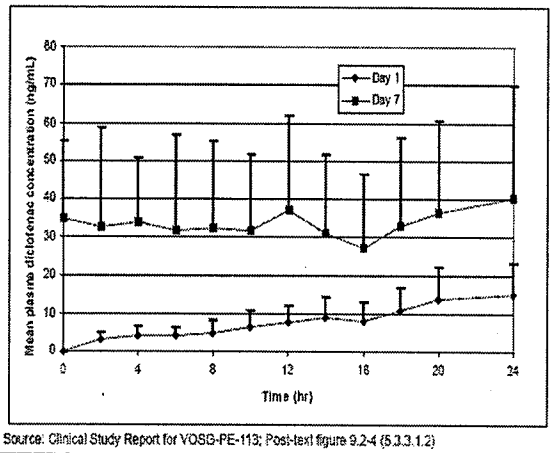
Plasma Profiles:

Figure 2-4 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatments A and B (n = 39)



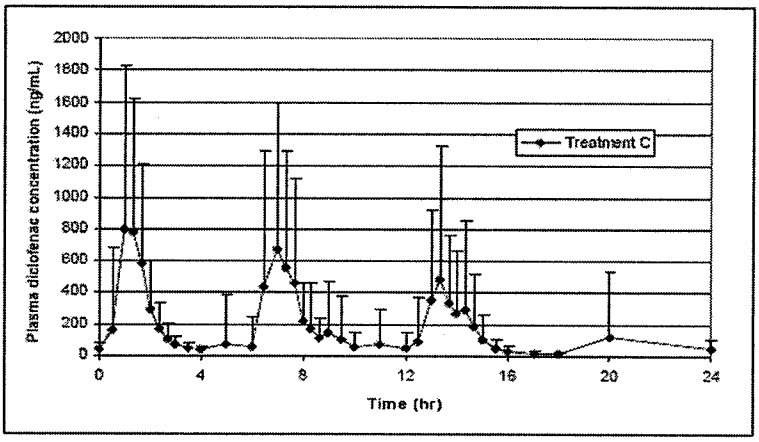
Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-2 (5.3.3.1.2)

Figure 2-6 Day 1 and Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatment B (n = 39)



Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-4 (5.3.3.1.2)

Figure 2-5 Day 7 Mean (+SD) plasma diclofenac concentrations (ng/mL) vs. time (hr) for Treatment C (n = 39)



Source: Clinical Study Report for VOSG-PE-113; Post-text figure 9.2-2 (5.3.3.1.2)

PK parameters:

Plasma:

Table 2-5 Day 7 C_{max}, t_{max} and AUC_{0-24} by treatment (n = 39)

	Treatment	C_{max}* (ng/mL)	t_{max}** (hr)	AUC_{0-24}* (ng•h/mL)
A	DSG, 1% (4 g on 400 cm^2, qid)	15.0 ± 7.33	14 (0 - 24)	233 ± 128
B	DSG, 1% (12 g on 1200 cm^2, qid)	53.8 ± 32.0	10 (0 - 24)	807 ± 478
C	Diclofenac sodium 50 mg tablet tid	2270 ± 778	6.5 (1 - 14)	3890 ± 1710

*Mean (± SD); **Median (Range).

Source: Clinical Study Report for VOSG-PE-113; Post-text table 9.2-4 (5.3.3.1.2)

Table 2-6 Ratios of Day 7 plasma pharmacokinetic parameters for the experimental treatments (n = 39)

Comparison	C_{max} (%)	AUC_{0-24} (%)
B/A	349 (302 - 403)	340 (294 - 394)
A/C	0.633 (0.548 - 0.733)	5.79 (5.00 - 6.70)
B/C	2.21 (1.91 - 2.56)	19.7 (17.0 - 22.8)

C_{max}, AUC_{0-24} ; ratio (test / reference) of least squares geometric means calculated using ANOVA with 90% CI.

A: DSG,1% on 1 knee; B: DSG, 1% on 2 knees and 2 hands; C: diclofenac sodium tablets

Source: Clinical Study Report for VOSG-PE-113; Post-text table 9.3-2 (5.3.3.1.2)

Urine:

Table 2-7 Day 1 and Day 7 24-hour urinary excretion of diclofenac and 4'-OH-diclofenac (Mean ± SD)

Treatment	Diclofenac Ae_{0-24} (µg/24 hr)		4'-OH-diclofenac Ae_{0-24} (µg/24 hr)	
	Day 1	Day 7	Day 1	Day 7
A DSG, 1% (4 grams on 400 cm^2, qid)	64.1 ± 64.1	265 ± 164	95.0 ± 85.5	539 ± 332
B DSG, 1% (12 grams on 1200 cm^2, qid)	249 ± 118	672 ± 300	333 ± 160	1270 ± 602
C Diclofenac sodium 50 mg tablet tid		10300 ± 3980		23400 ± 6280[a]

[a] n = 38

Source: Clinical Study Report for VOSG-PE-113; Post-text table 9.2-5 and Post-text table 9.2-6 (5.3.3.1.2)

Table 2-8 Ratios of urinary excretion parameters on Day 7

Comparison	Ratio(as %) of Ae_{0-24} diclofenac	Ratio(as %) of Ae_{0-24} 4'-OH-diclofenac
B/A (n = 39)	273 (224-332)	250 (207-302)
A/C (n = 39)	2.51 (2.06-3.06)	2.21 (1.82-2.68)[a]
B/C (n = 39)	6.85 (5.63-8.34)	5.52 (4.56-6.69)[a]

A: DSG,1% on 1 knee; B: DSG, 1% on 2 knees and 2 hands; C: diclofenac sodium tablets

[a] n = 38

Estimate of test / reference ratio of least squares geometric means (90% confidence interval) derived from ANOVA

Source: Clinical Study Report for VOSG-PE-113; Post-text table 9.3-2 (5.3.3.1.2)

Table 2-9 Day 7 to Day 1 ratios of 24-hour urinary excretion of diclofenac and 4'-OH-diclofenac

Treatment	Ratio (as %) of Diclofenac Ae_{0-24} (µg/24 hr)	Ratio (as %) of 4'-OH-diclofenac Ae_{0-24} (µg/24 hr)
	Day 7/Day 1	Day 7/Day 1
A DSG, 1% (4 grams on 400 cm^2, qid)	493 (417-581)	666 (561-790)
B DSG, 1% (12 grams on 1200 cm^2, qid)	285 (248-327)	402 (350-462)

Estimate of test / reference ratio of least squares geometric means (90% confidence interval) derived from ANOVA

Source: Clinical Study Report for VOSG-PE-113; Post-text table 9.3-4 (5.3.3.1.2)

Pharmacodynamics:

1. Oral diclofenac treatment
    a. Inhibited platelet aggregation
    b. TXB_2 (indicative of COX1 inhibition) by at least 30%
    c. PGE_2 (indicative of COX2 inhibition) by 100%.

2. Platelet aggregation did not appear to be inhibited by either of the topical treatments.

3. Treatment A (typical topical dose: one knee)
    a. Did not appear to reduce the plasma concentration of TXB_2
    b. Appeared to produce a reduction of approximately 50% in PGE_2.

4. Treatment B (maximal topical dose: two knees and two hands)
    a. Appeared to produce a reduction of TXB_2 by at least 30%
    b. Appeared to produce a reduction of PGE_2 by 90%

Safety

Table 4-2 Number (%) of subjects with most frequent AEs by preferred term - for terms with frequency > 1 event for any treatment. Study VOSG-PE-113

	DSG 4 g to one knee QID x 7 days n (%)	DSG 4 g to each knee 2 g to each hand QID x 7 days n (%)	oral diclofenac 50 mg TID x 7 days n (%)
Subjects Studied			
Total no. of subjects	39 (100)	39 (100)	40 (100)
Total no. with an AE	14 (36)	18 (46)	12 (30)
Preferred term			
Headache	6 (15)	0 (0)	2 (5)
Nasopharyngitis	2 (5)	4 (10)	1 (3)
Influenza-like illness	2 (5)	2 (5)	0 (0)
Gastroenteritis	1 (3)	1 (3)	2 (5)
Back pain	0 (0)	2 (5)	0 (0)
Dry mouth	0 (0)	0 (0)	2 (5)
Loose stools	0 (0)	0 (0)	2 (5)

Source: Clinical Study Report for VOSG-PE-113; Post-text table 10.1-1 (5.3.3.1.2)

Special Safety Trials

Table 1-2 Summary of special safety trials

Study No.	Study objective, population	Subjects enrolled / completed	Treatment duration	Dosage of topical diclofenac	Type of control
VOSG-PN-108 (USA)	Study of the skin cumulative irritation potential of diclofenac sodium gel, 1%, when applied topically to normal, healthy volunteers (21-day cumulative irritation test)	42/36	21 days	15 x 200 µL	Active and vehicle
VOSG-PN-111 (USA)	Study of the skin sensitization potential of diclofenac sodium gel, 1%, when applied topically to healthy volunteers	260/233	3 weeks	9 x 200 µL	Active and vehicle
VOSG-PE-112 (UK)	Assessment of photo-toxicity potential of Diclofenac Sodium Topical Gel, 1%, after single cutaneous application and UV exposure in healthy volunteers	35/35	1 day	3 x 200 µL	Active and vehicle

Source: VOSG-PN-108 (5.3.4.1.1), VOSG-PN-111 (5.3.4.1.2), VOSG-PE-112 (5.3.4.1.3), Module 5.2, Tabular Listing of all Clinical Studies

Summary:

VOSG-PN-108:

"The cumulative irritation effect of DSG, 1%, applied occlusively on the skin over 21 days was minimal when compared to that of SLS, and only slightly higher than that of the blank patch."

VOSG-PN-111:

"No evidence of sensitization potential."

VOSG-PN-112:

"No evidence for any phototoxicity potential."

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/s/

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2/16/2007 09:41:08 AM
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