The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Diclofenac

Study Number: A2500522

Title: A Pilot Study to Evaluate the Relative Bioavailability of Diclofenac as Measured by Microdialysis after Repeated Doses of Two Topical Diclofenac Formulations

Rationale: This was a pilot study with five subjects intended to provide a preliminary evaluation of the formulations' penetration profile.

Phase: III

Study Period: 16 May 2008 to 23 Jun 2008

Study Design: This clinical study was a single-center, randomized, open-label, multiple-dose, and two-way crossover in design. In this study, two topical diclofenac gel formulations were evaluated in healthy Caucasian males. Subjects who fulfilled all the inclusion/exclusion criteria participated in two study sessions. One study session with 1% Diclofenac Gel applied topically to the anterior thigh four times daily (QID) for three consecutive days and one study session with 1.16% Diclofenac gel applied topically to the contra-lateral anterior thigh QID for three consecutive days.

On the evening of the third day of treatment of each study session, subjects were confined to the clinic facility for approximately 24 hours. After two microdialysis catheters were inserted into the subcutaneous adipose and the skeletal muscle layers of each subject's thigh on the following morning, the final dose of study treatment was applied. Microdialysate samples and blood samples were collected every hour for the next 10 hours. The two study sessions were separated by at least a 14 days of washout period.

Centre: 1, Austria

Indication: Pain

Treatments:
Test Product: Diclofenac Gel 1%: 20mg/100cm^2 1% diclofenac sodium applied topically to the anterior thigh QID.

Reference Product: Diclofenac Gel 1.16%: 20mg/100cm^2 1.16%diclofenac diethylammonium gel applied topically to the anterior thigh QID

Objectives:
Primary objective: To determine if quantifiable concentrations of diclofenac could be measured in microdialysis samples of subcutaneous adipose tissue and skeletal muscle and to ascertain the associated plasma concentration of diclofenac after repeated topical administration of Diclofenac Gel 1%.
Secondary objectives:
1. To determine if quantifiable concentrations of diclofenac could be measured in microdialysis samples of subcutaneous adipose and skeletal muscle and to ascertain the associated plasma concentration of diclofenac after repeated topical administration of Diclofenac Gel 1.6%.
2. To assess the safety and tolerability of both study regimens as measured by the incidence of adverse events (AEs).

Primary Outcome Endpoints:
1. Concentrations of the diclofenac Gel 1% in plasma, subcutaneous adipose tissue and skeletal muscle, and
2. Pharmacokinetics (PK) variables of Diclofenac Gel 1%
   a) $AUC_{0\text{-}10\ hours:}$ the area under the plasma concentration time curve from zero to 10 hours.
   b) C_{max}: maximum plasma concentration.
   c) T_{max}: time to maximum plasma concentration

Secondary Outcome Endpoints:
1. Concentrations of the diclofenac Gel 1.6% in plasma, subcutaneous adipose tissue and skeletal muscle
2. PK variables for the Diclofenac Gel 1.6%.
   a) $AUC_{0\text{-}10\ hours}$
   b) C_{max}
   c) T_{max}
3. AEs.

Statistical Methods: All the PK endpoints, $AUC_{0\text{-}10\ hours}$, C_{max}, and T_{max} were summarized using descriptive statistics, separately for adipose and skeletal muscle tissue and by treatment.
Diclofenac plasma concentration was summarized for each time point for each subject in each treatment.

All subjects who receive treatment were included in the analysis and reporting of safety data. AEs were summarized by treatment groups.
AEs occurring after completion of a study period to administration of the first treatment in the next study period (i.e. during the washout period) were assigned to the treatment received in the previous study period.

Study Population:

Subject Disposition (All Randomized Subjects)

	Overall
Subjects Randomized, n (%)	5 (100)
Complete at least one period, n (%)	5 (100)
Completed the study, n (%)	5 (100)
Did not complete, n (%)	0

Demographics (All Randomized Subjects)	**Overall**
Sex, n (%)	
Male	5 (100.0)
Age	
Mean Age, years (SD)	32.4 (7.30)
Race, n (%)	
Caucasian	5 (100)

Primary Outcome Results (PK population N=5):

Table 1: Mean (Std. Dev) of Diclofenac Gel 1% Concentration (pg/mL)

Time points (Hours)	**Diclofenac Gel 1% concentration**		
	Adipose (Mean [SD])	**Skeletal Muscle (Mean [SD])**	**Plasma (Mean [SD])**
0*	1476.2 (830.4)	2497.2 (2460.8)	5766.1 (6500.7)
1	2008.9 (1449.9)	1129.1 (711.8)	6281.5 (7063.1)
2	871.3 (544.3)	1572.2 (1966.8)	6608.2 (7678.6)
3	411.3 (238.5)	364.3 (139.9)	6242.9 (6524.6)
4	516.7 (529.3)	475.7 (292.9)	5636.1 (5896.9)
5	310.2 (125.1)	318.8 (135.0)	4819.2 (4749.7)
6	1047.2 (NA)	605.8 (399.6)	5847.8 (6867.7)
7	952.6 (1116.7)	369.0 (46.0)	4995.5 (4844.2)
8	736.8 (265.8)	316.4 (47.4)	4889.5 (4195.6)
9	226.8 (10.8)	258.9 (82.2)	5438.7 (5010.5)
10	348.50 (180.5)	227.25 (24.68)	6081.0 (6337.6)

**Collected before application of final dose of study treatment.*
Note: NA (not applicable) indicates that standard deviation could not calculated because there was only one observation

Table 2: Summary of Diclofenac Gel 1% PK Variables in Adipose Tissue, Muscle Tissue and Plasma

Treatment	**Diclofenac Gel 1% concentration**		
	Adipose (Mean [SD])	**Skeletal Muscle (Mean [SD])**	**Plasma (Mean [SD])**
$AUC_{0\text{-}10\ hours}$ (mins.pg/mL)			
n	5	5	5
Mean (SD)	5035.960 (1627.4691)	4408.840 (2323.6373)	55431.100 (59220.6407)
C_{max} (pg/mL)			
n	5	5	5
Mean (SD)	2161.960 (1266.0529)	1984.540 (1811.0263)	6982.160 (7451.2128)
T_{max} (mins)			
n	5	5	5
Mean (SD)	3.000 (3.0822)	2.000 (1.2247)	5.600 (3.7815)

Secondary Outcomes Results (PK population N=5)

Table 3: Mean (Std. Dev) of Diclofenac Gel 1.6% Concentration (pg/mL)

Time points (Hours)	Diclofenac Gel 1.6% concentration		
	Adipose (Mean [SD])	Skeletal Muscle (Mean [SD])	Plasma (Mean [SD])
0*	1755.3 (1749.3)	3128.5 (4528.2)	3870.6 (3273.7)
1	765.3 (674.3)	1148.1 (1144.5)	3839.6 (4042.9)
2	326.8 (50.3)	696.7 (488.6)	3634.7 (3166.5)
3	533.7 (464.9)	590.3 (575.1)	4399.4 (4741.6)
4	518.3 (286.8)	554.8 (560.2)	4009.0 (4716.5)
5	770.7 (590.0)	991.7 (NA))	3460.6 (3834.3
6	825.8 (605.6)	416.7 (375.5)	3794.8 (4246.8)
7	295.2 (NA)	907.5 (636.5)	4294.9 (4467.8)
8	438.4 (NA)	398.7 (324.7)	4899.8 (5561.1)
9	943.5 (1201.1)	696.6 (559.2)	5489.2 (6909.7)
10	369.5 (50.6)	362.8 (279.9)	5713.6 (6636.3)

**Collected before application of final dose of study treatment.*
Note: NA (not applicable) indicates that standard deviation could not calculated because there was only one observation

Table 4: Summary of Diclofenac Gel 1.6% PK Variables in Adipose Tissue, Muscle Tissue and Plasma

Treatment	Diclofenac Gel 1.6% concentration		
	Adipose (Mean [SD])	Skeletal Muscle (Mean [SD])	Plasma (Mean [SD])
$AUC_{0\text{-}10\ hours}$ (min.pg/mL)			
n	5	5	5
Mean (SD)	3845.220 (553.7879)	3410.240 (4544.7430)	39921.560 (37226.6666)
C_{max} (pg/mL)			
n	5	5	5
Mean (SD)	1648.280 (721.6281)	1097.420 (1014.5719)	7593.860 (6716.7649)
T_{max} (mins)			
n	5	5	5
Mean (SD)	4.000 (3.4641)	2.400 (2.6077)	6.800 (4.3818)

Safety Results (Safety population, N=5)

Table 5: Treatment Emergent AEs

Treatments	Diclofenac Gel 1%	Diclofenac Gel 1.6%
N	5	5
Number of subjects with AEs n (%)	4 (80.0)	1 (20.0)
General Disorders and Administration Site Conditions		
Application Site Irritation	2 (40.0)	0
Application Site Erythema	4 (80.0)	0
Application Site Dryness	1 (20.0)	0
Eye Disorders		
Eye Irritation	1 (20.0)	0
Gastrointestinal Disorders		
Gastrooesophageal Reflux Disease	0	1 (20.0)
Nervous System Disorders		
Headache	1 (20.0)	0

n (%) = Number (percent) of subjects

Serious Adverse Events (SAEs) - On-Therapy

No SAE was reported.