15 November 2018
EMA/33272/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution[1] and associated names

INN/active substance: Diclofenac sodium

Procedure number: EMEA/H/A-29(4)/1467

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] Name of product in RMS

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1. Background Information

An application was submitted under the mutual recognition procedure for Diclofenac sodium 4% cutaneous spray, solution and associated names on the basis of the marketing authorisation granted by the United Kingdom on 13 May 2002.

The application under the current wave was submitted to the concerned Member States (CMS) : Italy, Spain and Germany.

The names and MAHs of this medicinal product currently authorised following previous MRPs are listed in Annex I of the CHMP opinion.

The mutual recognition procedure UK/H/0563/001/E/002 started on 12 October 2017.

On day 90, major issues on efficacy, raised by Germany and Spain, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by the United Kingdom on 11 January 2018. The CMDh 60 day procedure was initiated on 29 January 2018.

Day 60 of the CMDh procedure was on 29 March 2018, and since there could be no agreement the procedure was referred to the CHMP.

On 04 April 2018 the RMS United Kingdom therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. Germany and Spain raised potential serious risk to public health due to objections on establishing efficacy for the medicinal product and the bridging between the literature and the applied formulation.

2. Scientific discussion

2.1. Introduction

The UK national marketing authorisation for Diclofenac sodium 4% cutaneous spray, solution (in this report referred to as “spray gel”) was granted on under the legal basis Article 4.8(a)(ii) of Directive 65/65/EEC – a bibliographic application. The concerned Member States (CMS) involved in the first use and repeat use first wave MRP were: Austria, Ireland, Estonia, Hungary, Lithuania, Latvia and Slovenia.

The application subject to this referral concerns a repeat-use mutual recognition procedure (UK-H-0563-001-E-002) for Diclofenac sodium 4% cutaneous spray, solution (PL 18017/0006) with UK as RMS and which involves Italy, Spain, Germany as Concerned Member States.

The specific indication for the product proposed by the applicant is for the” local symptomatic relief of mild to moderate pain and inflammation following acute blunt trauma of small and medium-sized joints and periarticular structures”.

As the product was a new pharmaceutical form and strength, the UK national application dossier was supplemented with bridging data from pharmacokinetic studies and a clinical study (9702 SUV P 9902). The clinical data from study 9702 SUV P 9902 has since been published and this is now considered as additional bibliographic data as part of the second wave application.

For the second wave MRP application, the MAH has in addition submitted a recent literature review of selected articles of the PK, efficacy and safety of 'topical diclofenac' in the treatment of mild to moderate pain and inflammation following trauma. Most of the efficacy literature is of Voltarol/Voltaren Emulgel formulation (referred to in this report as "Emulgel"); however there is one publication (Predel 2013) of the 9702 SUV study, which used the proposed cutaneous spray solution. To bridge the evidence of efficacy from the diclofenac Emulgel formulation, the applicant used qualitative comparisons, systemic PK & local exposure comparisons and efficacy comparisons between the 4% spray gel and Emulgel.

The qualitative comparison is based on comparability in composition, degree of ionization and complete solubility of active substance. Although the strength of the proposed cutaneous spray is 4% as compared to the Emulgel (1% or 2%), this difference in the cutaneous spray is claimed to deliver a similar amount of diclofenac to local tissues as the Emulgel.

Since DE and ES raised concerns regarding potential serious risk to public health (PSRPH) related to lack of efficacy for the specific 4% spray gel product and inadequate bridging to the other topical diclofenac formulation (Voltarol Emulgel) for which it was acknowledged that there was adequate evidence of efficacy, the procedure was referred to the CHMP by the RMS on 4 April 2018.

On 4 April 2018 the UK triggered a referral under Article 29(4) of Directive 2001/83/EC, requesting the CHMP to assess the impact of the objections raised in the notification of 04 April 2018 that were considered to constitute a potential serious risk to public health.

CHMP requested the applicant to justify the positive benefit/risk balance for this product in the light of the bibliographic data provided, in particular, why this bibliographic data can be bridged with the data for Diclofenac Sodium Spray Gel 4% provided in the application.

2.2. Quality

The drug product is presented as a solution with the drug substance dissolved in a solvent system comprising purified water, alcohol/isopropyl alcohol and propylene glycol. The solution is stabilised with lecithin which prevents crystallisation during storage.

The container is a glass bottle with a metered-dose spray pump. Each spray delivers 8 mg diclofenac sodium (200 mg solution).

After spraying onto the skin and rubbing gently, the product thickens to a gel-like consistency due to evaporation of volatile solvents and the presence of lecithin.

Spray gel and EmulGels are both hydro-alcoholic and propylene glycolic formulations containing an inner lipophilic phase whose function is the enhancement of the solubilization of the lipophilic active ingredient in the hydrophilic formulation vehicle.

According to literature and microscopic appearance, in both formulations spray gel and EmulGels the active ingredient (Diclofenac Sodium salt and Diclofenac Diethylamine salt, respectively) is fully dissolved; the absence of active ingredient suspended crystals eliminates the influence of possible differences of the active ingredient crystalline habit on the skin permeability.

The pH of both spray gel and EmulGels formulations is about 7.0. Since the dissociation constant (pKa) of Diclofenac (acid form) is about 4, it can be concluded that in both formulations Diclofenac is contained predominantly in a dissociated form (in similar ratio), implying a similar ability to permeate skin.

According to “Ex Vivo Study of transdermal permeation of four diclofenac salts from different vehicles Minghetti. P, Cilurzo F., Casiraghi A., Montanari L., Fini A., Journal of Pharmaceutical Sciences, 2006 Vol 96, based on ex-vivo permeations studies, the permeability coefficient (cm/h) through human skin membrane for Diclofenac Sodium and Diclofenac Diethylamine was calculated, dividing the measured flux (µg/cm2/h) by the drug donor concentration (mg/mL) in the donor phase. The permeability coefficients in different solvents were reported in the following table:

Table 1 Permeability Coefficients of Diclofenac in Different Solvents

Solvent	***Permeability coefficient pKp (cm/h)***	
	Diclofenac Sodium	***Diclofenac Diethylamine***
Water	4.21 ± 0.07	3.56 ± 0.19
Propylene glycol	5.67 ± 0.02	6.04 ± 0.05
Oleic acid	4.13 ± 0.04	4.38 ± 0.15

The values of permeability coefficient are similar between the Sodium and the Diethylamine salts, with the slight differences for each solvent are counterbalanced by the mixture of solvents in the formulations spray gel vs EmulGels. It can be concluded that, on the basis of the above mentioned ex-vivo permeation studies, the skin permeability of the different Diclofenac salts will be similar between spray gel and EmulGels.

Despite the different concentrations of the formulations (4% vs 1% or 2%, respectively), after application the ratio “API dose / area” is comparable between spray gel and EmulGels, as shown in the following table.

Table 2 Posologies of spray gel and EmulGels

ACTIVE SUBSTANCE*: dose per application site*	***spray gel***	***EmulGel 1%***	***EmulGel 2%***
SINGLE dose	32 - 40 mg	20 - 40 mg	40 – 80 mg
SINGLE dose / area**	0.08 - 0.10 mg/cm^2	0.05 – 0.10 mg/cm^2	0.10 - 0.20 mg/cm^2
DAILY dose	96 - 120 mg [tid]	60 - 120 mg [tid] 80 - 160 mg [qid]	80 - 160 mg [bid]
DAILY dose / area**	0.24 – 0.30 mg/cm^2	0.15 – 0.40 mg/cm^2	0.20 – 0.40 mg/cm^2

** Calculated as DICLOFENAC SODIUM salt*
*** Estimated application area: 400 cm^2 (knee / ankle)*

Discussion on Quality

The CHMP considered that the compositions of Diclofenac spray gel (4%) and Voltarol EmulGel formulations are qualitatively and quantitatively different, but the products upon application are similar with respect to pharmaceutical form, method of administration and posology. Indeed, the spray gel

was intentionally designed and quantified to produce a similar effect in terms of quantity of active delivered to the target tissue.

Furthermore, the pH of both products is controlled at approximately 7.0 and it is argued, based on pKa for diclofenac, that the API would be predominantly in dissociated (acid) form at the product pH such that the difference in salt form (diclofenac sodium vs. diclofenac diethylamine) is unlikely to be critical to skin permeation of the drug substance. This is supported by comparative ex vivo human skin permeability data of different diclofenac salts, including diclofenac sodium and diethylamine salts, in different solvents.

Table 1 above shows that different diclofenac salts can have similar permeability. Table 2 comparing the estimated dose/area for spray gel and 2 concentrations of Emulgel shows how the posology has been adapted to provide a similar quantity of the formulation to the local area.

In accordance with the guidance document [Guidance on the clinical requirements for locally applied; locally acting products (CMP/EWP/239/95)] the differences between the spray gel and Emulgel formulations have been compensated by adjusting the posology in order to achieve similar penetration of the active at the target organ.

The data provided do not raise any significant concern from a quality perspective on potential differences in quality between Diclofenac spray gel and Diclofenac Emulgel.

2.3. Clinical Pharmacology

Pharmacokinetics

Systemic bioavailability

Data from studies referenced by the applicant indicate that concentrations attained are equivalent to or higher than those achieved after dose-equivalent oral administration of Voltaren Tablets.

The below table provodes an overview of the relevant studies presented by the applicant.

Table 3 spray gel 4% Plasma Pharmacokinetics (total diclofenac (bound + unbound))

AUTHOR	METHODOLOGY	PK DATA (UNITS)	
Diclofenac 4% Spray Gel			
Menke 2002 Study MD 0102 n = 2	**48mg tds spray gel tds vs 50mg Voltaren© EC tablets tds for 72h**	**Diclofenac 4% Spray Gel Median [95% CI]**	**Voltaren© 50mg oral Median [95% CI]**
	C_{max} (ng/mL)	4.89 [3.37; 7.68]	1240.21 [787.03; 1388.91]
	Css ng/ml % of 100% systemic administration	2.23%	100%
	t_{max} (h)	2.0 [0.0; 7.0]	2.0 [2.0; 3.0]
	$AUC_{0-\infty}$ (ng*h/mL)	32.77 [22.66; 52.94]	1569.72 [1255.75; 1849.75]
	Relative Bioavailability	2%	100%
Efe 2013 n = 39	**spray gel 40mg diclofenac sodium tds for 72h before knee surgery**	**Diclofenac 4% Spray Gel 48 mg bd topical** n=17	**Diclofenac 4% Spray Gel 48 mg tds topical** n=14
	Cmax ng/mL (range)	4.1 (1.3-7.9)	4.2 (1.1-23.0)

AUTHOR	METHODOLOGY	PK DATA (UNITS)	
Diclofenac 4% spray gel vs Voltaren® Emulgel			
Martin et al 1997 (half licensed dose)	**Single dose 60 mg crossover** (n=8 females)	**Diclofenac 4% spray gel Mean ± SD**	**Voltaren® Emulgel Mean ± SD**
	*$C_{max0-48}$ (ng/mL)	3.87 ± 2.47	4.69 ± 2.3
	$t_{max0-48}$ (h)	22.9 ± 10.3	22.5 ± 6.0
	AUC_{0-48} (ng*h/mL)	81.17 ± 16.97	123.77 ± 62.31
	Urinary excretion total diclofenac 0-48 (μg)	86.49 ± 41.48	160.53 ± 141.02
	Urinary excretion total 4-OH diclofenac 0-48h (μg)	357.21 ± 188.59	577.62 ± 473.87
	Multiple dose 15mg qds (13 doses) (n=4 females) 1st dose 2-24h/ last-dose (0-24h)	**Mean ± SD**	**Mean ± SD**
	C_{max} (ng/mL)	2.20 ± 2.02 / 1.99 ± 1.51	3.3. ± 1.77 / 2.23 ± 0.36
	t_{max} (h)	12.5 ± 13.3 / 101.5 ± 3.8	18.5 ± 11.0 / 102.0 ± 4.3
	AUC_{0-24} (ng*h/mL)	17.73 ± 11.01	40.26 ± 17.41
	Urinary excretion total diclofenac 0-24 (μg)	13.69 ± 8.53 / NA	29.05 ± 26.72 / NA
	Urinary excretion total 4-OH diclofenac 0-24h (μg)	17.58 ± 12.72 / NA	20.54 ± 2.09 / NA

*Free and conjugated diclofenac

Voltaren® Emulgel			
Riess et al. 1986 n = 8	Voltaren® Emulgel 2.5g tds (75 mg diclofenac/day)	C_{max} (ng/mL)	~5ng/ml (mean estimated from graph)
		Css ng/ml	7.6-15.2 ng/mL
Radermacher 1991 n= 10 patients with inflamm. arthropathies (8RA)	Voltaren® Emulgel 80mg tds applied to knee as 2 strips and occluded for 4,4,12h daily for 4 days vs placebo	Cmax ng/mL	40.6 ± 4.7
Gondolph-Zink et al. 1996	Emulgel 80mg tds 2-5 days before knee surgery	Ipsilateral (n=14)	**{Plasma}ss** 4.92-46.34 (mean 16.69; median 13.38; SD 12.61)
		Contralateral (n=9)	6.30-28.39 (mean 16.69; median 15.21; SD 6.36) p = n.s.
Dehghanyar 2004 n=6 males, 2-way crossover		**Plasma**	**Mean (±SEM)**
	60mg tds 4 days on 100cm² unoccluded skin	Cmax (ng/mL)	8.54 (1.49)
		AUC (ng.h/mL)	2.53 (0.38)
	300mg single dose on 100cm² unoccluded skin	Cmax (ng/mL)	1.45 (0.48)
		AUC (ng.h/mL)	0.17 (0.06)
VOSG-PN-107	Steady-state, relative	**Voltaren (sodium)**	**Voltaren (diethylamine)**

n=18	bioavailability (N=18) 160 mg (4g over 400 cm^2 to one knee qid) for 7 days	**1% Gel** **Mean ± SD** (except tmax median (range))	**1.16% Emulgel** **Mean ± SD** (except tmax median (range))
	Css ng/ml	15.7 ± 11.9	14.0 ± 8.86
	$t_{max\ ss}$ (h)	18 ± (0-24)	20 ± (0-24)
	AUC_{0-24} (ng*h/mL)	207 ± (140)	194 ± (95.9)
VOSG-PE-113 n=126 20M, 20F 7 day crossover	Dose linearity and Relative Bioavailability of topical 160mg / 480mg daily Emulgel with 150mg daily oral diclofenac sodium tabs	**Voltaren Emulgel 1% 4g (160mg)**	**Voltaren Emulgel 1% 12g (480mg)**
	Cmax (ng/mL)	15.0 ± 7.33	53.8 ± 32.0
	t_{max} (h)	14 ± (0-24)	10 ± (0-24)
	AUC_{0-24} (ng*h/mL)	233 ± 126	807 ± 478

Authorised doses:

Spray gel	120 mg diclofenac daily
Emulgel	120-160mg diclofenac daily

Local Bioavailability

The available data are summarized in the table 4 below. Comparisons across formulations need to take into account recent improvements to assay technique, different tissues investigated with spray gel and Voltarol, study size, permeation differences to different tissues due to local physiology such as blood flow, lack of AUC calculation from Voltaren studies, interstudy variability, and factors such as skin of varying thickness, temperature and internal vasculature and the nature and depth of the target peri-articular tissues [subcutaneous, muscular, synovial].

Table 4 Tissue Pharmacokinetics

AUTHOR	DETAILS	FORMULATION	
		DICLOFENAC 4% SPRAY GEL	
Efe 2013 n=39	spray gel 40mg diclofenac sodium tds	**Diclofenac 4% Spray Gel 48 mg bd topical**	**Diclofenac 4% Spray Gel 48 mg tds topical**

	for 72h before knee surgery	**n=17**	**n=14**
	Synovial fluid (ng/mL)	3.0 (0.4–408.5)	2.7 (0.3–47.1)
	Synovial tissue (ng/g)	40.9 (1.2–1232.0)	74.9 (4.3–594.0)
Menke 2002 Study MD 0102 n=12		**Diclofenac 4% Spray Gel Median [95% CI]**	**Voltaren© 50mg oral Median [95% CI]**
	Subcutaneous tissue	13.12 [9.34; 33.56]	1.90 [1.58; 2.54]
		3.0 [0.0; 7.0]	3.0 [3.0; 5.0]
		21.47 [19.36; 50.48]	8.62 [7.00; 10.63]
	Muscle tissue	12.28 [6.22; 22.01]	2.55 [2.00; 3.99]
		0.0 [0.0; 7.0]	2.0 [2.0; 6.0]
		18.22 [11.78; 28.10]	8.78 [7.75; 12.25]
		EMULGEL	
Riess et al 1986	2.5g Voltaren® Emulgel qds (≡100mg/day) for 13 doses	Tissue	Range
		Synovial fluid (ng/mL)	141-3810
		Synovial tissue (ng/g(ml))	160-3280
Radermacher 1991 N= 10 patients with inflammatory arthropathies (8RA)	Voltaren® Emulgel 80mg tds to knee as 2 strips and occluded for 4,4,12h daily for 4 days vs placebo	Synovial fluid (ng/mL) diclofenac-treated knee	25.5 ± 3.6
		Synovial fluid (ng/mL) placebo-treated knee	21.6 ± 2.0
Dehghanyar et al 2004 n= 6 males, 2-way crossover		**Subcutaneous Tissue Mean (±SEM)**	**Plasma Mean (±SEM)**
60mg tds 4 days on 100cm^2 unoccluded skin	Cmax (ng/mL)	0.96 (0.06)	8.54 (1.49)
	AUC (ng.h/mL)	0.10 (0.06)	2.53 (0.38)
	$AUC_{subcutis/plasma}$ ratio	0.08 (0.02)	
300mg single dose on 100cm^2 unoccluded skin	Cmax (ng/mL)	116.74 (101.78)	1.45 (0.48)
	AUC (ng.h/mL)	5.34 (4.69)	0.17 (0.06)
	$AUC_{subcutis/plasma}$ ratio	60.85 (57.59)	
Gondolph-Zink et al. 1996 80mg Voltaren Emulgel tid to single knee: ipsilateral (n=14), contralateral (n=9)		**Compartment**	**Mean (Range)** (ng/mL)
		Plasma IK	18.56 (7.55-28.39)
		Plasma CK	16.69 (4.92-46.31)
		Skin Ipsilateral knee (IK)	35700 (4770-85830)
		Skin Contralateral knee (CK)	430 (23-2020)
		Subcutaneous IK	120 (5.9-1000)
		Subcutaneous CK	13 (99-540)
		Muscle IK	10 (0-479)
		Muscle CL	6 (0-23)
		Synovium IL	020 (5-90)
		Synovium CK	19 (2.3-40)
		Synovial tissue IK	26 (6-84)
		Synovial tissue CK	26 (0-84)

Overall, the CHMP considered that a number of varied pharmacokinetic studies and comparisons have been covered by the applicant from many different and international centres with variable methodological quality. Additional variables to take into consideration in quantifying the comparative pharmacokinetics of topical formulations result from trying to apply similar quantities upon a similar area of skin of varying thickness, temperature and internal vasculature and the nature and depth of the target peri-articular tissues [subcutaneous, muscular, synovial].

Applying 80-125% confidence intervals as with bioequivalence studies would not be appropriate and clinical judgement from a less well-defined approach is required.

The overall picture from these different studies does show some phamacokinetic consistency across these diclofenac-containing formulations, notwithstanding the above variabilities.

Considering all the variability, tissue concentrations for spray gel and other topical diclofenac formulations including Emulgel are within what is considered to be an effective efficacy range around the target tissues. Furthermore, the plasma concentrations [as evidenced in Martin et al 1997 – table 4 above] reveal similar and very low levels for both spray gel and Emulgel [3.8 v 4.6 ng/ml and 2.2 v 3.3 ng/ml for single dose and steady state comparisons respectively] – confirming the very small potential for systemically associated side effects.

In summary, the systemic absorption is low enough that the adverse event profile seen with oral or other systemically administered NSAIDs is not problematic and the levels of diclofenac in the target tissues for these topical products lie within the range thought to exert clinical benefit.

Pharmacodynamics

Inhibition of the COX-1 enzyme is believed to be responsible for the deleterious GI effects of NSAIDs, while the anti-inflammatory effects are primarily derived from inhibition of COX-2. Although diclofenac is a non-selective COX-1/2 inhibitor, the topical application intended for Diclofenac Sodium 4% Spray Gel should minimize the systemic amount available and thus reduce the GI effects. In order to investigate this, a pharmacodynamic study was performed comparing the effects on gastric prostaglandin synthesis (mediated via COX-1) of Diclofenac Sodium 4% Spray Gel, a selective COX-2 inhibitor (Celecoxib), a non-selective COX-1/COX-2 inhibitor (Naproxen), and placebo. Data from this study (TD-04-01) has been submitted in support of the available literature for this application and it is part of the current dossier, as it has been submitted previously during the renewal procedure (UK/H/0563/001/R01) in 2006.

<u>TD-04-01: A Safety Study of TDS-943 (Diclofenac Sodium 4% Spray Gel,) Hawkey, 2006</u>

This study, a phase III, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover study in outpatients, investigated the effects of a 15-day dosing regimen compared (a) ex vivo gastric mucosal prostaglandin synthesis (primary parameter), (b) whole blood COX-1 and COX-2 activity, and (c) acute gastroduodenal ulcers/erosions in the following treatment groups for

1) 120 mg/day (40 mg tds) of Diclofenac Sodium 4% Spray Gel applied to one knee (n=26)
2) the COX-2 selective inhibitor oral Celecoxib 200 mg od (n-39)
3) the non-selective COX-1/2 inhibitor oral Naproxen 500 mg b.i.d. (n=13)
4) placebo (n=39).

<u>Methods</u>

Following an overnight fast, subjects provided 3 blood samples for COX-1 (assayed using thromboxane B2 [TXB2]), COX-2 (assayed via lipopolysaccharide [LPS]-stimulated prostaglandin E2 [PGE2]), and diclofenac plasma assays, and immediately underwent gastro-duodenal endoscopy at the baseline visit of each study period. Those without remarkable endoscopic findings received double-blind study medication for the next 15 days.

On Day 15, fasted subjects again provided blood samples and underwent an endoscopy which included a gastric biopsy for the determination of gastric mucosal prostaglandin E2 (PGE2) synthesis. These procedures were repeated over each study period after a 14-21 day washout period.

Results
51 subjects were randomized and treated (26 received Diclofenac Sodium 4% Spray Gel).

Table 5 Effects of tested NSAIDs on prostaglandins and COX enzymes (TD-04-01)

Analyte	Mean ± SD			
	Placebo (n=39)	Diclofenac Spray (n=26)	Celecoxib (n=39)	Naproxen (n=13)
Gastric PGE2 (pg/mL/min)	341.2 ± 186.8	309.2 ± 153.6	193.7 ± 159.9	57.8 ± 39.1
p-value vs. placebo	-	0.817	<0.001	<0.001
COX-1 Inhibition (TXB2)	–0.3 ± 33.6	–17.7 ± 34.7	–18.4 ± 31.7	–99.4 ± 1.0
p-value vs. placebo	-	0.112	0.051	<0.001
COX-2 Inhibition (LPS-PGE2)	–22.4 ± 25.5	–29.4 ± 52.1	–71.7 ± 24.5	–85.3 ± 14.2
p-value vs. placebo	-	0.130	<0.001	<0.001

These results following the topical administration of Diclofenac Sodium 4% Spray Gel to one knee for 15 days show minimal effects on COX-1 and COX-2 activity, no inhibition of gastric prostaglandin synthesis, and does no evident gastric lesions, entirely consistent with very low systemic absorption of diclofenac from this topical formulation.

Discussion on Clinical Pharmacology

The CHMP considered that the active substance diclofenac and its general pharmacodynamics and pharmacokinetics have been well-described in the medical literature.

While only sub-therapeutic, non-toxic plasma concentrations of diclofenac are achieved in the systemic circulation following administration of therapeutic doses of Diclofenac Sodium 4% Spray Gel, therapeutically relevant concentrations of diclofenac are achieved in the target tissue beneath the application site with Cmax concentrations higher in tissue than plasma.

The concentrations attained are equivalent to or higher than those after dose-equivalent oral administration of the marketed product, Voltaren Tablets. Diadermal penetration to the target tissue is clearly preferred to distribution to the systemic circulation. The very low relative systemic bioavailability of not more than 2% reduces the high incidence of ADRs commonly seen for oral NSAIDs, especially those related to the GI tract and of more recent concern with diclofenac cardiovascular side effects observed at low frequency.

2.4. Clinical Efficacy

Supporting Efficacy / Safety study (Study 9702 SUV)

The application was supported by a double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of diclofenac 4% spray gel in the treatment of ankle injury (published as *Predel HG et al. A randomized, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of diclofenac 4% spray gel in the treatment of acute uncomplicated ankle sprain. Journal of International Medical Research 41(4) 1187–1202. 2013.*

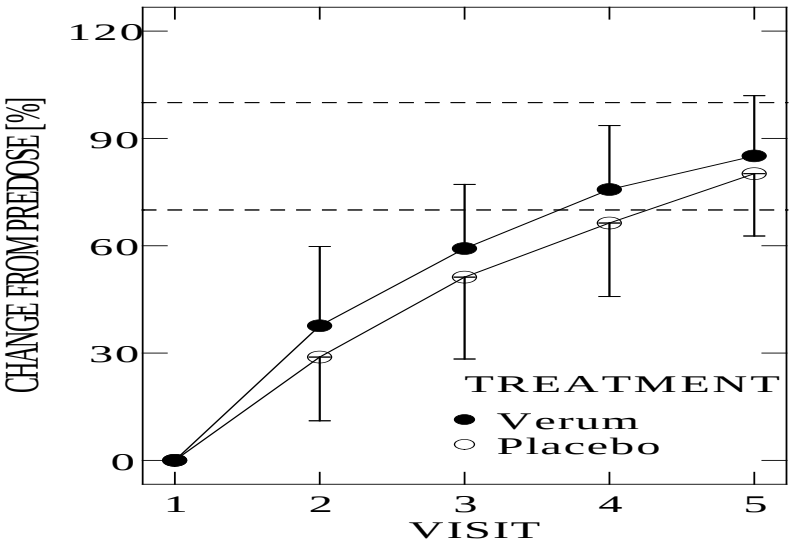
The primary endpoint was an objective measurement of swelling (50% decrease by day 10), marked with tattooing points and based on ITT population. Other efficacy endpoints included the decrease of spontaneous pain VAS and symptoms, pain on active movement, tenderness, the consumption of analgesics and global assessments of therapeutic efficacy by investigator and patients. The study duration was two weeks, measurements at days 3, 7, 10 and 14.

Two-hundred and thirty six (236) patients entered the study and 120 and 116 patients, respectively, were randomised into the verum and the placebo group. One centre (centre 9) including 40 (20 active, 20 placebo) patients was excluded, having shown signs of false documentation. The 40 patients were excluded from the “All randomised patients set” resulting in 100 patients in the Verum treatment group and 96 patients in the Placebo treatment group. Five other patients were excluded to leave a ‘Full Analysis Set’ with 97 patients on active, and 94 on placebo.

Primary endpoint

The defined primary endpoint response, expressed as a decrease in swelling of at least 50% during 10 days of treatment for the ‘Full Analysis Set’ (FAS) was reached in 87/97 patients treated with diclofenac spray gel (89.7%) compared to 74/94 treated with placebo (78.7%); p = 0.0292 (one-tail) and p = 0.0467 (two-tail). The study was designed and powered to demonstrate superiority with a significant level of 5% one-sided, which was achieved but the current requirement is now that a significance level of 2.5% one-sided needs to be demonstrated.

Figure 1 **Relative change in Swelling (mean ± standard deviation) (verum 97, placebo 94 patients). Full analysis set. Dashed lines represent the 50 and 100 % limits.**



At each visit, there was also a statistically significant difference in favour of the diclofenac spray gel for decrease in swelling.

There was a trend towards less swelling in those patients on the 'active' medication at baseline, so this assessment was evaluated as relative change calculated as a percentage. 97 patients taking verum and 94 patients taking placebo were eligible for efficacy analysis.

A later analysis of medians of the population of patients who did not take rescue medication was provided comparing to the FAS using 95% Confidence Intervals.

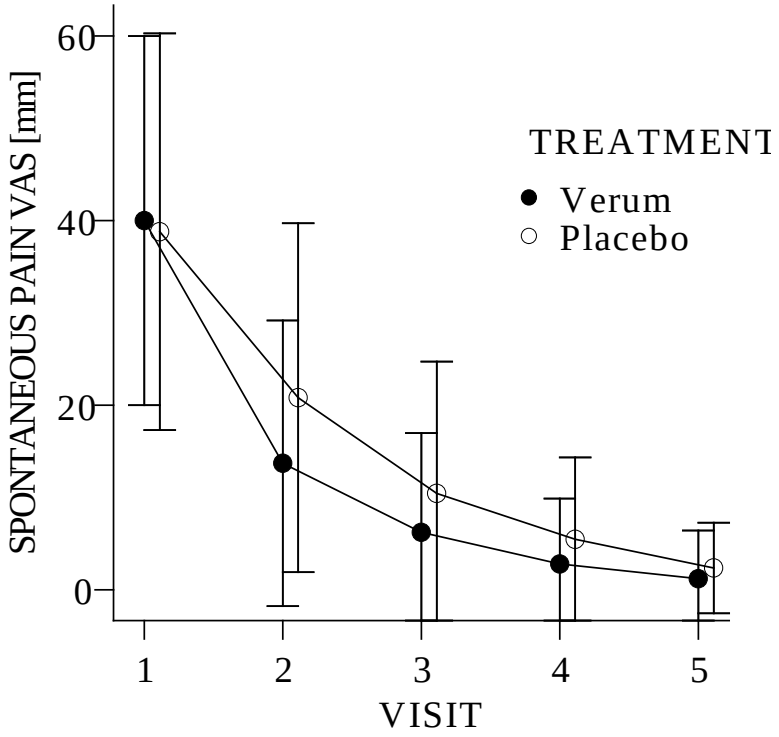
The confirmed statistically significant superiority of verum against placebo in swelling reduction was seen across the analyses of "Full analysis set", "Full analysis set, no rescue medication subgroup set", the "Per protocol set" and the "All randomised patients set" after exclusion of the 20 patients taking verum and 20 patients taking placebo from Centre 9 in whom a severe violation of protocol arose.

Though the primary endpoint was not statistically significant, all the results are in favour of the active treatment. Particularly the endpoint of main interest which is pain. The study can be considered supportive of efficacy in the context of this bibliographic application.

Secondary endpoint

An effect was seen on the critical secondary endpoint of spontaneous pain VAS. The difference in median VAS score was 8mm at day 4. Baseline pain was higher on the active arm which led to more use of rescue medication. However, in the subgroup of patients who did not receive rescue medication, the results also favour the diclofenac arm with a difference of 9mm in median VAS at day 4.

Figure 2 **Spontaneous pain VAS (mean ± standard deviation) in patients with uncomplicated ankle distortion before and under topical t.i.d. treatment with Verum (97 patients) and Placebo (94 patients). Full analysis set.**



Spontaneous pain (verbal score)

This showed a comparable result and demonstrated superiority of verum on study days 10-11 and 13-15 (p=0.0037 ** and p=0.0028 **).

Pain on active movement

This demonstrated superiority of verum vs placebo on study day 3-4 (p=0.0114 *) and study day 7-8 (p=0.0252 *).

Global Efficacy

This was judged by investigators as "Very good" in 67/97 verum patients and 52/94 placebo patients. Patient judgement frequencies were “Very good” in 67/97 verum and 53/94 placebo. Between group statistics were made separating between "Very good" and the remaining categories with verum statistically significantly superior (p=0.0349 * (investigators) and p=0.0479 * (patients)).

Other Secondary Analyses

In terms of tenderness and impairment of passive joint movability, there were no significant differences between verum and placebo.

Rescue medication results for paracetamol 500 mg tablets (1-7 tablets range) were: 32/97 (33.0 %) verum patients vs 20/94 (21.3 %) placebo patients, which is considered to be driven by a higher level of baseline pain in the verum arm.

The MAH also provided a cross-study comparison of the results from this study with other similar studies conducted with the Emulgel/other topical diclofenac formulations to show the efficacy was comparable and thus provide additional evidence on bridging between the formulations.

Discussion on clinical efficacy

This study [9702 SUV] was considered to be a 'pivotal' part of the data in the original National bibliographic application in 2001/2. However after its publication and during this wave it was accepted by that it should be relegated to a supporting literature study [*Predel HG et al. A randomized, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of diclofenac 4% spray gel in the treatment of acute uncomplicated ankle sprain. Journal of International Medical Research 41(4) 1187–1202. 2013.]*

It is accepted that the results of this study are not considered compelling. The choice of an unvalidated parameter – joint swelling – may be considered in retrospect to have been unwise [although objective] and perhaps, less reliable than pain as a measure of efficacy. Hence, because of the recent discussions, further analyses were requested for consideration on secondary criteria – not as a substitute for the primary criterion but as a check and confirmation that all or most of the analyses favoured the active spray gel over placebo.

The CHMP also noted that the centre 9 was excluded as data from this centre are considered unreliable from both efficacy and safety considerations, and may have not have been based on any actual patients.

The main pre-defined criterion for efficacy was compromised by a change in statistical and regulatory definitions and may not have been the ideal parameter for judging efficacy in the clinical environment. Study 9702 SUV was planned in 1998 with a significance level of 5% one-sided and it achieved that level for the primary endpoint of swelling reduction. However regulatory requirements have changed over time and it is now considered necessary to demonstrate superiority with a significance level of 2.5% one-sided. The study did not achieve this level but it was not powered to do so at the time. Focusing on the point estimates the results indicate superiority of the active over placebo.

Nonetheless the analyses, including some post-hoc analyses requested during the procedure, can all be taken as supportive of the superiority of spray gel over placebo.

Overall, these data are consistently supportive with modest beneficial effects for spray gel over the placebo arm in a type of clinical study where a potent clinical difference would not be anticipated as VAS score improvements are generally smaller in this clinical area than deemed clinically significant in many other fields. In summary, in this study:

- The response rate for swelling (primary endpoint) was 87/ 120 (73%) on active and 74/116 (64%) on placebo.
- An effect was also seen on spontaneous pain. The difference in median VAS score was 8 mm at day 4.
- Baseline pain was higher on the active arm which led to more use of rescue medication.
- However in the subgroup of patients who did not receive rescue medication the results also favour the diclofenac arm with a difference of 9 mm in median VAS at day 4.
- Therefore, although the primary endpoint is not now considered statistically significant, all the results are in favour of the active treatment.

In conclusion, this study is not considered a pivotal part of the application but can be considered supportive of spray gel efficacy in the context of this bibliographic application. It is not claimed to show compelling clinical efficacy.

In view of the provided data on bridging of efficacy data from spray gel to other topical diclofenac products there is an overall conclusion that despite variability, topical NSAIDs including diclofenac formulations have a well-established role with modest efficacy benefits but more importantly their use avoids systemic adverse effects associated with oral diclofenac and other NSAIDs.

2.5. Clinical Safety

Supporting Efficacy / Safety study (Study 9702 SUV)

Until visit 4 the number of patients from the "Safety evaluation set" (100 patients verum and 96 patients placebo that started the trial) in the Predel study had slightly decreased to 95 verum under 92 placebo. Due to a considerable portion of patients prematurely withdrawn caused by premature healing that was allowed according to trial protocol, the number of patients fell to 70 verum and 82 placebo at Visit 5.

The safety analysis was also conducted with the exclusion of the 40 patients from centre 9.

Seven adverse events occurred in 6 patients given diclofenac spray gel while 8 events occurred in 8 patients taking placebo. One patient from each group was prematurely withdrawn, moderate stomach pain being reported in one patient who had also resorted to taking oral diclofenac, whilst a case of flu occurred in the placebo group. Laboratory tests, including a minority of patients tested for the presence of blood in the stool, showed no clinically significant changes.

Discussion on clinical safety

CHMP is of the view that topical NSAIDs, including this diclofenac spray gel product have a proven safety record. In particular their use reduces the risk of gastrointestinal and other serious adverse events compared to oral and other systemically administered NSAIDs, which is supported by the published clinical data provided by the applicant.

3. Benefit-risk balance

Diclofenac is an NSAID whose main mechanism of action is attributed to the inhibition of prostaglandin synthesis, although other mechanisms have been identified, such as interactions with other mediators and enzyme systems, effects on the immune reaction, and inhibition of the synthesis of oxygen radicals. Among the NSAIDs, diclofenac on a molar basis is one of the most effective inhibitors of COX (i.e. of antipyretic properties). The efficacy and safety of diclofenac is well described. Systemic toxicity of oral NSAIDs is dose-related and topical formulations have therefore been developed to achieve high local concentrations of the active ingredient at the affected site together with low plasma concentrations in order to minimize systemic adverse events.

Topical NSAIDs such as Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution provide modest benefits across a range of symptomatic musculoskeletal conditions, and importantly reduce the potential for the more serious AEs that can be associated with systemically-introduced NSAIDs.

The qualitative comparison between spray gel and Emulgel is based on composition, degree of ionization and complete solubility of active substance. Although the strength of the proposed

cutaneous spray is 4% as compared to the Emulgel which is 1% or 2%, this difference in the cutaneous spray was designed to deliver a similar amount of diclofenac to local tissues as the Emulgel.

In view of clinical pharmacology, the plasma and tissue pharmacokinetic (PK) data of spray gel in healthy volunteers, and patients with acute inflammation, are compared to those of Voltaren Sodium Gel and Voltaren Emulgel. Most of the data are cross-study comparisons which are affected by different doses and methods and so no robust conclusions can be drawn from these cross-study comparisons. Nevertheless, it is consistently seen across studies that measurable levels of diclofenac have been reported after application of the spray gel both in systemic exposure and topical exposure (subcutaneous tissue and muscle tissue) at the site of action. The only intra-study comparative data that is available is from study Martin et al. 1997 which indicated that the systemic absorption is comparable for spray gel and Emulgel, but a conclusion on equivalence - and clinical relevance of systemic absorption - cannot be drawn. Numerically, the exposure of spray gel is lower than Emulgel and its impact on efficacy cannot be ascertained accurately. However, the systemic exposure is low enough that the adverse event profile seen with oral or other systemically administered NSAIDs is not problematic.

On clinical efficacy the applicant included a review of the Predel 2013 study [previously known as Study 9702SUV] on the efficacy of spray gel in acute ankle injury. The defined primary endpoint response, expressed as a decrease in swelling of at least 50% during 10 days of treatment for the 'Full Analysis Set' (FAS), was reached in 87/97 patients treated with diclofenac spray gel (89.7%) compared to 74/94 treated with placebo (78.7%); p = 0.0292 (one-tail) and p = 0.0467 (two-tail). The study was designed and powered to demonstrate superiority with a significant level of 5% one-sided, but the current requirement is now that a significance level of 2.5% one-sided, which the study could not reach.

An effect was seen on the critical secondary endpoint of spontaneous pain visual analogue scale (VAS). The difference in median VAS score was 8 mm at day 3-4 and 4.6mm at day 7-8. Particularly the endpoint of main interest is pain. However, this study cannot be considered to provide confirmatory evidence on efficacy of spray gel as the primary endpoint is not validated and statistical analysis does not meet regulatory requirements. However, the study can be considered supportive of efficacy to infer that spray gel has beneficial activity in the context of this bibliographic application.

The applicant has also reviewed the available published clinical trial literature on topical diclofenac which includes a study on effects of Emulgel on Joint Pain (Predel 2012), study on DHEP (Diclofenac hydroxyethylpyrrolidine plaster), Heparin plaster or placebo plaster (Constantino C et al. 2011) and an uncontrolled study on DHEP gel. All these studies provide evidence on modest efficacy for authorised topical diclofenac formulations of which the most robust is study Predel 2012 with Emulgel,. Further as the systemic and topical exposure data of Emulgel is available for comparison to spray gel, the Marketing Authorisation Holder bridged the efficacy of Emulgel to spray gel based on a cross-study comparison of the efficacy endpoints, which are however confounded by differences in study methods and populations. Nevertheless, while it is acknowledged that the efficacy of Emulgel cannot be directly attributed to Diclofenac Sodium Spray Gel 4 %, it is also reasonable to infer that Diclofenac Sodium Spray Gel 4 % has a beneficial effect based on the supportive Predel 2013 study, PK comparisons and cross-study comparisons in a similar range as seen for other topical diclofenac products.

Overall, these data are consistently supportive with modest beneficial effects for spray gel over the placebo arm in a type of clinical study where a potent clinical difference would not be anticipated as VAS score improvements are generally smaller in this clinical area than deemed clinically significant in many other fields.

The data from the published clinical study SUV 9072 can – despite the acknowledged limitations - be taken as supportive of the superiority of spray gel over placebo.

In view of safety, the CHMP agreed that topical NSAIDs, including Diclofenac Sodium Spray Gel 4 %, have a proven safety record over many more than 10 years, which is supported by their low systemic bioavailability compared to e.g. oral pharmaceutical forms. In particular their use and substitution for oral and other systemically administered NSAIDs makes a major contribution to patient well-being in view of the available safety data, which supports a markedly lower risk of potentially serious adverse events compared to systemically administered diclofenac containing products.

The literature on topical diclofenac, when taken in conjunction with the diclofenac tissue concentrations achieved with the spray gel, provides sufficient reassurance on the efficacy and safety of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution achieved by its use.

Taken together, the available data support a positive benefit-risk balance.

4. Grounds for Opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC,
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as a potential serious risk to public health. The Committee considered the available data submitted in support of the use of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution and associated names , which included a comparison of quality aspects in relation to authorised topical diclofenac products, and literature covering pharmacokinetic (local and systemic) as well as efficacy and safety data.
- The Committee was of the view that the totality of data submitted justified the efficacy of the applied medicinal product as well as the bridging to the literature, in particular to existing data on topical diclofenac formulations including Voltarol Emulgel formulations.

The Committee, as a consequence, considers that the benefit-risk balance of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution and associated names. The product information remains as per the final version achieved during the Coordination group procedure.

Appendix 1 Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1467

Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution and associated names (INN: Diclofenac sodium)

Divergent position

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution indicated for "local symptomatic relief of mild to moderate pain and inflammation following acute blunt trauma of small and medium-sized joints and periarticular structures".

In line with the requirements for a well-established use application, the applicant must ensure that the published data referred to are relevant for the product applied for. In the view of the divergent CHMP members, an adequate bridge between Diclofenac Sodium Spray Gel 4 % Cutaneous Spray and the submitted published studies using other diclofenac-containing topical products has not been established for the following reasons:

- As Diclofenac Sodium Spray Gel 4% is a complex formulation and the formulations used in the published studies including Voltaren 1% and 2% Emulgel are very different, the approach of bridging by means of *in vitro* data only is not acceptable.
- Only one study compared the systemic absorption of Diclofenac Sodium Spray Gel 4% and Voltaren 1% Emulgel. This study MD 0102 [Martin et al. 1997] demonstrated a lower systemic bioavailability of Diclofenac Sodium Spray Gel 4% suggesting a lower tissue penetration and thus lower efficacy compared with Voltaren 1% Emulgel.
- Presented across study comparisons with published results on Voltaren® 2% Emulgel [Predel HG et al. 2012] and other diclofenac products [Costantino C et al. 2011, Mahler P et al. 2003] are hampered by differences in patient populations and primary efficacy endpoints studied.
- The (supportive) clinical study 9702 SUV P 9902 [Predel HG et al. 2013], conducted with Diclofenac Sodium Spray Gel 4%, failed to show statistical significance with respect to the primary endpoint "reduction of swelling" (irrespective whether this endpoint would be acceptable or not). Considering other secondary endpoints in order to "rescue" the study is not acceptable.

Thus, efficacy of Diclofenac Sodium Spray Gel 4% in the claimed indication has not been sufficiently demonstrated rendering the B/R relationship of this product unfavourable.

CHMP Members expressing a divergent opinion:

- Alexandre Moreau
- Blanka Hirschlerova
- Concepcion Prieto Yerro
- Constantinos Markopoulos
- Jan Mueller-Berghaus

- Johann Lodewijk Hillege
- Martina Weise
- Ondrej Slanar
- Rajko Kenda
- Sinan B.Sarac
- Sol Ruiz