Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Voltarol 12 Hour Emulgel P 2.32% Gel/ Voltarol Extra Strength Emulgel P 2.32% Gel

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(diclofenac diethylamine)

UK Licence No: PL 00030/0444 and 0447

Novartis Consumer Health UK Limited, trading as Novartis Consumer Health

LAY SUMMARY

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(diclofenac diethylamine)

This is a summary of the Public Assessment Report (PAR) for Voltarol 12 Hour Emulgel P 2.32% Gel/Voltarol Extra Strength Emulgel P 2.32% Gel (PL 00030/0444) and Voltarol 12 Hour Emulgel 2.32% Gel/Voltarol Extra Strength Emulgel 2.32% Gel (PL 00030/0447). For ease of reading, the products may be collectively referred to as 'Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL)' in this lay summary. It explains how Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL).

For practical information about using Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL), patients should read the package leaflets or contact their doctor or pharmacist.

What are Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) and what are they used for?

Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) are used to relieve pain and reduce inflammation and swelling in a number of painful conditions affecting the joints and muscles.

These medicines can be used to treat:
• muscle and joint injuries (e.g. sprains, strains, bruises, backache, sports injuries), relieving pain and helping recovery back to normal function;
• tendonitis (e.g. tennis elbow), swelling around elbow or knee.

These medicines are intended for use in adults and children aged 14 years and older.

How do Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) work?

Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) contain the active substance diclofenac diethylamine (also known as diclofenac diethylammonium) which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). The medicines are specially formulated for rubbing into the skin.

How are Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) used?

Voltarol Emulgel P Gel is Pharmacy (P) medicine, available in pharmacies under the supervision of a pharmacist.

Voltarol Emulgel Gel (GSL) is a General Sale List (GSL) medicine, which can be obtained without a prescription, at pharmacies, supermarkets and other retail outlets.

The products are available in the pharmaceutical form of a gel and are specially formulated for rubbing into the skin.

The patient should always use these medicines exactly as described in the package leaflet. The patient should check with his/her doctor or pharmacist if they are not sure.

How much Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) to use

<u>For adults and adolescents 14 years and over</u>
The gel should be applied twice a day (preferably morning and evening) on the painful area.

How to apply Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL)

1. To remove the seal before first use, unscrew and remove the cap. Use the reverse side of the cap to insert, twist and remove the seal from the tube.
2. The patient should gently squeeze out a small amount of gel from the tube and apply to the painful or swollen area, slowly rubbing into the skin. The amount needed will vary depending upon the size of the painful or swollen area; an amount ranging in size from a 1 penny to a 2 pence piece will usually be sufficient (2–4g). The patient may notice a slight cooling effect when the gel is rubbed in. The patient should only use the smallest amount of Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) needed to relieve the pain but should never use more than 8g per day and 56g in one week.
3. Unless the hands are the site being treated, the patient should wash his/her hands after rubbing in the gel, to avoid accidental contact with the mouth and eyes (see section 4 of the package leaflet).

Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) are for external use only.

How long should Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) be used for?
The patient should not use Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) for more than 14 days unless longer treatment is recommended by a doctor.

If the pain and swelling do not improve within 7 days, or if they get worse, the patient should tell his/her doctor.

In children aged 14 years and over, if the product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) have been shown in studies?
Novartis Consumer Healthcare UK Limited, provided some data on efficacy and safety of diclofenac from its own studies. In addition, data were provided from the published literature on diclofenac. These studies have shown that Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) are effective in the proposed indications to relieve pain in adults and children aged 14 years and older.

What are the possible side effects of Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL)?
Like all medicines, Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) can cause side effects, although not everybody gets them.

Some rare and very rare side effects might be serious
If the patient experiences any of the following signs of allergy, he/she should stop using Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) and tell a doctor or pharmacist immediately:

- Skin rash with blisters; hives. (These side effects are likely to affect 1 to 10 people in every 10,000).
- Wheezing, shortness of breath or feeling of tightness in the chest (asthma). (These side effects are likely to affect less than 1 person in every 10,000).
- Swelling of the face, lips, tongue or throat. (These side effects are likely to affect less than 1 person in every 10,000).

Other side effects which may occur are usually mild, passing and harmless (if the patient is concerned, he/she should tell a doctor or pharmacist).

Common side effects (likely to affect between 1 and 10 in every 100 patients)

- Skin rash, itching, reddening or smarting of the skin.

For the full list of all side effects reported with Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL), see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL).

Why are Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) approved?
It was concluded that, in accordance with EU requirements that, for Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL), its benefits are greater than the risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL)?
Safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL), including the appropriate precautions to be followed by healthcare professionals and patients.

During the national assessment procedure, Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) were re-classified from a Prescription Only Medicine (legal status POM) to a Pharmacy (P) medicine and General Sales List (GSL) medicine, respectively; an annex following this report describes the reclassification in more detail.

Marketing Authorisations for Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL)l were granted in the UK to Novartis Consumer Health UK Ltd, trading as Novartis Consumer Health, on 20 March 2013.

The Marketing Authorisations were cancelled on 30 March 2016 and 22 July 2016, respectively, following the grant of change of ownership procedures in which the Marketing Authorisations were transferred to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0154 and 0160).

The full PAR approved for Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL) follows this summary.

For more information about treatment with Voltarol Emulgel P Gel and Voltarol Emulgel Gel (GSL), read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in March 2019.

SCIENTIFIC DISCUSSION

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Scientific discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Novartis Consumer Health UK Ltd Marketing Authorisations for the medicinal products Voltarol 12 Hour Emulgel P 2.32% Gel/Voltarol Extra Strength Emulgel P 2.32% Gel and Voltarol 12 Hour Emulgel 2.32% Gel/Voltarol Extra Strength Emulgel 2.32% Gel (PL 00030/0444 and 0447) on 20 March 2013.

For ease of reading, the products may be collectively referred to as 'Voltarol 12 Emulgel P Gel and Voltarol 12 Hour Emulgel Gel' or 'Voltarol 12 Hour Emulgel P Gel/Voltarol 12 Hour Emulgel Gel' in this scientific discussion. In addition, the products may be referred to as 'diclofenac diethylamine 2.32% gel', 'diclofenac DEA 2.32% gel' or 'DDEA 2.32% gel', the proposed names used during the assessment of the applications.

Voltarol 12 Hour Emulgel P Gel is a Pharmacy (P) medicine, available through supply under the supervision of a pharmacist.

Voltarol 12 Hour Emulgel Gel is a General Sale List (GSL) medicine, which can be obtained without a prescription, at pharmacies, supermarkets and other retail outlets.

Voltarol 12 Hour Emulgel P Gel is indicated for the:

- local symptomatic relief of pain and inflammation in:
  - trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises
  - localised forms of soft tissue rheumatism
- relief of pain of non-serious arthritic conditions

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  - localised forms of soft tissue rheumatism

These national line extension applications were submitted under Article 8(3) of Directive 2001/83/EC, as amended, relating to a known active substance. Voltarol 12 Hour Emulgel P Gel and Voltarol 12 Hour Emulgel Gel are double the strength of the previously approved non-prescription Voltarol Emulgel formulations (Voltarol Emulgel P, PL 00030/0174; P legal status and Voltarol Pain-eze Emulgel, PL 00030/0212; GSL legal status). The proposed indication of the higher strength GSL product is identical to the previously approved GSL product Voltarol Pain-eze Emulgel, PL 00030/0212; however, the indication for Voltarol 12 Hour Emulgel P Gel is not identical to that for the previously approved P product (Voltarol Emulgel P, PL 00030/0174).

In the UK, the originator products for the active substance, diclofenac, are Voltarol 25mg, and 50mg tablets (PL 00001/0036, PL 00001/0082 and PL 00001/0134). These were former Ciba-Geigy licences which were later transferred to Novartis Pharmaceuticals UK Limited.

The applicant considered that the advantage of a double-strength formulation was the less frequent application (twice daily compared with up to four times a day), and the improved patient convenience and compliance that would follow.

Given that this is a higher strength formulation compared to the Marketing Authorisation Holder's existing lower strength products, reclassification applications were submitted in parallel. Details of the assessment of the reclassification are provided in Annex '1' at the end of this Scientific Discussion.

DDEA 2.32% gel contains the active substance, diclofenac (as diclofenac diethylamine). Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of

diclofenac.

Non-clinical studies conducted in support of these applications for a gel containing 2.32% diclofenac diethylamine included *in vitro* absorption studies across human cadaver skin, local tolerance studies of up to 90 days duration in rabbits, sensitisation and phototoxicity/photoallergenicity studies in guinea pigs and *in vitro* genotoxicity studies and single or repeated dose toxicity studies to qualify related substances. All the non-clinical studies were performed under GLP controlled conditions, with the exception of the *in vitro* skin penetration studies.

The supporting clinical programme consists of 5 studies examining systemic absorption, skin safety and tolerability (including sensitisation, irritancy and phototoxicity potential) as well as pivotal efficacy and safety findings in the ankle sprain model of soft tissue pain and inflammation. The clinical studies are stated to have been conducted in accordance with the current ICH – GCP guidelines.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of using DDEA 2.32% gel outweigh the risks, and Marketing Authorisations were granted.

The Marketing Authorisations were cancelled on 30 March 2016 and 22 July 2016, respectively, following the grant of change of ownership procedures in which the Marketing Authorisations were transferred to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0154 and 0160).

II. QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Voltarol Emulgel P Gel/Voltarol Emulgel Gel is a white to practically white, soft, homogeneous, cream-like gel.

Each 100 g of Voltarol 12 Hour Emulgel P Gel/Voltarol 12 Hour Emulgel Gel contains 2.32 g of the active substance diclofenac diethylamine (also known as diclofenac diethylammonium), which corresponds to 2 g diclofenac sodium. Voltarol 12 Hour Emulgel P Gel/Voltarol 12 Hour Emulgel Gel also contains pharmaceutical excipients, namely butylhydroxytoluene, carbomers, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, oleyl alcohol, propylene glycol, perfume eucalyptus sting and purified water.

Voltarol 12 Hour Emulgel P Gel/Voltarol 12 Hour Emulgel Gel is packaged in aluminium laminated tubes ([low density polyethylene/aluminium/high density polyethylene (internal layer)], each fitted with a high-density polyethylene shoulder and closed by a moulded seal. The tubes are each closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.

Voltarol 12 Hour Emulgel P Gel is packaged in pack sizes of 20 g, 30 g, 50 g and 100 g tubes. Voltarol 12 Hour Emulgel Gel is packaged in pack sizes of 20 g, 30 g and 50 g tubes.

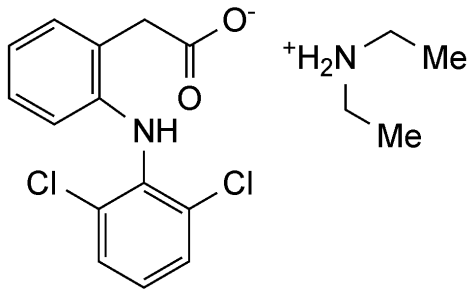
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Diclofenac diethylamine

INN: Diclofenac diethylamine
Chemical name: Diethylammonium 2-[(2,6-dichloroanilino)phenyl]acetate
Molecular formula: $C_{18}H_{22}Cl_2N_2O_2$
Structure:



Mr: 369.29
Appearance: White or light beige crystalline powder.
Solubility: Sparingly soluble in water, freely soluble in ethanol and methanol.

Diclofenac diethylamine is not the subject of a European Pharmacopoeia monograph, but it is the subject of a monograph of the British Pharmacopoeia.

The information provided on all aspects of the manufacture and control of the active substance diclofenac diethylamine is in line with that previously provided for Voltarol Emulgel. This is accepted.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a stable gel preparation that contained 2.32% of diclofenac diethylamine, double the strength of the currently licensed Voltarol Emulgel formulations (PL 00030/0174; P and PL 00030/0212; GSL). Suitable pharmaceutical development data have been provided for these applications.

With the exception of perfume eucalyptus sting, all the excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.

Voltarol Emulgel P Gel/Voltarol Emulgel Gel does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 3 years, with the special storage conditions “Do not store above 30°C.” has been approved.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the pharmacokinetic study. The pharmacokinetic study is discussed in Section IV.2, Clinical Aspects, Pharmacokinetics.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted, from a quality point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac are well-known.

The non-clinical dossier is comprised of studies conducted with the 2.32% diclofenac diethylamine (DEA) gel (local tolerance studies, a phototoxicity and a photoallergenicity test and *in vitro* skin permeation tests) and studies to qualify degradation products, as well as a summary of previous studies conducted to investigate the toxicity of diclofenac and submitted in support of the Marketing Authorisation Application for Voltaren Emulgel (1.16% diclofenac diethylamine gel). In addition, the photo-mutagenicity of diclofenac sodium was assessed in an Ames test and a chromosome aberration study, and a GLP-compliant *in vivo* clastogenicity study was also conducted.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

A summary of the submitted studies and the published references is included in the sections below.

III.2 Pharmacodynamics
New pharmacology studies have not been conducted in support of these applications and are not required. Information on the pharmacodynamics of diclofenac is available in the literature and there is extensive clinical experience. Non-clinical pharmacology has been discussed in the applicant's non-clinical overview and pharmacology written summary.

A summary of the pharmacology is provided below:

The anti-inflammatory, analgesic and antipyretic activity of diclofenac sodium have been described and reviewed in the literature.

The anti-inflammatory activity of topically applied diclofenac has also been demonstrated in animal models. Diclofenac sodium applied topically showed anti-inflammatory activity in carrageenan-induced skin and paw oedema, croton oil induced ear oedema and in the adjuvant arthritis model in rats. Gel containing 1.16% diclofenac diethylamine reduced inflammation in various models including carrageenan-induced paw oedema, an investigation of vascular permeability, an ultraviolet-induced erythema test, Randall and Selitto's test, an adjuvant arthritis study and a cotton granuloma test.

The mechanism of action involves inhibition of cyclo-oxygenase (COX), thus affecting the arachidonic acid cascade and inhibiting prostaglandin synthesis. Diclofenac also appears to inhibit leukotriene formation by decreasing arachidonic acid release and increasing its uptake, probably into triglycerides, thus limiting the availability of arachidonic acid entering the COX and lipoxygenase pathways.
The pharmacological activity of the primary hydroxy-metabolites of diclofenac has been investigated. These do not appear to contribute significantly to the activity of diclofenac sodium.

Secondary Pharmacology
Diclofenac retained its full anti-inflammatory activity in the kaolin-induced paw oedema test using adrenalectomised rats compared with sham operated rats indicating that the anti-inflammatory effect is not mediated by activation of the pituitary-adrenal axis.

Safety pharmacology
Diclofenac sodium did not produce any distinct behavioural, neurological or autonomic changes when given orally to mice at 25, 50 or 100 mg/kg.

Diclofenac sodium caused no effect at 1 µg/mL *in vitro* in an isolated guinea pig heart preparation. At 10 µg/mL there was a small increase in coronary blood flow and a slight reduction in heart rate with a variable effect on myocardial contraction. At 100 µg/mL, cardiac arrest occurred.

In conscious trained dogs given intravenous injections of diclofenac sodium at 1, 3 or 10 mg/kg, there was a slight decrease in heart rate at the high dose only; ECGs and blood pressure were not affected.

In anaesthetised domestic cats following intravenous diclofenac sodium at doses ranging from 0.1 mg/kg up to the lethal dose, slight transient increases in blood pressure were noted at doses of 0.3-10.0 mg/kg. There was no effect on respiratory volume. Biphasic effects and bradycardia were seen in two cats at 30 mg/kg, and 60 mg/kg was lethal to all four animals used. At 0.3-1.0 mg/kg, there was an increase in the pressure effects of adrenaline, but the effects of noradrenaline and acetylcholine were not influenced.

Pharmacodynamic Drug Interactions
Specific studies have not been conducted in support of this application. Potential interactions between oral diclofenac and other drugs have been extensively investigated in humans and are likely to be based on the high protein binding.

III.3 Pharmacokinetics
Distribution, metabolism, excretion and pharmacokinetic drug interactions have been discussed in the non-clinical overview and pharmacokinetic written summary and a summary of these are provided below.

Absorption
In vitro permeation studies with prototypes of the 2.32% gel in human cadaver skin and *in vivo* studies in guinea pig, rabbit and baboon with topical administration of 1.16% gel and/or oral administration were reported. A summary of the studies completed are provided below.

In vitro studies
In study **0650A**, dermal permeation of diclofenac from prototype formulations across human cadaver skin was investigated using formulations containing 2.32% diclofenac DEA and 0.5%, 0.75% or 1% oleyl alcohol. Increased permeation of diclofenac, in comparison with DDEA 1.16% gel, was seen, with similar levels of permeation observed from the prototypes containing the three different concentrations of oleyl alcohol (mean cumulative permeation ± SEM at 24 hours was 4.92±0.84, 6.11±1.27 and 5.95±1.22 µg/cm^2 for 0.5%, 0.75% and 1% oleyl alcohol, respectively). In comparison, the mean cumulative permeation ± SEM at 24 hours for Voltarol Emulgel (1.16% DDEA) was 2.07±0.38 µg/cm^2, which is about 2.5-fold to 3-fold lower than the values obtained for the 2.32% gel.

Differences in permeation as a result of changes in pH and viscosities were evaluated using human cadaver skin in studies 0806A and 0807A, respectively. Neither parameter appeared to affect permeation of diclofenac to any great extent, although there was possibly a tendency to increased permeation with increasing pH at a dose of 20 mg/cm^2 (mean cumulative permeation ± SEM at 24 hours was 1.7±0.3, 2.8±0.6 and 3.3±0.7 µg/cm^2 at pH 7.0, 7.6 and 7.9, respectively), although not at 5 mg/cm^2.

In study **0715A**, the mean cumulative permeation of diclofenac across human cadaver skin from diclofenac DEA 2.32% gel was 23.7±7.32 µg/cm^2 at 24 hours compared with 9.27±2.9 µg/cm^2 for DDEA 1.16% gel, which is about 2.5-fold higher for diclofenac DEA 2.32% gel than for diclofenac DDEA 1.16 % gel and thus in agreement with study **0650A**.

In vivo studies
Study **B90/1984** reported the extent of percutaneous absorption of diclofenac from 1.16% gel in guinea

pig (200, 400 or 800 mg/kg), rabbit (400 mg/kg) and baboon (40 mg/kg). In guinea pigs, about 8% of the dose was absorbed. In male rabbits, 16% of the dose was absorbed, but in female rabbits, absorption seemed to be much higher, at 40%. In baboons, 27% of the dose was absorbed. Absorption was calculated from total radioactivity in excreta for guinea pigs and rabbits and as total diclofenac and metabolites in urine in baboons.

This information on absorption is provided in the table below, taken from the applicant's pharmacokinetic written summary:

Table 1 Percutaneous absorption of diclofenac

Species	Sex	Dose mg/kg	Rate mg/cm2	Absoprtion % of dose	Uptake, mg/kg as:	
					Diclofenac diethylamine	Diclofenac sodium
Guinea pig	Male	200	5	8.3	0.19	0.17
		400	10	8.1	0.38	0.32
		800	20	7.8	0.72	0.62
Rabbit	Male	400	10	16	0.74	0.64
	Female	400	10	40	1.86	1.60
Baboon	Male	40	1	27	0.13	0.11

Study **B90/1984** appears to be a summary report of the results from two other studies, **B91/1984** (absorption, distribution and excretion after oral and topical application in guinea pigs and percutaneous absorption in the rabbit) and **B34/1984** (percutaneous absorption of diclofenac after topical application of DDEA salt compared to absorption after oral application of diclofenac sodium in baboons). Further details of these studies are given below.

In study **B91/1984**, approximately 8% of a single topical dose of [^{14}C]-DDEA in DDEA 1.16% gel, applied to guinea pigs with intact skin under an occlusive dressing, was recovered in urine and faeces over six days. This percentage was similar irrespective of the applied dose (200-800 mg/kg, applied at 5-20 mg/cm). When applied without occlusive dressings, about 5% of the dose (400 mg gel/kg) was recovered in the excreta over the same period. In both cases, most of the radioactivity was recovered during the first 24 hours. When the skin was stripped prior to application of the gel and an occlusive dressing was used, nearly 70% of the dose (400 mg gel/kg) was recovered, mostly within the first 24 hours.

In rabbits **[B91/1984]**, application of 400 mg gel/kg under occlusion resulted in a marked sex difference in absorption. In males, a total of 16% of the applied dose was recovered, the majority in the first 24 hours. Only 0.24% was recovered in the period 120-144 hours. In females, a total of 40% of the applied dose was recovered, most in the period 48-120 hours. Less than 1% was recovered in the first 48 hours and, although only 0.6% was recovered in the period 120-144 hours, the possibility of further excretion, indicating even greater absorption, cannot be excluded. The reason for these differences is not known.

In study **B34/1984**, absorption following topical and oral administration to 2 baboons was investigated. Following topical application of DDEA 1.16% gel (non-occluded), 11.6% of the dose (40 mg/kg) was recovered in urine in 72 hours. This included diclofenac and four hydroxylated metabolites. 3.3% of the dose was recovered in the 24-72 hour period, suggesting a continuing excretion.

Following an equivalent diclofenac dose, administered orally as diclofenac sodium to the same animals, 44% of the dose was recovered in the urine in 72 hours (<2% in the 48-72 hour period). Comparison of the percutaneous and oral absorptions reveals that the mean percutaneous absorption of diclofenac from the DDEA gel (11.6%) was 27% of the amount absorbed from an equivalent oral dose of diclofenac sodium (44%).

Distribution
Diclofenac is extensively bound to plasma proteins. Diclofenac has been reported to cross the placental barrier but to have no special affinity for any fetal tissues and is eliminated from the fetus at about the same rate as from the dam (pregnant rat). Diclofenac is found in milk but only in very small amounts.

An absorption, distribution and excretion study (**B91/1984)** in guinea pigs (3 males) was reported following topical administration of Voltaren Emulgel (400 mg/kg twice daily to non-occluded intact skin for 6 days) or a single oral dose of 1 mg/kg [^{14}C]-diclofenac DEA. This study was stated to be conducted prior to the introduction of GLP requirements.

Following the oral dose, radioactivity was measured at 1, 6, 24, 48 and 96 hours. Highest radioactivity levels were seen at 1 hour in all tissues except the kidney and sciatic nerve, where levels were highest at 6 hours post-dose. Highest levels were seen in the kidney, stomach, liver and small intestine, with lowest levels in the eye, brain and muscle. Following topical application (16 hours after the final dose), about 22% of the sum of all applied doses was absorbed percutaneously. Steady state ^{14}C concentrations in blood were reached after 3 days. The ^{14}C concentrations in the muscle under the treated skin area were about 4-fold those in muscle tissue distant from the application site. The highest levels of radioactivity were noted in the kidney and liver, reflecting the major sites of excretion.

Application of 2 g DDEA 2.32% gel twice daily for 7 days in humans reportedly led to similar systemic levels (generally below 10 ng/mL) as repeated application of 2 g DDEA 1.16% gel four times daily for 7 days.

Metabolism
No new studies were conducted. The metabolism of diclofenac is reviewed in the non-clinical overview. Diclofenac is extensively metabolised in all species examined, mainly, except in the dog, by hydroxylation of one or both of the two aromatic rings. The hydroxylated compounds formed occur mainly as conjugates and the conjugates formed differ between species. In the dog, conjugates of the unchanged drug are predominant; the major metabolite eliminated in the urine is the taurine conjugate. Conjugation of the carboxyl group on the side chain also occurs.

In rats there were substantial quantitative differences in the metabolite pattern following oral and intravenous administration, suggesting significant first pass effects in this species.

The metabolism of diclofenac in the liver is mediated both by glucuronidation and cytochrome P450 (CYP) oxidative biotransformation.

Excretion
No new studies were conducted. The excretion of diclofenac is reviewed in the non-clinical overview and in the pharmacokinetic written summary.

Pharmacokinetic drug interactions
No new studies were conducted. The potential interactions between diclofenac and other drugs have been extensively investigated in humans with orally administered diclofenac oral. No interactions have been reported with topical diclofenac.

Other pharmacokinetic studies
No studies were reported.

III.4 Toxicology
Local tolerance studies including 28-day and 90-day dermal toxicity studies, sensitisation studies and photosensitisation studies have been conducted in support of the DDEA 2.32% Gel formulation. The *in vivo* studies are shown in the table below:

Table 2

Study type and duration	Route of administration	Species	Compound administered*
7-Day repeated skin irritation in rabbits	Topical with 25mg/cm2 test product	Rabbits	DDEA 2.32% Gel
Cumulative 28 days skin irritation study in rabbits	Topical with 25mg/cm2 test product	Rabbits	DDEA 2.32% Gel
Cumulative 90 days local tolerance	Topical with 10mg/cm2 and 20mg/cm2 test product	Rabbits	DDEA 2.32% Gel
Sensitisation test using Maximisation (Magnusson and Kligman) Protocol	Topical	Albino guinea-pigs	DDEA 2.32% Gel
Photosensitisation test	Topical	Albino guinea-pigs	DDEA 2.32% Gel

The toxicity of the active substance has also been reviewed by the applicant.

Systemic exposure was not measured in the studies conducted with the 2.32% gel.

Single Dose Toxicity Studies
An acute limit test with Voltaren Emulgel 1.16 mg/g Gel and placebo gel was reported in rats (5/sex), in which the product was administered dermally at 40mg/cm^2 under occlusion [**83-5083**]. There were no deaths or signs of local irritation. Transient toxic signs, limited to the first 48 hours after treatment, included reduced spontaneous activity, ataxia, dyspnea and muscular hypertonia. There were no pathological changes at necropsy.

IV.2 Repeated Dose Toxicity Studies

Repeated dose toxicity studies using topical application were performed with DDEA 2.32% Gel for 28 and 90 days. These studies are discussed below in the sub-section 'Local tolerance'.

Repeated dose studies with various diclofenac salts have been reported and are reviewed in the applicant's non-clinical overview and toxicology written summary. Most of the studies undertaken during development of diclofenac predate the introduction of GLP regulations. However, they appear to have been carried out to a suitable standard; the consistency of findings repeatedly observed in different studies gives a high degree of confidence in the quality of the data. Because of the age of the studies, there are a number of gaps that might be expected in a more up-to-date package. These omissions are not thought to seriously compromise the assessment.

Rats produce the primary hydroxylated human metabolites of diclofenac although, because of enterohepatic circulation, they appear sensitive to the toxic effects of the drug. The metabolism in baboons is similar to that of man. The dog is not a relevant species since its metabolism differs significantly from that in humans.

The following effects were consistently seen in the animal studies:
- deaths associated with gastrointestinal ulceration and peritonitis;
- anaemia, neutrophilia, haemopoietic stimulation and reactive hyperplasia of the mesenteric lymph nodes, secondary to gastrointestinal changes;
- renal toxicity in two three-month baboon studies but not found a 52-week study or in rats;
- skin ulceration in one three-month baboon study and in the one-year baboon study;
- plasma chemistry changes comprising disturbances of plasma proteins, typified by reduced albumin concentrations, and variations in enzyme activities, particularly alkaline phosphatase.

Toxicokinetics
As most animal studies were carried out many years ago there is generally little data on the toxicokinetics of diclofenac. Limited exposure data is presented in the complete rodent carcinogenicity assays which suggests increasing exposure with dose, with slightly higher exposure in female than in males.

Genotoxicity Studies
***In vitro* studies**
Diclofenac was not photomutagenic in an Ames test [**v4405/02**] using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and the *Escherichia coli* strain WP2uvrA at up to 5 mg/mL, using 4 different levels of UV radiation.

In a photoclastogenicity study in Chinese hamster ovary (CHO) cells, diclofenac was photoclastogenic at the highest concentration of 25 µg/mL and the longest duration (16 minutes) of UV radiation [**v4402/02**]. Lower doses (up to 8.33 µg/mL) were not photoclastogenic following UV irradiation for up to 16 minutes; 8 minutes of UV radiation did not produce photoclastogenicity at any dose (up to 25 µg/mL).

***In vivo* studies**
In a GLP-complaint study in rats, [**V4402/14**], diclofenac was not clastogenic at doses up to the maximum tolerated orally administered dose of 100 mg/kg.

Carcinogenicity Studies
Long-term Studies
No additional studies have been conducted.

IV.4.2 Short or Medium-Term Studies
No studies have been conducted.

Other Studies
No studies have been conducted.

Reproductive and developmental toxicity
Reproduction toxicity studies have not been carried out with DDEA 2.32% gel nor with DDEA 1.16% gel. Reproduction toxicity studies conducted with diclofenac sodium are discussed in the non-clinical overview. These studies used oral or parenteral administration. Segment I and III rat reproduction studies with diclofenac sodium were completed in the early 1970s and were conducted to state-of-the-art at that time. An extensive series of segment II studies in mice, rats and rabbits were also conducted more than 20 years ago and therefore are of pre-ICH designs. Consequently, not all of the investigations that would be expected in studies conducted today have been carried out.

Fertility and early embryonic development
See 'Reproductive and developmental toxicity' section above.

Embryo-fetal development
Studies have been reported in mice, rats and rabbits. Discussion is provided in the applicant's toxicology written summary and non-clinical overview.

Prenatal and postnatal development, including maternal function
See comment above.

Studies in which offspring (juveniles) are dosed and/or further evaluated
No studies reported.

IV.6 Local tolerance
Three 7-day studies with different times of exposure or occlusive conditions and one 28-day cumulative irritation study were carried out with the DDEA 2.32% gel. The doses were 25 mg gel/cm^2 for the 2.32% product and 50 mg gel/cm^2 for the 1.16% Voltarol Emulgel.

Study 1
In a 7-day local tolerance study in NZW rabbits comparing 2.32% gel with 1.16% gel under occlusive dressing for 4h/day, 4/6 animals had slight erythema on day 5 and 2/6 had slight erythema on day 6 in the 2.32% group compared with 1/6 rabbits on each of days 4, 6 and 7 in the 1.16% group.

Study 2
Following 18 hours exposure/day to 2.32% gel under semi-occlusive dressing for 7 days, erythema was noted from day 2 (4/6 animals) and from day 4, the score was >1 in an increasing number of animals until day 6. For the 1.16% gel, erythema of score 1 was present on all 7 days, with a maximum of 4/6 animals on day 5.

Study 3
Following 18 hours exposure/day to 2.32% gel under occlusive dressing for 7 days, slight erythema was seen in 3/6 animals on day 1 and by day 5, all animals showed erythema. On days 2, 3 and 4, there were 1, 2 and 3 rabbits, respectively, with scores >1. For the 1.16% gel, slight erythema was present on all 7 days (5/6 animals had erthyema on days 2 to 5). No animal receiving 1.16% gel had a score >1 throughout the study.

Comment on the 7-day studies
In this series of studies, slight erythema was seen with both 2.32% and 1.16% gels and as may be expected, increasing numbers of animals were affected with increasing daily duration of exposure. A slightly higher irritation was seen for the 2.32% gel. However, the effects were transient.

Study 4
A 28-day repeated-dose dermal toxicity study of the 2.32% DDEA gel was conducted in NZW rabbits in comparison with 1.16% DDEA gel (Voltaren Emulgel), placebo gel and 0.1% sodium lauryl sulphate (SLS) under occlusive dressing for 4 hour/day. No mortality nor signs of systemic toxicity were noted during the period of observation. In the animals treated with DDEA 2.32% gel, 2/6 animals were observed with slight erythema on day 2, and 1/6 on day 4. Slight erythema was observed in 1/6 animals treated with Voltaren Emulgel on days 3, 4, 5 and 7. No other dermal reactions (erythema and oedema) were observed during the rest of the treatment period in either group.

Both DDEA gels were well tolerated in this 28-day study.

Study 5
A 90-day repeated dose dermal toxicity and local tolerance study was conducted in NZW rabbits. The 2.32% DDEA gel was applied daily during 6 hours for 90 consecutive days at 10 mg/cm^2 (total 150 mg) and 20 mg/cm^2 (total 300 mg). Dermal irritation was assessed before each test item application. Another group of animals was kept for 4 weeks after treatment to check for reversibility of treatment. Neither mortality nor any clinical signs resulting from systemic toxicity were observed. Transient and reversible erythema was seen only during the first week at both doses. Skin biopsy and histological examination at the end of the treatment period did not reveal any relevant histological lesions. No cutaneous reactions were observed during the recovery period.

The 2.32% DDEA gel was well tolerated in the 90-day study.

Other toxicity studies
The sensitising potential of DDEA 2.32% gel was assessed in guinea pigs using the maximisation test [**SMK-PH-07/0062**]. Preliminary results showed the presence of necrosis following intradermal injection of the test material at 25% and above. Slight erythema was observed following topical application under occlusion for 24 hours at 50% and 100%. The concentration determined to be appropriate for intradermal and topical induction was 12.5% and 100%, respectively. Concentrations of 25% and 12.5% were used for the challenge phase. After induction using non-irritating conditions determined from the preliminary tests and a 10-day rest period, animals were challenged with a single topical application of test material. No macroscopic cutaneous reactions attributable to allergy following the challenge phase were recorded. The results indicated that under the experimental conditions used, DDEA 2.32% gel did not have sensitisation potential.

The phototoxic and photosensitisation potential of DDEA 2.32% gel were evaluated in Dunkin-Hartley guinea pigs [**PTPS-PH- 07/0330**]. No significant macroscopic cutaneous reactions were observed following application of 0.5 ml DDEA 2.32% gel and irradiation with 7 J/cm^2 UVA and 0.15 J/cm^2 UVB. These results indicate that DDEA 2.32% gel is not phototoxic.

The photoallergenic potential of DDEA 2.32% gel was evaluated following induction in animals who have received intradermal injections of 50% Freund's Complete Adjuvant and 4 topical treatments with 0.5 ml test product and irradiation with 7 J/cm^2 UVA within 10 days. Challenge consisted of topical treatment with 0.5 ml test product and irradiation with 7J/cm^2 UVA. Six of 21 guinea pigs died, reportedly due to systemic toxicity. An increase in skin absorption of test article could have resulted as the skin of the animals were wax-depilated resulting in hair follicle removal and enhanced transfollicular delivery. In addition, possible oral intake following dermal application cannot be discounted. Slight to moderate erythema were observed in 85% of the animals in the test product treated group following the induction phase. Slight to moderate erythema were observed in 13% (2/15) of the animals in the treated group 72h after the challenge phase. These results indicate that DDEA 2.32% gel has mild photosensitising potential under conditions associated with systemic toxicity.

The photoallergenic potential of DDEA 2.32% gel was evaluated in a further study in Dunkin-Hartley guinea pigs following induction with intradermal injections of 50% Freund's Complete Adjuvant and 4 topical treatments with 0.15 ml test product and irradiation with 7 J/cm^2 UVA within a 10-day period [**PAC-PH-07/0330**]. Challenge consisted of topical treatment with 0.26 ml undiluted (100%), 50% and 25% test product and irradiation with 7J/cm2 UVA. No mortality and no macroscopic cutaneous reactions attributable to photosensitisation were observed under these conditions. These results indicate that DDEA 2.32% gel did not have photosensitising potential.

Overall comment on phototoxic and photosensitisation potential of DDEA 2.32% gel
Overall, the gel is not considered to be phototoxic or photosensitising.

Antigenicity
No studies were conducted.

Immunotoxicity
No studies were conducted.

Dependence
No studies were conducted.

Metabolites
No studies were conducted.

IV.7.5 Studies on impurities
Diclofenac related substances were suitably qualified in acute or repeated dose toxicity studies and *in vitro* genotoxicity tests.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
An Environmental Risk Assessment based on published ecotoxicology data for diclofenac has been provided.

The log Kow for diclofenac diethylamine is reported to be 0.932; that for diclofenac is 1.90 and therefore further investigation of persistence, bioaccumulation or toxicity is not required as these values are <4.5.

On the basis of a maximum daily dose of 8 g of 2.32% gel, corresponding to a daily dose of 185.6 mg diclofenac diethylamine, the Predicted Environmental Concentration (PEC) for diethylamine was calculated to be 0.93 µg/L, using the default values provided in the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00):

$$\text{PEC surfacewater} = \frac{\text{DOSE ai* Fpen}}{\text{WASTEwinhab*DILUTION}}$$

PEC surfacewater of diclofenac diethylamine resulting from DDEA 2.32% gel with maximum daily dose of 185.6 mg and default values of Fpen= 0.01, WASTEWinhab =200 and DILUTION=10 is

$$\frac{185.6*0.01}{200*10} = \mathbf{0.93\ \mu g/L},.$$

As this value exceeds the trigger value of 0.01 µg/L, a Phase II Tier A assessment was required. The applicant has provided this based on available ecotoxicological studies presented in a published paper.

Using the values provided in this paper for the No Observable Effect Concentrations (NOEC) from chronic toxicity studies in fish, water fleas, algae and rotifers and assessment factors of 10 as provided in the guideline (or 100 in the case of microorganisms, which is considered more conservative), the calculated PEC/PNEC ratios were below the trigger values for further investigations in any compartment in Tier B.

Hence it is not expected that environmental exposure of diclofenac will increase following approval of the Marketing Authorisation for the proposed product.

Overall conclusion on toxicity
Topical treatment with DDEA 2.32% gel appeared to be well tolerated in rabbits following 4-hour or 18-hour treatment daily for a period of 7 days. Slightly higher irritation indices were seen with DDEA 2.32% gel than with the marketed Voltaren Emulgel (DDEA 1.16% gel), but irritation was classed as slight and was transient. In addition, DDEA 2.32% gel was well tolerated in 28-day and 90-day cumulative irritation studies in rabbits.

Systemic exposure was not measured in the studies conducted with the 2.32% gel. In the *in vitro* studies using human cadaver skin, the absorption of diclofenac from 2.32% gel containing permeation enhancer (oleyl alcohol) was about 2.5 to 3-fold that from 1.16% gel. However, this did not appear to affect systemic exposure in man as it was reported that application of 2 g DDEA 2.32% gel twice daily for 7 days in humans led to similar systemic levels (generally below 10 ng/mL) as repeated application of 2 g DDEA 1.16% gel four times daily for 7 days.

In an earlier distribution study conducted with 1.16% ^{14}C-DDEA gel in guinea pigs, topical administration at 400 mg/kg twice daily to non-occluded intact skin for 6 days resulted in 4-fold higher ^{14}C concentrations in the muscle under the treated skin area than in muscle tissue distant from the application site. Thus, it likely that the increased absorption from the 2.32% gel compared with the 1.16% gel results in higher concentrations of diclofenac in tissues underlying the application site without increasing systemic exposure.

DDEA 2.32% gel did not have sensitisation potential in a maximisation test in guinea pigs. The phototoxic and photosensitisation potential of DDEA 2.32% gel were also evaluated in guinea pigs. There was no phototoxic potential, but the gel had mild photosensitising potential under conditions where systemic toxicity (including deaths) was seen. A further study using lower doses did not exhibit systemic toxicity or photosensitisation potential. Overall, the gel is not considered to be phototoxic or photosensitising.

Related substances have been suitably qualified in *in vitro* genotoxicity studies and single dose or 14-day repeated dose toxicity studies. The proposed limits in the finished product specification are acceptable.

Apart from the studies conducted specifically to support this application for DDEA 2.32% gel, the extensive published information on diclofenac has been reviewed in the applicant's non-clinical

dossier. This information includes acute and chronic toxicity, *in vitro* and *in vivo* genotoxicity, teratogenicity, fertility, peri- and post-natal toxicity, carcinogenicity and special safety pharmacology studies performed in rats, mice, rabbits, dogs and baboons. These studies and the extensive clinical experience with oral forms of diclofenac are considered to provide adequate information on diclofenac and further studies are not required.

However, exposure data are limited. As mentioned in the non-clinical overview, plasma concentrations obtained from the dietary rat and mouse carcinogenicity studies demonstrate exposure to diclofenac. The reported levels are relatively low compared with human C_{max} levels following oral treatment, but they probably reflect steady state concentrations since the rats and mice were fed *ad libitum*.

An environmental risk assessment based on published ecotoxicology data for diclofenac was provided. The use of the 2.32% gel is not considered to pose a risk to the environment.

III.6 Discussion of the non-clinical aspects

In conclusion, there are no objections to the approval of Voltarol Emulgel P Gel and Voltarol Emulgel Gel, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of diclofenac is well-known.

The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier. The issues associated with the non-prescription use of the proposed DDEA 2.32% Gel are discussed in the applicant's clinical overview.

The Clinical Development Programme evaluated clinical efficacy, compared to placebo (vehicle), of a once to thrice daily dosing regimen as well as safety (including systemic absorption, phototoxicity and skin sensitisation).

The following five studies, involving 315 healthy subjects and 513 patients with acutely sprained ankles, were conducted, to support the applications. Of the 315 heathy subjects, 654 were exposed to the DDEA 2.32% gel.

Studies:

- **Study VOPO-PE-102**: comparative pharmacokinetic study to look at systemic absorption potential
- **Study VOPO-PE-201** 7-day placebo-controlled efficacy and safety study comparing once and twice daily application in acute ankle sprain
- **Study VOPO-P-307:** 7-day placebo-controlled efficacy and safety study comparing twice and thrice daily application
- **Study VOPO-P-105:** skin sensitisation and irritancy study
- **Study VOPO-P-103:** phototoxicity study

These studies are discussed in detail in the sections which follow.

IV.2 Pharmacokinetics

To support the applications, the results of the following pharmacokinetic study was submitted:

Study VOPO-PE-102
A Randomised, 4-Period, Crossover Study on the Systemic Exposure to diclofenac in Healthy Volunteers after Treatment with Topical Diclofenac Diethylamine 2.32% Gel under Non-Occlusive and Semi-Occlusive Conditions, Topical Diclofenac Diethylamine 1.16% Gel, and Oral Diclofenac Sodium 50mg Tablets.

This was a single-centre, randomised, open-label, multiple-dose, 4 period crossover study in healthy

subjects comparing exposure to diclofenac after topical application of the new DDEA 2.32% gel to the licensed 1.16% Voltaren Emulgel and 50mg oral diclofenac sodium tablets (Voltaren).

- **Objectives**

Primary:
- to determine systemic exposure with repeated applications of DDEA 2.32% gel and to evaluate the effects of semi-occlusion

Secondary:
- to compare systemic exposure from twice daily DDEA 2.32% gel compared to four times daily application of the licensed 1.16% gel (Voltaren Emulgel) and three times daily oral diclofenac-Na 50 mg tablets (Voltaren)

- to assess the local tolerability and general safety of topical DDEA 2.32% gel under non-occlusive and semi-occlusive conditions

- **Test and reference products**

Test Product
2g DDEA 2.32% gel, 5mg/cm^2 applied to one ankle (approximately 400cm^2) twice a day.
Total daily dose 4g (corresponding to 80mg of diclofenac applied to a 400cm^2 area [0.2mg/cm^2])

Reference Product - Topical
2 g of DDEA 1.16% gel, 5 mg/cm^2 applied to one ankle (approximately 400 cm^2)
4x/day under non-occlusive conditions (8 g total daily dose, corresponding to 80 mg of diclofenac applied on 400 cm² [0.2 mg/cm²])

Reference Product - Oral
50 mg diclofenac-Na gastric-coated tablet 3x/day (150 mg total daily dose).

Study design
Subjects were randomised to one of four treatment sequences; treatments being given over 7 days in each treatment period.

A C B D
C D A B
B A D C
D B C A

Where:

A=Test product 2g DDEA 2.32% gel applied twice daily *non-occluded*
B=Test product 2g DDEA 2.32% gel applied twice daily *under a semi-occlusive dressing*
C=Reference product 2g DDEA 1.16% gel applied four times in 24 *non-occluded*
D=Reference 50mg oral diclofenac sodium three times daily

Subjects were instructed to apply the test product to a 400 cm² area covering the anterior, posterior, lateral and medial surfaces of the right ankle. If required (according to the randomisation schedule) an elastic bandage (semi-occlusive dressing) was applied after the gel.

A 14-day washout period separated each dosing period.

Blood samples for plasma diclofenac were collected:
- immediately before the first dose on Day 1, Day 2 and Days 5 through 7 (all treatments); up to 24 hours after the first dose on Day 1 and Day 7 (treatment A, B and C only),
- in the morning of Study day 91±1, Day 98±1 and Day 105±1, if treatment A, B or C was given in Period 4
- up to 24 hours after the first dose on Day 7 [(including sampling up to 6 hours (before second administration) and up to 12 hours (before the third administration] for treatment D.

Urine collections for diclofenac and 4'-OH-diclofenac assay were collected as follows:

- on Day 1, urine was sampled immediately before the morning dose (all treatments), and urine voided for the subsequent 24 h was collected (treatments A, B, and C).
- on Day 7, urine was collected for 24 h after the morning administration (all treatments).

Results
All 40 subjects received study treatment and were thus included in the safety population. However, two subjects discontinued during Period II and 38 subjects were therefore included in the pharmacokinetic (PK) analysis.

Plasma Pharmacokinetics

Table 3: Plasma PK parameters

	A N = 38	B N = 38	C N = 38	D N = 38
Day 1				
AUC_{0-24} [ng·h/mL]	21.7 (15.2) 2.8 – 62.7	18.1 (13.1) <LLQ – 58.2	15.7 (12.2) <LLQ – 48.4	
Day 7				
AUC_{0-24} [ng·h/mL]	74.6 (39.7) 38.2 – 255.2	72.5 (35.2) 22.1 – 190.4	68.7 (34.3) 31.8 – 184.0	3111 (1112) 249 - 5955
C_{max} [ng/mL]	5.4 (4.6) 2.2 – 29.4	5.4 (3.4) 1.2 – 17.4	5.7 (4.7) 2.0 – 24.1	1547 (721) 88 - 4240
t_{max} [h]	19 (0-24)	20 (0-24)	20 (0-24)	7.3 (1-24)
C_{min} [ng/mL]	1.8 (0.8) <LLQ – 4.2	1.7 (0.7) <LLQ – 3.3	1.6 (0.7) 0.8 – 3.9	4.5 (3.0) <LLQ – 13.4
C_{av} [ng/mL]	3.1 (1.7) 1.6 – 10.6	3.0 (1.5) 0.9 – 7.9	2.9 (1.4) 1.3 – 7.7	130 (46) 10 - 248
PTF [%]	105 (46) 45 - 237	115 (53) 43 - 241	126 (72) 46 - 436	1234 (475) 540 - 2644

Note: The table shows mean (SD) and range. For t_{max} the table shows median (range)
A: 2 g DDEA 2.32% bid for 7 days, non-occlusive
B: 2 g DDEA 2.32% bid for 7 days, semi-occlusive
C: 2 g DDEA 1.16% qid for 7 days, non-occlusive
D: 50 mg diclofenac-Na tablet p.o. tid for 7 days

Several concentrations were < lower limit of quantitation (LLQ) on Day 1 and in those cases the AUC, C_{min}, C_{av} and Peak-trough fluctuation (PTF; = $(C_{max-Cmin})/C_{av}$) were derived using the imputation rule rather than precise calculation.

Day 7: For all topical treatments, steady-state AUC_{0-24} had increased approximately 4-fold compared to the value at Day 1 and followed the same trend in that it was lowest for treatment C (DDEA 1.16% gel without dressing) and highest for treatment A (DDEA 2.32% gel without dressing); however, again the difference between topical treatments was minimal and not clinically important. C_{max}, C_{min} and C_{av} were also similar for the three topical treatments. Median Day 7 t_{max} occurred at 19 to 20 hours after the morning dose and PTF ranged from 105% to 126% across the 3 treatments.

In contrast, following oral dosing, AUC_{0-24} was about 45-fold higher and C_{max} was about 300-fold higher than after topical application with a median t_{max} occurring much more rapidly, at around at 7.3 hours.

Furthermore, the application of a semi-occlusive dressing did not affect systemic absorption of DDEA 2.32% – see ratio B/A in Table 4.

Table 4: Statistical analysis of C_{max} and AUC ratios (%)

	B/A Ratio (90% CI) N = 38	C/A Ratio (90% CI) N = 38	D/A Ratio (90% CI) N = 38
Day 1 AUC_{0-24} (%)	76.8 (58.8,100.3)	64.2 (49.1,83.8)	
Day 7 AUC_{0-24} (%)	95.9 (82.2,112.0)	92.2 (79.0,107.6)	4168 (3572,4864)
Day 7 C_{max} (%)	99.4 (82.2,120.2)	101.2 (83.7,122.3)	30016 (24829,36286)

A: 2 g DDEA 2.32% bid for 7 days, non-occlusive
B: 2 g DDEA 2.32% bid for 7 days, semi-occlusive
C: 2 g DDEA 1.16% qid for 7 days, non-occlusive
D: 50 mg diclofenac-Na tablet p.o. tid for 7 days

In summary, the plasma pharmacokinetic results demonstrated that, compared to oral diclofenac administration, systemic exposure following twice daily DDEA 2.32% gel (with or without semi-occlusive dressing) remained extremely low, even on multiple dosing. Furthermore, it remained comparable to that seen with the currently licensed 1.16% gel applied four times daily. Steady state systemic exposure (AUC_{0-24}) was around 40 times lower, with peak concentrations (C_{max}) around 300 times lower, compared to oral diclofenac sodium 50mg three times daily.

Urinary Pharmacokinetics

Cumulative urinary excretion, as determined by Ae_{0-24} values above LLQ for the 3 topical treatments, were measured only for 4'-OH-diclofenac and only on day 7. In ANOVA-based comparisons at day 7, Ae_{0-24} of 4'-OH-diclofenac were generally low and comparable whether or not DDEA 2.32% gel was applied twice daily under a non-occlusive dressing (ratio=110.1%) and was also comparable to excretion after application of the 1.16% reference gel four times daily under non-occlusive conditions (ratio=96.8%). Because within-subject variability was high, the 2-sided 90% confidence intervals were not entirely within the conventional 80% to 125% limits for either comparison (see Table 5). The data have shown that, on Day 7, the cumulative urinary excretion of the metabolite with the topical formulations was around 140 times lower than following conventional oral therapy (50mg diclofenac – Na three times daily).

Table 5: Statistical analysis of Day 7 Ae_{0-24} ratios (%)

	B/A Ratio (90% CI) N=38	C/A Ratio (90% CI) N=38	D/A Ratio (90% CI) N=38
Diclofenac	N/A	N/A	N/A
4'-OH-diclofenac	110.1 (88.9, 136.4)	96.8 (78.4, 119.7)	14119 (11499, 17335)

N/A: Not applicable; below LLQ for at least 2/3 of subjects
A: 2 g DDEA 2.32% gel b.i.d. for 7 days, non-occlusive
B: 2 g DDEA 2.32% gel b.i.d. for 7 days, semi-occlusive
C: DDEA 1.16% gel q.i.d. for 7 days, non-occlusive
D: 50 mg diclofenac sodium tablet p.o. for 7 days.

Safety evaluation

No drug-related adverse events were reported after topical treatments but 7.7% of subjects reported gastrointestinal AEs that were considered to be related to (oral) treatment.

Overall conclusions on pharmacokinetics

Study VOPO-PE-102 has demonstrated that the exposure and peak plasma concentrations achieved after single application and at steady-state after repeated application of DDEA 2.32% gel is comparable to that seen with the lower strength licensed 1.16% gel (Voltaren Emulgel). Furthermore, following topical application with either strength formulation, exposure is about 40 times lower and peak concentration about 300 times lower than for oral diclofenac therapy.

Furthermore, urinary excretion of the metabolite 4'-OH-diclofenac was found to be similar after 7 days of treatment with DDEA 2.32% gel under semi-occlusive and non-occlusive conditions and DDEA 1.16% gel under non-occlusive conditions and, as expected, was much greater after oral dosing by a factor of 120-150 times.

It is considered that the pharmacokinetic comparability of the two topical formulations as well as the very large margin between the topical exposure and peak concentration compared to the oral 50mg three times daily, provide adequate reassurance that there would be no clinically relevant systemic exposure associated with the new 2.32% formulation.

No safety concerns (including that related to systemic absorption or local tolerability) arose from this study.Section IV.5, Clinical Safety, below includes a discussion of the phototoxicity study (VOPO-P-103) and skin sensitisation and irritancy study (VOPO-P-105).

The product is intended for patients aged 14 and above, and, given the lack of systemic absorption associated with this topical product, no specific studies in special populations is warranted. Skin permeability is not expected to vary appreciably with age, gender or ethnicity.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of diclofenac are well-known. No new pharmacodynamic studies have been conducted, and none are not required for these applications.

DDEA gel is an anti-inflammatory and analgesic preparation designed for topical application. Its primary mechanism of action is inhibition of prostaglandin synthesis (see Summary of Clinical-Efficacy for a more detailed discussion).

IV.4 Clinical Efficacy

To demonstrate efficacy, the results of the following studies were submitted:

1. **Study VOPO-P-201**: a double-blind, placebo controlled, parallel group study in patients evaluating the efficacy and safety of diclofenac diethylamine 2.32% gel applied once or twice daily in acute ankle sprain.
2. **Study VOPO-PE-307**: a double-blind, placebo-controlled, parallel group study in patients evaluating the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice or three times daily in acute ankle sprain.

According to the *Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain* (CPMP/EWP/612/00), an indication of mild to moderate acute pain management be supported by two or more studies on mild to moderate pain using different pain models (e.g. one study in pain following tooth extraction and one study in sprains). However, the applicant has justified using a single pain model. on the basis that DDEA 2.32% gel is simply a stronger version of an established product for which multiple pain models have already been studied.

The ankle sprain model has been specifically chosen because it can be considered a clearly defined clinical model for acute pain, suitable for topical treatment and amenable to visual analogue scale evaluation (2000; 2004). A one-week duration of treatment was chosen on the basis of previous experience with topical NSAIDs (2004) which have shown that maximum pain relief is achieved at around Day 5.

Study VOPO-P-201 failed to demonstrate that DDEA 2.32% gel administered either once or twice daily for a week showed significant superiority over its vehicle on either the primary efficacy endpoint of Pain on Movement (POM) at Day 5 or on multiple secondary endpoints. For this reason, the efficacy results of Study VOPO-P-201 have been disregarded and a second pivotal study (VOPO-P-307), incorporating a different study design was conducted. No safety concerns arose from Study VOPO-P-201. Study VOPO-P-307 is discussed below.

Study VOPO-P-307
A randomised, double-blind, multi-centre, placebo controlled, 3-treatment arm, parallel group study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice or three times daily in patients with acute ankle sprain.

Methods
This was a second 7-day study designed to assess the efficacy and safety of DDEA 2.32% gel applied twice or three times a day, compared to placebo (vehicle), in the treatment of acute mild to moderate ankle sprain.

- **Study Participants**

Patients included were male or female, aged at least 18 years, in generally good health with an acute mild or moderate (Grade I-II) sprain of the lateral ankle. The sprain must have occurred within the 12 hours preceding randomisation with a Pain-On-Movement (POM) score of at least 50 (by 100mm VAS; as assessed below) and provided no analgesic medication had been used within the 12 hours prior to randomisation.

Patients were excluded if they had suffered any sprain in the same ankle within the previous three months, or a Grade II-III sprain, other significant injury to or surgery on the same ankle or foot within the previous six months, if they had pain or instability in the same ankle resulting from a previous ankle sprain or other trauma, or if their ankle sprain was attributable to a known disease affecting the ligaments. They were also excluded if they had applied topical analgesic or anti-inflammatory treatment over the previous month in the area to be treated.

- **Treatments**

Subjects received one of the following treatments, according to the randomisation schedule (ratio1:1:1):

• Treatment A:
DDEA 2.32% gel three times a day (morning, noon and evening)
Tube 1 = DDEA 2.32%, Tube 2 = DDEA 2.32%, Tube 3 = DDEA 2.32%

• Treatment B:
DDEA 2.32% gel twice-a-day (morning and evening), placebo gel once-a-day (noon)
Tube 1 = DDEA 2.32%, Tube 2 = Placebo*(vehicle*).*, Tube 3 = DDEA 2.32%

• Treatment C:
Placebo gel three times a day (morning, noon and evening)

Tube 1 = Placebo(vehicle)., Tube 2 = Placebo(vehicle*)., Tube 3 = Placebo (vehicle*).*

*[*Vehicle - identical in composition to DDEA 2.32% gel apart from the absence of the active ingredient.]*

At each application, approximately 2 g (5cm extruded length) of study medication was applied topically, using the fingertips for approximately one minute, to both sides of the ankle and covering an area of approximately 200cm^2. Patients, randomised to twice daily application of active gel, applied vehicle at noon.

- **Rescue medication**

Rescue medication (paracetamol 500 mg tablets) was supplied at baseline and, if necessary, at Day 5. Patients were instructed to take only the rescue medication provided for pain (ankle or otherwise) and its use had to be recorded (amount taken and reason). No rescue medication was permitted within the 12 hours prior to scheduled study visits.

- **Prior/Concomitant therapy**

The use of a crutch and exercise was allowed. The physician instructed the patient to start Achilles' tendon stretching on Day 1.

Use of the following treatments was not permitted after the start of study drug:

- analgesics administered by any route (i.e., topical, oral, rectal, injected, or inhaled), except permitted rescue medication (see above) or low dose aspirin taken for at least 30 days on a stable dose (≤ 162 mg) for non-analgesic reasons.
- pain medication taken prior to the injury was to be washed out for at least 12 hours before randomisation
- steroids (injected or oral, except inhaled topical asthma and hay fever treatments)
- topical dermal treatments not applied to the sprained ankle)
- physiotherapy (including, but not exclusive to, transdermal electro neural stimulation, ultrasound, massage, and spinal manipulation) or any other kind of pain therapy throughout the course of the study
- tranquilisers, anxiolytics, hypnotics, or sedatives, unless the patient's prescribed daily dose had been unchanged for a month before the randomisation visit; this regimen had to continue unchanged for the entire study
- amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine, and tetrahydrocannabinol
- traditional, herbal or homeopathy treatments (oral and topical)
- adhesive and/or immobilising casts, bandages, "Aircast" splints, treatment by RICE were not permitted. This is in contrast to the first study where these measures were permitted.

- **Objectives**

Primary:
- To evaluate the efficacy of DDEA 2.32% gel applied twice daily or three times daily in patients with acute ankle sprain under 'in-use' conditions, in particular with regard to pain relief after the first 5 days of treatment and recovery of function.

Secondary:
-To assess the safety of DDEA 2.32% gel twice daily or three times daily for one week under 'in-use' conditions.

- **Outcomes/endpoints**

Primary endpoints
Efficacy:

- **Ankle pain on movement (POM) score on Day 5** as assessed by a 100mm visual analogue scale (VAS). In this study this was assessed by a method involving passive manipulation by the investigator of the ankle joint with the patient reclining in a supine position.

  In order to conduct this evaluation, the investigator gently lifted the leg up at an angle of 45º then passively inverted (supinated) the foot of the injured ankle to an angle of approximately 30°. The degree of ankle pain elicited during this manoeuvre was rated, by the patient on a 100 mm VAS (0 = no pain, 100 = extreme pain) in answer to the question: "How would you describe your ankle pain right now?"

Secondary Endpoints
Efficacy evaluation

- POM on VAS on Days 3 and 8 (±1), respectively;
- Ankle pain-at-rest assessed on VAS on Days 3, 5 and 8 (±1);
- Tenderness measured by pressure algometry on Days 3, 5 and 8 (±1) – see below.
- Circumference measurement of swelling (compared to non-affected side) by "Figure-of-eight-method" on Days 3, 5, and 8 (±1).
- Ankle joint function (Karlsson Scoring Scale) on Days 3, 5, and 8 (±1) – see Table 6
- Total rescue medication consumed (paracetamol) overall and for ankle pain specifically
- Global assessment of benefit on 5-point Likert scale on Days 3, 5 and 8 (±1) – Table 7
- Global assessment of treatment satisfaction on 5-point Likert scale on Days 5 and 8 (±1) – Table 8
- Time to improvement of POM on VAS of at least 40 mm

- Time to first POM on VAS of 30 mm or less
- Time to a 50% reduction in POM from Day 1 – this outcome was added to the statistical analysis plan (SAP) prior to unblinding in order to comply with EU guidelines which indicated that a dichotomous response outcome should be pre-specified.

Tenderness (pressure algometry) i.e. the pain threshold measured as the minimum pressure required to cause pain.

Tenderness was measured by calibrated algometers in an area of 1 cm^2 at the centre of the injured area. The position of measurement was marked with a water-resistant marker on the patients' skin to ensure consistent measuring points throughout the study. The investigator applied the pressure gauge to the marked tender point of maximum sensitivity by placing the gauge at a 90° angle vertical to the skin. The patient was instructed to indicate the onset of pain (pressure pain threshold). Measurements were performed with a covered scale so that the investigator and patient could not see the values. The values were evaluated after the measurement. For assessment of a treatment effect, the tenderness of the treated painful area was compared with the tenderness at the corresponding anatomical position of the healthy uninjured contralateral side.

Circumference measurement of swelling (Figure-of-Eight Method) as validated on healthy volunteers with an intra-class correlation coefficient of 0.99 for inter-tester reliability and 0.99 for intra-tester reliability

Patients were seated with both feet extended in slight dorsiflexion. The ankle circumference was recorded with a tape measure then the tape measure was then wrapped around the ankle as shown in Figure 1: the start of the tape measure was placed midway between the tibialis anterior tendon and lateral malleolus and was then continued across an anatomically defined course forming a figure of eight over the ankle joint (1995). A marker pen was used to ensure anatomical consistency of repeated measurements. On each occasion, three measurements were taken and averaged.

Figure 1: Figure-of-eight method

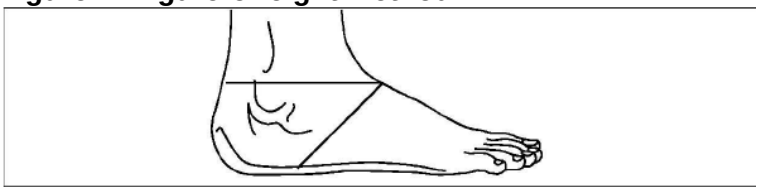


Table 6: Karlsson Scoring System for Evaluation of Ankle Joint Function

Category	Degree	Score
Pain	None	20
	During exercise	15
	Walking on uneven surface	10
	Walking on even surface	5
	Constant (severe)	0
Swelling	None	10
	After exercise	5
	Constant	0
Instability (Subjective)	None	15
	Walking on uneven surface	10
	Walking on even surface	5
	Constant (severe) using ankle support	0
Stiffness	None	5
	Moderate (morning, after exercise)	2
	Constant, severe	0
Stair Climbing	No problems	10
	Impaired (instability)	5
	Impossible	0
Running	No problems	10
	Impaired	5
	Impossible	0
Work Activities	Same as before injury	15
	Same work, less sports, normal leisure activities	10
	Lighter work, no sports, normal leisure activities	5
	Severely impaired work, decreased leisure activities	0
Support	None	5
	Ankle support during exercise	2
	Ankle support during daily activities	0

Table 7: 5-Point Likert Scales –Global Assessment of Benefit

The answer to the following question was recorded according to the 5-point scale below: ***"Considering all the ways this treatment has affected you, how well are you doing?"***	
Grade	**Description**
0	**Very Good – No symptoms and no limitation of normal activities***
1	**Good – Mild symptoms and no limitation of normal activities**
2	**Fair – Moderate symptoms and limitation of some normal activities**
3	**Poor – Severe symptoms and inability to carry out most normal activities**
4	**Very Poor – Very severe symptoms which are intolerable, inability to carry out all normal activities**
****Normal activities defined as all activity the subject does on a routine basis, including work and recreation.***	

Table 8: 5-Point Likert Scales –Global Assessment of Treatment Satisfaction

The answer to the following question was recorded according to the 5 point scale below: ***"How do you rate this medication as a treatment for the pain of an ankle sprain?"***	
Grade	**Description**
4	**Excellent**
3	**Very Good**
2	**Good**
1	**Fair**
0	**Poor**

Safety evaluation:
The assessment of safety was based mainly on the frequency of treatment-emergent adverse events (AEs). Vital signs were measured, and a general physical examination was performed on Day 1 and at the final visit.

- **Sample size**

The overall planned sample size was calculated to be 240 patients randomised in a 1:1:1 ratio to one of the three treatment arms.

Results

- **Participant flow**

A total of 242 subjects were randomised and, of these, 236 (98%) received treatment:

80 DDEA 2.32% three times daily
80 DDEA 2.32% twice daily
82 placebo (vehicle)

.
There were six dropouts:

- 1 was due to adverse event(s) – vehicle group
- 1 was lost to follow-up (DDEA 2.32% t.i.d
- 4 had major protocol violations – one each in the active groups and 2 on vehicle.

Protocol violations – leading to discontinuation
1. in one subject in the twice daily DDEA 2.32% group, the sprain was found to be consistent with a Grade III sprain.

There were several minor protocol deviations, most commonly applying treatment for more than 7 days, for reasons which are not clear, but none is considered to have compromised the validity of the study findings.

- **Baseline data**

The patients were comparable in terms of demographic characteristics across all three treatment arms. The mean age of the patients was 32.4 years (range 17-81). It is noted that the youngest subject was aged 17 years when 18 was stated in the protocol to be the lower age limit for recruitment. However, this is not considered to have any bearing on the study results. The age range (and other demographic parameters) were comparable across all thee treatment arms. Comparative baseline characteristics of the presenting sprain are shown in Table 9.

Table 9: Baseline ankle sprain characteristics by treatment – all patients (safety) set (t.i.d=three times daily; b.i.d=twice daily).

	DDEA 2.32% t.i.d. (N = 80)		DDEA 2.32% b.i.d. (N = 80)		Placebo (N = 82)	
Grade of sprain – n (%)						
I	56	(70.0)	52	(65.0)	66	(80.5)
II	24	(30.0)	28	(35.0)	16	(19.5)
Pain-on-movement (100 mm VAS)						
Mean ± SD	75.4 ± 12.2		75.4 ± 13.0		74.6 ± 11.2	
Median	75.0		74.5		73.5	
Min - Max	51 – 100		50 – 100		52 – 100	
Pain-at-rest (100 mm VAS)						
Mean ± SD	36.8 ± 24.7		36.5 ± 24.6		36.0 ± 25.4	
Median	31.5		31.5		29.0	
Min - Max	0 – 92		0 – 88		0 – 88	
Ankle joint function score (Karlsson Scoring Scale)						
Mean ± SD	29.2 ± 15.6		29.1 ± 14.5		29.2 ± 13.8	
Median	28.5		30.0		27.0	
Min - Max	5 – 57		5 – 60		5 – 57	
Pressure pain threshold (tenderness, contralateral – injured ankles, N/cm^2)						
Mean ± SD	2.9 ± 1.8		3.0 ± 1.8		3.0 ± 1.3	
Median	2.5		2.6		2.7	
Min - Max	-4 – 10		1 – 11		0 – 9	
Swelling (injured – contralateral ankles, cm)						
Mean ± SD	1.8 ± 1.3		1.6 ± 1.5		1.7 ± 1.3	
Median	1.5		1.3		1.4	
Min - Max	-1 – 6		-1 – 8		-2 – 5	
Elapsed time from sprain to treatment (h)						
Mean ± SD	3.9 ± 3.4		4.0 ± 3.7		3.7 ± 3.2	
Median	2.5		2.5		2.5	
Min - Max	0.4 - 11.5		0.3 - 11.7		0.3 - 12.0	

DDEA = Diclofenac diethylamine

Overall, the majority (72%) of patients had a mild (Grade I) ankle sprain but a greater proportion in the active treatment groups had the more severe Grade II sprains.

The mean POM scores were approximately 75 mm in all three groups and a mean interval of 3-4 hours (median 2.5 hours) had elapsed from ankle sprain to application of the first dose of study medication and this was comparable across all treatment groups.

- **Numbers analysed**

All 242 patients randomised were included in the safety analysis set and the Intent to Treat (ITT) set.

The safety analysis set was defined as all randomised patients who received at least one dose of the study drug.

The ITT population was defined as all randomised patients who received at least one dose of study drug and was used for the primary analysis of efficacy.

- **Outcomes and estimation**

The results for the primary efficacy variable (POM on Day 5) as assessed by 100mm Visual Analogue Scale are shown below in Tables 10 and 11.

Table 10: Primary efficacy variable: Pain-on-movement (mm) on Day 5 (t.i.d=three times daily; b.i.d=twice daily).

Primary efficacy variable: Pain-on-movement (mm) on Day 5

	n	Mean ± SD	Change from Day 1 Mean ± SD	Difference from placebo LSMean (95% C.I.)	p-value
DDEA 2.32% gel t.i.d.	80	43.2 ± 19.1	-32.2 ± 19.9	-13.9 (-18.7, -9.2)	<0.0001
DDEA 2.32% gel b.i.d.	80	43.1 ± 21.7	-32.4 ± 19.6	-14.1 (-18.8, -9.4)	<0.0001
Placebo	82	56.5 ± 19.8	-18.1 ± 14.9		

LS Mean = Least squares mean

LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline pain-on-movement as a covariate.

Over 70% of patients treated with DDEA 2.32% gel, whether applied twice or three times daily, experienced a 50% or greater reduction in POM between Day 1 and Day 5; in comparison, the success rate in the placebo group was just 21% ($p < 0.0001$ for both three times and twice daily application of active treatment).

Table 11: Primary efficacy results – pain on movement (POM) – Day 5

	DDEA 2.32% t.i.d. (N = 80)	DDEA 2.32% b.i.d. (N = 80)	Placebo (N = 82)
Day 5			
Mean ± SD	25.7 ± 17.7	26.4 ± 18.2	49.2 ± 18.8
Median	25.5	28.5	50.5
Min – Max	0 – 65	0 – 69	0 – 86
Change from Baseline			
Mean ± SD	-49.7 ± 21.5	-49.1 ± 19.3	-25.4 ± 14.8
Median	-47.5	-48.0	-24.5
Min – Max	-95 – -4	-94 – -13	-88 – 12
Difference from placebo			
LS Mean (95% C.I.)	-23.8 (-28.7, -19.0)	-23.2 (-28.0, -18.4)	
p-value	<0.0001	<0.0001	

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline pain-on-movement as a covariate.

Four days after starting treatment, patients using either DDEA 2.32% gel three times daily or DDEA 2.32% gel twice daily experienced a decrease in POM of almost 50 mm on a 100 mm VAS, which was approximately twice the 25.4 mm decrease observed in the placebo group. DDEA 2.32% gel, whether applied three times daily or twice daily, was highly significantly superior in efficacy to placebo ($p < 0.0001$).

Over 70% of patients treated with either DDEA 2.32% gel three times daily or DDEA 2.32% gel twice daily experienced at least a 50% reduction in POM (i.e. successful response) between Day 1 and Day 5 (Table 12). These response rates compared with a success rate of just 21% in the placebo group ($p < 0.0001$ for both three times and twice daily application of active treatment).

Table 12: Reduction in pain on movement (POM) by at least 50% (successful response) from Day 1 to Day 5

	DDEA 2.32% t.i.d. (N = 80)		DDEA 2.32% b.i.d. (N = 80)		Placebo (N = 82)	
Category	n	(%)	n	(%)	n	(%)
Success	59	(73.8)	57	(71.3)	17	(20.7)
Failure	21	(26.3)	23	(28.8)	65	(79.3)
p-value vs placebo +	<0.0001		<0.0001			

DDEA = diclofenac diethylamine
+ p-value obtained from logistic regression with main effect of treatment and baseline pain-on-movement as a covariate.

Secondary efficacy variables:
POM on Days 3 and 8: (see Table 13). On Day 3, patients on active treatment, whether applied three times (t.i.d) or twice daily (b.i.d) showed a 32 mm decrease in POM, whereas scores in the placebo group had decreased by only 18 mm. By Day 8, POM had decreased by 58 – 61 mm in the two groups treated with DDEA 2.32% gel, versus only 34 mm in the placebo group. The differences between the two active treatments and placebo were highly significant at both visits ($p < 0.0001$).

Table 13: POM on Days 3 and 8 compared to baseline

			Change from Day 1	Difference from placebo	
	n	Mean ± SD	Mean ± SD	LS Mean (95% C.I.)	p-value
Day 3					
DDEA 2.32% gel t.i.d.	80	43.2 ± 19.1	-32.2 ± 19.9	-13.9 (-18.7, -9.2)	<0.0001
DDEA 2.32% gel b.i.d.	80	43.1 ± 21.7	-32.4 ± 19.6	-14.1 (-18.8, -9.4)	<0.0001
Placebo	82	56.5 ± 19.8	-18.1 ± 14.9		
Day 8					
DDEA 2.32% gel t.i.d.	80	14.4 ± 13.8	-61.0 ± 18.4	-26.0 (-30.8, -21.2)	<0.0001
DDEA 2.32% gel b.i.d.	80	17.3 ± 15.6	-58.1 ± 19.9	-23.1 (-27.9, -18.3)	<0.0001
Placebo	82	40.1 ± 20.0	-34.5 ± 17.1		

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline pain-on-movement as a covariate.

Pain-at-rest on Days 3, 5 and 8: (see Table 14). Mean pain-at-rest scores in the two groups treated with DDEA 2.32% gel fell further and faster than in the placebo group. The difference between the mean score in the two active treatment groups and that in the placebo group was 5 – 7 mm on Day 3, 7 – 9 mm on Day 5, and 8 mm on Day 8; these differences were all highly statistically significant.

Table 14: Pain at rest on Days 3, 5 and 8 compared to baseline

	n	Mean ± SD	Change from Day 1 Mean ± SD	Difference from placebo LS Mean (95% C.I.)	p-value
Day 3					
DDEA 2.32% gel t.i.d.	80	15.4 ± 16.5	-21.4 ± 18.7	-6.7 (-9.3, -4.0)	<0.0001
DDEA 2.32% gel b.i.d.	80	17.5 ± 19.7	-19.0 ± 17.7	-4.7 (-7.4, -2.0)	<0.001
Placebo	82	21.9 ± 20.0	-14.1 ± 15.2		
Day 5					
DDEA 2.32% gel t.i.d.	80	6.9 ± 11.9	-29.9 ± 22.4	-9.0 (-11.5, -6.5)	<0.0001
DDEA 2.32% gel b.i.d.	80	8.8 ± 12.8	-27.7 ± 20.0	-7.3 (-9.8, -4.8)	<0.0001
Placebo	82	15.9 ± 17.0	-20.1 ± 17.5		
Day 8					
DDEA 2.32% gel t.i.d.	80	3.0 ± 7.1	-33.8 ± 23.6	-7.9 (-10.3, -5.4)	<0.0001
DDEA 2.32% gel b.i.d.	80	3.1 ± 5.8	-33.4 ± 23.1	-7.9 (-10.3, -5.4)	<0.0001
Placebo	82	10.8 ± 14.3	-25.1 ± 20.8		

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline pain-at-rest as a covariate.

Tenderness (pressure pain threshold) on Days 3, 5 and 8: (see Table 15) The difference in tenderness between the contralateral and injured ankles from Day 1 to Day 3 and Day 5 decreased approximately twice as rapidly in patients treated with DDEA 2.32% gel versus placebo. By Day 8, the difference in tenderness between ankles had decreased from 2.9 – 3.0 N/cm2 on Day 1 to 0.7 - 0.8 N/cm^2 in the two groups given active treatment, but only to 1.7 N/cm^2 in the placebo group.

Table 15: Difference in pressure pain threshold (tenderness, N/cm^2) between the contralateral and injured ankles on Days 3, 5 and 8 compared to placebo

	n	Mean ± SD	Change from Day 1 Mean ± SD	Difference from placebo LS Mean (95% C.I.)	p-value
Day 3					
DDEA 2.32% gel t.i.d.	80	1.9 ± 1.2	-1.0 ± 1.4	-0.7 (-1.0, -0.4)	<0.0001
DDEA 2.32% gel b.i.d.	80	1.9 ± 1.0	-1.1 ± 1.7	-0.7 (-1.0, -0.4)	<0.0001
Placebo	82	2.6 ± 1.3	-0.4 ± 1.0		
Day 5					
DDEA 2.32% gel t.i.d.	80	1.1 ± 1.1	-1.8 ± 1.5	-1.0 (-1.2, -0.7)	<0.0001
DDEA 2.32% gel b.i.d.	80	1.2 ± 1.1	-1.8 ± 1.5	-0.9 (-1.1, -0.6)	<0.0001
Placebo	82	2.1 ± 1.2	-0.9 ± 0.9		
Day 8					
DDEA 2.32% gel t.i.d.	80	0.7 ± 1.3	-2.2 ± 1.7	-1.0 (-1.3, -0.7)	<0.0001
DDEA 2.32% gel b.i.d.	80	0.8 ± 1.0	-2.3 ± 1.6	-1.0 (-1.3, -0.7)	<0.0001
Placebo	82	1.7 ± 1.2	-1.3 ± 1.2		

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline difference in pressure pain threshold as a covariate.

Swelling on Days 3, 5 and 8: (see Table 16) In both active treatment groups, the mean differences between the Figure-of-eight measurements of the injured and contralateral ankles decreased rapidly after the start of treatment, from 1.6 – 1.8 cm on Day 1 to 1.1 cm on Day 3, 0.6 cm on Day 5 and 0.3 cm on Day 8. In the placebo group, swelling came down more slowly, from 1.7 cm on Day 1 to 1.5 cm on Day 3 and 1.2 cm on Day 5; it remained at 0.9 cm on Day 8. The differences in swelling between both active treatments and placebo were highly significant at all three post-treatment time points.

Table 16: Difference in swelling (cm) between the injured and contralateral ankles

Day/Treatment	n	Observed value Mean ± SD	Change from Day 1 Mean ± SD	Difference from placebo LS Mean (95% C.I.)	p-value
Day 3					
DDEA 2.32% gel t.i.d.	80	1.1 ± 0.9	-0.7 ± 1.0	-0.4 (-0.6, -0.3)	<0.0001
DDEA 2.32% gel b.i.d.	80	1.1 ± 0.9	-0.5 ± 1.0	-0.3 (-0.5, -0.1)	0.0012
Placebo	82	1.5 ± 1.1	-0.2 ± 0.6		
Day 5					
DDEA 2.32% gel t.i.d.	80	0.6 ± 0.7	-1.2 ± 1.3	-0.7 (-0.9, -0.5)	<0.0001
DDEA 2.32% gel b.i.d.	80	0.6 ± 0.6	-1.0 ± 1.3	-0.6 (-0.8, -0.3)	<0.0001
Placebo	82	1.2 ± 1.1	-0.5 ± 0.6		
Day 8					
DDEA 2.32% gel t.i.d.	80	0.3 ± 0.5	-1.4 ± 1.4	-0.6 (-0.7, -0.4)	<0.0001
DDEA 2.32% gel b.i.d.	80	0.3 ± 0.6	-1.3 ± 1.4	-0.5 (-0.7, -0.3)	<0.0001
Placebo	82	0.9 ± 0.8	-0.8 ± 1.0		

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline difference in swelling as a covariate.

Ankle joint function (Karlsson Scoring Scale): See Table 17. In patients treated with DDEA 2.32% gel, the mean ankle joint function score rose rapidly over the treatment period. The mean Karlsson score in the placebo group at Day 5 (45) was comparable to mean Karlsson scores in the DDEA 2.32% gel treated groups at Day 3 (42-45). By Day 8, patients treated with placebo still had a mean score of 53 and had not achieved the level of ankle joint function that patients given active treatment had achieved on Day 5 (score = 58-63). Differences between the DDEA 2.32% gel groups and placebo were highly statistically significant at Days 3, 5 and 8 (p≤0.0011). Table 10 above provides details of Karlsson Scoring System.

Table 17: Total ankle joint function score (Karlsson scoring scale)

Day/Treatment	n	Observed value Mean ± SD	Change from Day 1 Mean ± SD	Difference from placebo LS Mean (95% C.I.)	p-value
Day 3					
DDEA 2.32% gel t.i.d.	80	44.9 ± 13.9	15.7 ± 11.7	7.4 (4.6, 10.2)	<0.0001
DDEA 2.32% gel b.i.d.	80	42.0 ± 13.9	12.9 ± 10.9	4.6 (1.9, 7.4)	0.0011
Placebo	82	37.4 ± 15.2	8.2 ± 9.4		
Day 5					
DDEA 2.32% gel t.i.d.	80	62.8 ± 11.5	33.6 ± 16.7	17.8 (14.3, 21.2)	<0.0001
DDEA 2.32% gel b.i.d.	80	58.3 ± 12.9	29.2 ± 13.5	13.4 (9.9, 16.8)	<0.0001
Placebo	82	45.0 ± 15.4	15.8 ± 9.9		
Day 8					
DDEA 2.32% gel t.i.d.	80	73.1 ± 13.1	43.9 ± 20.1	20.3 (16.3, 24.4)	<0.0001
DDEA 2.32% gel b.i.d.	80	70.9 ± 12.8	41.8 ± 17.3	18.1 (14.1, 22.2)	<0.0001
Placebo	82	52.7 ± 15.6	23.5 ± 12.3		

DDEA = diclofenac diethylamine
LS Mean = Least squares mean
LS Mean and p-values obtained from ANCOVA with treatment and center as main effects and baseline ankle joint function score as a covariate.

Use of rescue medication: Over 90% of patients in all three treatment groups required no rescue medication for ankle pain during the 7-day treatment period and those who used any rescue medication used it sparingly. There was no difference between treatments either in the number of tablets of rescue medication used, or in the number of days on which rescue medication was used. Results for all use of

rescue medicine, regardless of reason, differed minimally from the results for use of rescue medication to treat ankle sprain. There was little use of rescue medication for any reason other than to treat ankle sprain.

Global Assessment of Benefit (see Table 7 for relevant 5-point Likert scale)
On Days 3, 5 and 8, patients were asked the following question: “Considering all the ways this treatment has affected you, how well are you doing?”.

By Day 3, 76% of patients who applied DDEA 2.32% gel three times daily and 63% of those who applied it twice daily assessed benefit as good or very good, compared to 23% of patients who rated their treatment similarly in the placebo group. By Day 8, the proportion of patients who assessed benefit as very good or good had risen to 91% in the group treated with DDEA 2.32% gel three times daily and 85% in those treated with DDEA 2.32% gel twice daily. However, the proportion reporting similar satisfaction had only risen to 29% in the placebo group. The assessments of benefit were significantly higher in the active groups compared to placebo at each time point ($p < 0.0001$). Assessments in the DDEA 2.32% gel three times daily group were slightly better than in the twice daily group, however assessments in both groups were generally favourable.

Global assessment of treatment satisfaction (see Table 8 for relevant 5-point Likert scale):
On Days 5 and 8, patients were asked the following question: “How do you rate this medication as a treatment for the pain of ankle sprain?”.

On Day 5, 90% of patients who applied DDEA 2.32% gel three times daily and 84% of those who applied DDEA 2.32% gel twice daily rated their treatment satisfaction as good, very good or excellent compared to only 23% of patients in the placebo group.

Similar results were obtained on Day 8. Treatment satisfaction in either active treatment group was significantly greater than in the placebo group on each of Day 5 and Day 8 ($p < 0.0001$). Assessments in the DDEA 2.32% gel three times daily group were somewhat better than in the twice daily group, although assessments in both groups were considered to be highly favourable.

Times to specified reductions in pain-on-movement
Three events were defined with respect to POM and time to each event was captured as an efficacy parameter:
• a 40 mm reduction from Day 1,
• a score of 30 mm or less, and
• a 50% reduction in score from Day 1.

Because the mean POM at Baseline (Day 1) was approximately 75 mm in all three treatment groups, the 3 events were comparable and the findings for the 3 efficacy parameters similar.

The median time to a 40-point reduction in POM was 4 days in both groups treated with DDEA 2.32% gel, but 8 days in the placebo group ($p < 0.0001$ for both comparisons between active treatment and placebo). The median time to a VAS score of 30 mm or less for POM was 4 days in both active treatment groups, versus 9 days in the placebo group ($p < 0.0001$ for both comparisons between active treatment and placebo).

Corresponding Kaplan-Meier curves for time to achieving a 50% reduction from Day 1 in POM were generally similar in appearance to Kaplan-Meier curves for time to achieve a 40-point reduction in pain-on-movement. The median time to a 50% reduction in POM was 4 days in both active treatment groups, versus 8 days in the placebo group ($p < 0.0001$ for both comparisons between active treatment and placebo).

The applicant therefore claims that treatment with DDEA 2.32% gel, whether twice or three times daily accelerated healing by 4 days or more, as reflected by median time to the events discussed above.

Safety results
See Section IV5, Clinical Safety, below.

Overall Conclusions On Clinical Efficacy
Following the failure of the first pivotal study (VOPO-PE-201) to show superiority against vehicle it is agreed that that suboptimal study design was likely to have confounded the data. In particular, it is agreed that the primary evaluation of active pain-on-movement could have been obscured by the concomitant use of ancillary measures such as Aircast splints in the first study.

The efficacy findings in Study VOPO-P-307 are sufficiently compelling to support the applications in the proposed indications in soft-tissue pain and inflammation, since these conditions are sufficiently pathophysiologically similar to allow extrapolation from the superiority shown against vehicle in a single, ankle sprain, model:

IV.5 Clinical Safety

Safety data were derived from the following studies comprising the clinical development programme:

- **Study VOPO-PE-102:** comparative pharmacokinetic study to look at systemic absorption potential
- **Study VOPO-PE-201:** 7-day placebo-controlled efficacy and safety study comparing once and twice daily application in acute ankle sprain
- **Study VOPO-P-307:** 7-day placebo-controlled efficacy and safety study comparing twice and thrice daily application
- **Study VOPO-P-103:** phototoxicity study
- **Study VOPO-P-105:** skin sensitisation and irritancy study

General Safety findings from Pharmacokinetic and Pivotal Studies
The reported adverse events (AEs) arising from the various studies are discussed below.

- **Study VOPO-PE-102**

The overall incidence of adverse events (AEs) ranged between 7.7% and 17.9% after topical DDEA treatment and was greater, 25.6%, after oral treatment (Table 18). No AEs reported during or after topical diclofenac treatment were considered to be drug related by the investigator, whereas 7.7% of the subjects (3 of 39 subjects) reported drug related AEs during or after oral treatment. The latter included two reports of constipation and one of mild abdominal pain.

AEs were of mild to moderate intensity and resolved within the study period apart from an isolated serious adverse event (SAE) of bilateral pulmonary emboli in a subject using twice daily (non-occluded) 2.32% DDEA. This subject was found to have an underlying Factor V Leiden mutation, and the SAE was considered to be unrelated to study medication. Another subject decided to withdraw because of postural dizziness while taking oral diclofenac although this was considered to be unrelated to study medication.

Table 18: Overview of AEs (Safety Population)

Number of subjects with - n (%): Preferred Term	A N=39	B N=39	A or B N=39	C N=39	D N=39
SOC: All					
Total	7 (17.9%)	3 (7.7%)	9 (23.1%)	4 (10.3%)	10 (25.6%
SOC: Gastrointestinal disorders					
Total	1 (2.6%)	0	1 (2.6%)	0	3 (7.7%)
Constipation	0	0	0	0	2 (5.1%)
SOC: General disorders and administration site conditions					
Total	2 (5.1%)	0	2 (5.1%)	0	0
SOC: Infections and infestations					
Total	2 (5.1%)	1 (2.6%)	3 (7.7%)	2 (5.1%)	1 (2.6%)
Nasopharyngitis	2 (5.1%)	1 (2.6%)	3 (7.7%)	2 (5.1%)	1 (2.6%)
SOC: Nervous system disorders					
Total	2 (5.1%)	2 (5.1%)	3 (7.7%)	2 (5.1%)	5 (12.8%)
Headache	2 (5.1%)	2 (5.1%)	3 (7.7%)	2 (5.1%)	3 (7.7%)
SOC: Respiratory, thoracic and mediastinal disorders					
Total	2 (5.1%)	0	2 (5.1%)	1 (2.6%)	0

Percentages are relative to all subjects receiving the respective treatment.
A: 2 g DDEA 2.32% bid for 7 days, non-occlusive
B: 2 g DDEA 2.32% bid for 7 days, semi-occlusive
C: 2 g DDEA 1.16% qid for 7 days, non-occlusive
D: 50 mg diclofenac-Na tablet p.o. tid for 7 days

- **Study VOPO-PE-201**

The application of DDEA 2.32% once or twice daily for 7 days was found to be well tolerated. The overall incidence of adverse events (AEs) was low and there were no clinically relevant differences between the treatment groups and only 1-2 subjects per treatment group were AEs thought by the investigator to be drug related.

AEs were generally mild to moderate in intensity, resolving prior to the end of the study. No AEs were considered serious but four subjects dropped-out voluntarily as a result of AEs on Days 4 or 5: two in the vehicle group due to mild erythema at the application site and one subject in the once daily DDEA group dropped-out because of mild pain in the extremities, which was not considered to be treatment related. The cases of erythema were suspected to be due to study medication. Marked erythema or erythema plus papules was noted in two subjects on Day 5 (one in the vehicle group and one in the twice daily DDEA group. In relation to the latter, erythema was stated to be already present pre-dosing. and one in the vehicle group). Both these subjects withdrew from the study.

- **Study VOPO-P-307**

Overall, DDEA 2.32% gel and its vehicle was found to be well tolerated. There were few reported adverse events: two (0.8%) of the 242 patients treated reported application site reactions (pain and pruritus) and one (0.4%) patient had skin exfoliation on the hand. These AEs were suspected of being related to study medication. The applicant has commented that this rate of local reaction was no higher than that known to occur with the currently licensed 1.16% DDEA gel.

One patient, randomised to vehicle, discontinued the study due to an adverse event as the Pain-On-Movement (POM) score increased (from 66 mm on Day 1 to 78 mm on Days 3 and 5 and scores for pain-at-rest remained relatively unchanged during treatment (56 mm on Day 1, 57 mm on Day 3 and 51 mm on Day 5). Swelling in the injured ankle also failed to improve between Days 1 and 5. The patient was therefore discontinued on Day 5, the reason cited being an AE. However, the applicant has commented that the reason for the AE and subsequent withdrawal was actually lack of efficacy on vehicle.

- **Study VOPO-P-103**

There was only one reported AE - a mild sore throat which was not considered to be related to treatment and it resolved spontaneously.

- **STUDY VOPO-P-105**

Fifty-three (22%) subjects experienced a total of 68 AEs, the most common being nasopharyngitis, in 18 (8%) subjects, followed by headache, in 11 (5%). There were no reports of AEs related to the patch application site, and none of the reported adverse events were considered to be related to study treatment.

Safety Studies - Skin Sensitisation and Phototoxicity

In addition to the general safety evaluation derived from the Pharmacokinetic and Pivotal efficacy studies, studies VOPO-P-105 and VOPO-P-103, which examined the potential for the proposed diclofenac 2.32% gel to cause local tolerability problems (sensitisation with and without UV light), were conducted

Study VOPO-P-105

A randomised, Phase I, evaluator-blinded, multiple application, intra-individual comparison, study involving a repeat insult patch-test (RIPT) in healthy volunteers.

This study was designed to evaluate the skin sensitisation and cutaneous irritation potential of diclofenac DEA 2.32% gel compared to a vehicle and blank controls; it consisted of the phases below (also see Table 19):

- **Induction phase**– which included drug application, drug removal and test site evaluation

- **Two-week rest phase**
- **Challenge phase** – a single application of drug with evaluation of signs of sensitisation at 48, 72 and 96 hours.
- **Rechallenge phase** after a further 3 weeks only in those exhibiting a previous '+' grade at any patch site at 72 or 96 hours.

Table 19: Study Design

Screening	Induction [A]	Rest	← Challenge →			
	Mon – Wed – Fri [B] Application / removal / evaluation		Mon Drug application	Wed Drug removal / evaluation	Thu & Fri Test site evaluation	Sat (optional) Test site evaluation
Days -14 - -1	Days 1-22	Days 23-35	Day 36	Day 38	Days 39 & 40	Day 41
Visit 1	Visits 2-11		Visit 12	Visit 13	Visits 14 & 15	Visit 16 [C]

[A] Flexibility due to scheduling difficulties was permitted for patch removal, as long as the drug remained in contact with the skin for the full 21 days.

[B] An alternate schedule was permitted provided the visit scheme and treatment duration were the same.

[C] If there was a "+" grade for any patch site at 72h or 96h (Visit 14 or 15), subject had to return to the study center for another assessment at 120h (Day 41, Visit 16).

The sensitisation, irritation and safety parameters used in this study were the standard parameters used for the purposes of such a study.

- **Study Participants and inclusion/exclusion criteria**

Healthy male or female subjects aged between 18 and 55 years of age who were willing to refrain from all activities (including heavy exercise) that might wet the test area of the back.

The main exclusion criteria were subjects with any of the following which could have interfered with the application of the test patches and/or interpretation of the results:

- scars, moles, sunburn, tattoos, abnormal skin pigmentation, excessive hair or blemishes in the test area

- systemic or skin disease
- known sensitivity to diclofenac, other NSAIDs, any component of the formulations being tested, or adhesive tape.

In addition, the use of the following medications during the study was prohibited:

- Sympathomimetics;
- Corticosteroids (with the exception of HRT and contraceptive steroids for females and
- nasal sprays with local mode of action);
- Anti-inflammatory drugs (with the exception of <200 mg/day aspirin);
- Topical/systemic analgesics and NSAIDs (use of acetaminophen was permitted instead).
- Antihistamines (including OTC sleep aids).
- Systemic antibiotics. Topical localised was permitted upon the Investigator's judgement.
- Topical products, treatments, or cosmetics applied to the patch sites.

- **Treatments**

Upon enrollment each subject was given a unique randomisation number that specified the order of application of the 3 study treatments to patch sites 1 through 3 on the subject's back.

There were 6 possible orders of application of the 3 study treatments to the 3 patch sites. The sequence to which the subject was randomised applied throughout the study. Each subject served as his/her own control, as all subjects received all study drugs (active patch, vehicle patch and blank patch.

Test product:

Diclofenac DEA (DDEA) 2.32% gel, 0.2 ml delivered to the subject's back; nine applications during induction phase and one application during challenge phase. Duration of treatment: 21 days during induction phase, 2 days during challenge phase.

Reference therapy:

1. Vehicle gel, dose and mode of administration as for diclofenac DEA 2.32% gel; 2. Blank control.

Upon enrollment each subject was given a unique randomisation number that specified the order of application of the 3 study treatments to patch sites 1 through 3 on the subject's back.

There were 6 possible orders of application of the 3 study treatments to the 3 patch sites. The sequence to which the subject was randomised applied throughout the study. Each subject served as his/her own control, as all subjects received all study drugs (active patch, vehicle patch and blank patch.

- **Objectives**

Primary: To confirm the lack of sensitisation potential of diclofenac DEA 2.32% gel as assessed by repeated topical occlusive applications to the skin of healthy human volunteers.

Secondary:

1. To evaluate the potential of diclofenac DEA 2.32% gel to cause cutaneous irritation by repeated topical occlusive applications to the skin of healthy human volunteers.
2. To assess safety by recording any adverse events (AEs) occurring during the study.

The study was completed as planned.

- **Outcomes/endpoints**

At least 30 minutes after patch removal, skin assessments were made independently by two trained dermatologist/allergy specialists. Assessments were made in accordance with the schedule. If the evaluations were at variance, a final score was mutually agreed upon.

Evidence of sensitisation (erythema, edema and vesicles) at the beginning of the induction phase was considered to be indicative of pre-sensitised to one or more of the patch components.

- ***Primary variable - sensitisation potential***

During the challenge phase, *using the International Contact Dermatitis Research Group (ICDRG) scale (1970) for the assessment of sensitisation,* sensitisation evaluation was based on the following criteria:

0 No reaction
? Weak and questionable reaction, equivocal
+ Erythema and edema (infiltration or papules)
++ Erythema, edema and vesicles
+++ Very severe reaction (bullous, spreading reaction)
IR Irritant reactions

A sensitisation reaction was defined as:
- an ICDRG score of ++ or greater at any time during the challenge phase,
or
- a crescendo evolution of intensity of scoring or the presence of a + score at any time during the challenge, followed by a recurrence of a dermatological response at rechallenge, equivalent to or more severe than that observed at challenge and judged by the Investigator or the designee to be positive.

- ***Secondary variable - irritation potential***

This was assessed during induction using the following scales - the reaction needed to be seen covering an area of 25% or more of the test site:

Irritation scale
0 = No evidence of irritation
1 = Minimal erythema, barely perceptible
2 = Moderate erythema, minimal edema, or minimal papular response
3 = Strong erythema or erythema and papules
4 = Definite edema
5 = Erythema, edema and papules
6 = Vesicular eruption
7 = Strong reaction spreading beyond test site

Superficial effects scale
A = Slightly glazed appearance
B = Marked glazing
C = Glazing with peeling and cracking
F = Glazing with fissures
G = Film of serous exudate covering all or part of the test site
H = Small petechial erosions and/or scabs

Patch test scores were calculated by combining the numerical and letter scores and for this purpose the letter grades were converted into numbers, as follows:
A = 0, B = 1, C = 2, F = G = H = 3, and added to the numerical score (e.g., 2 + C = 2 + 2 = 4).

If the level of irritation at a particular site reached 3 or above on the Irritation Scale, the next induction patch was applied to a different, unexposed (naïve), site. If a similar reaction was seen, a third patch was applied to another naïve site. If a similar reaction was once again seen, that particular product could be discontinued, at the discretion of the Investigator, and a score of 3 assigned to the and any subsequently assigned readings for the purpose of statistical analysis. Application of the rest of the patches without reaction was continued as planned.

Safety: Standard safety assessments consisted of monitoring and recording all adverse events, including serious adverse events.

Local reactions on non-patched areas and/or local reactions not accounted for by the scoring system/assessments described above were to be recorded and rated as adverse events linked to the specific patch site where they occurred.

Sensitisation potential:
The sensitisation potential of the three study treatments (diclofenac DEA 2.32% gel, vehicle gel and blank patch) was analysed in the sensitisation analysis set.

The number and percentage of subjects with a sensitisation reaction was tabulated by treatment. The distribution over all subjects of the ICDRG score by day for Days 38-41 as well as the maximum over Days 38-41 was tabulated for each treatment. Missing sensitisation scores were not imputed. No hypothesis relating to sensitisation was tested.

Irritation potential:
The irritation potential of the three study treatments (diclofenac DEA 2.32% gel, vehicle gel and blank patch) was analysed in the irritation analysis set.

The Frequency Index (FI) was calculated as the number of evaluations for a subject with a score of X or greater divided by the total number of evaluations for that subject:

$$\text{FI}(1) = \frac{\text{number of evaluations with a score} \geq 1}{\text{total number of evaluations}}$$

$$\text{FI}(2) = \frac{\text{number of evaluations with a score} \geq 2}{\text{total number of evaluations}}$$

$$\text{FI}(3) = \frac{\text{number of evaluations with a score} \geq 3}{\text{total number of evaluations}}$$

At each level of the irritation scale, FI was summarised for each treatment by the mean, standard deviation, median, minimum and maximum values. The three treatments were compared pairwise using the Cochran-Mantel-Haenszel test of treatment means stratified by subject.

Comparison of the treatments was primarily based on FI(3) since the differences in FI(3) are the most important for the irritation evaluation. Further comparisons on FI(2) and finally on FI(1) were also carried out.

Safety
Summary statistics were applied to all and treatment-emergent adverse events (AEs).

Results
- **Baseline data**

Safety analysis set:
Of the 240 subjects included in the safety analysis set, 232 (97%) completed the study to the end of the induction phase and 224 (93%) completed to Day 40/41 without the need for rechallenge. The primary reason for early discontinuation was withdrawal of consent (7 subjects).

- **Numbers analysed**

There were three analysis sets, as described below. All 240 subjects randomised were included in the safety set for all three treatments.

Sensitisation analysis set: (sensitisation potential).
This included subjects who completed the induction and challenge. To be considered a complete case, a subject had to have nine applications and at least eight subsequent readings during induction, at least 11 to 14 days of rest, and, for a particular treatment, at least three readings during the challenge phase. Subjects who demonstrated sensitisation were also included in this analysis set, even if they did not complete all visits.

Subjects who during induction were considered by the Investigator to be pre-sensitised to a treatment were excluded for that treatment.

Nine subjects were excluded from the sensitisation analysis set for all three treatments because they had fewer than nine patch applications during the induction phase (8 discontinued and one subject missed two visits). Another eight subjects were excluded from the sensitisation analysis set for all 3 treatments because they discontinued after completing the induction phase and had fewer than three readings during the challenge phase. Another subject was considered pre-sensitised to diclofenac and was excluded from the sensitisation analysis set for diclofenac DEA 2.32% gel.

Irritation analysis set: (cumulative irritation)
This included subjects who completed induction or discontinued with a score of 3 or greater. To complete the induction phase, a subject had to have nine consecutive induction phase applications and at least eight subsequent consecutive induction phase readings as well as no patch re-located for any reason other than a reaction of grade 3 or above. Subjects who demonstrated irritation were also included in this analysis set, even if they did not complete all visits.

As stated above, nine subjects had fewer than nine patch applications during the induction phase. However, three of these had a combined irritation score > 0 at one or more assessments with diclofenac DEA 2.32% gel, and four and two subjects, respectively, demonstrated irritation with vehicle gel and the blank control. These subjects were therefore included in the irritation analysis set for the treatment(s) inducing irritation. Overall, 237 subjects had one or more patches included in the analysis of irritation potential.

Safety analysis set (All Treated Population) this group included all 240 randomised subjects who each received study treatment.

- **Outcomes and estimation**

Sensitisation potential – Sensitisation analysis set:
There were no sensitisation reactions to any of the patches included in the sensitisation analysis set.

The diclofenac DEA patch application site in one subject was excluded from the sensitisation analysis because of pre-sensitisation. A vesicular skin reaction characteristic of contact sensitisation was seen at the site of patch application during induction and again during the challenge phase. The features of this reaction were considered to be characteristic of a pre-sensitisation (cf. an irritation) reaction, most probably due to previous contact with diclofenac.

Irritation potential – irritation analysis set:

Irritation rate

Table 20 shows the highest combined irritation scores recorded during the induction phase of the study.

Table 20 Highest combined irritation scores during induction – irritation analysis set

	Diclofenac DEA 2.32% gel (N = 234)		Vehicle gel (N = 235)		Blank control (N = 233)		
Score	n	(%)	n	(%)	n	(%)	p-value +
≥3	4	(1.7)	7	(3.0)	2	(0.9)	(1) 0.5488
2	117	(50.0)	30	(12.8)	8	(3.4)	(2) 0.6875
1	96	(41.0)	110	(46.8)	53	(22.7)	(3) 0.1797
0	16	(6.8)	88	(37.4)	170	(73.0)	
Excluded	1	(0.4)	0		0		

+ p-value for comparison of score = 0-2 vs score ≥3 is based on McNemar's test

(1) diclofenac DEA 2.32% gel vs vehicle gel
(2) diclofenac DEA 2.32% gel vs blank control
(3) vehicle gel vs blank control.

For comparison of score = 0-1 vs score ≥2, all pairwise p-values are <0.0001.

For comparison of score = 0 vs score ≥1, all pairwise p-values are <0.0001.

One subject discontinued on Day 5 and therefore did not complete the induction phase. The subject was included in the irritation analysis set for diclofenac DEA 2.32% gel because an irritation scale score of 1 was recorded on Day 3, but was not included in the irritation analysis sets for vehicle gel or the blank patch having demonstrated no irritation with either treatment.

Despite being in the analysis set, the subject discontinued due to a strong adhesive tape reaction at all three patch application sites, i.e. for a reason unrelated to test drug reactions, and therefore the subject's irritation scores for diclofenac DEA 2.32% gel were excluded from analysis.

The highest combined irritation score was ≤2 in almost all subjects for all three treatments. Irritation scores ≥ 3 were associated with each of the three treatments including the blank patch; however, diclofenac DEA 2.32% gel did not differ statistically compared to vehicle gel ($p = 0.5488$) or blank patch ($p = 0.6875$). The percentage of subjects with irritation scores ≥ 2 or any irritation (irritation ≥ 1) was higher for diclofenac DEA 2.32% gel compared to vehicle and blank control ($p < 0.0001$). However combined irritation scores >1 were infrequent for all treatments after the Day 12 visit. No irritancy reaction was seen in just 7% of subjects with diclofenac DEA 2.32% gel compared with 37% of subjects for its vehicle and 73% of subjects for blank patch.

Frequency index

Consistent with the highest combined irritation scores shown in Table 54, the mean value of FI(3) did not differ between treatments; the numerically highest mean value occurred with the vehicle gel. The mean values of FI(2) and FI(1) were higher with diclofenac DEA 2.32% gel than with vehicle gel, and higher with vehicle gel than with blank patch (Table 21).

Table 21: Irritation frequency index (FI) – irritation analysis set

Frequency Index/ Statistic	Diclofenac DEA 2.32% gel (N = 234)	Vehicle gel (N = 235)	Blank control (N = 233)	p-value +
FI (3)				
Mean ± SD	0.01 ± 0.06	0.02 ± 0.09	0.00 ± 0.05	(1) 0.2686
Median	0.00	0.00	0.00	(2) 0.5637
Min – Max	0.00 – 0.50	0.00 – 0.80	0.00 – 0.70	(3) 0.1189
FI (2)				
Mean ± SD	0.10 ± 0.14	0.04 ± 0.12	0.01 ± 0.06	(1) <0.0001
Median	0.10	0.00	0.00	(2) <0.0001
Min – Max	0.00 – 0.80	0.00 – 0.80	0.00 – 0.70	(3) 0.0021
FI (1)				
Mean ± SD	0.37 ± 0.22	0.16 ± 0.20	0.05 ± 0.10	(1) <0.0001
Median	0.40	0.10	0.00	(2) <0.0001
Min – Max	0.00 – 0.90	0.00 – 0.90	0.00 – 0.80	(3) <0.0001

+ p-value from Cochran-Mantel-Haenszel comparison of means stratified by subject.
(1) diclofenac DEA 2.32% gel vs vehicle gel.
(2) diclofenac DEA 2.32% gel vs blank control.
(3) vehicle gel vs blank control.

No sensitisation reactions occurred with any of the three treatments, except for one subject who was considered to be pre-sensitised to diclofenac gel (as discussed above).

However, some low-level irritancy was seen which was more marked in the active patch and to a lesser extent the vehicle patch compared to the blank patch; however combined irritation scores of >1 were generally infrequent. There were few combined irritation scores of 3 or higher in any of the treatments at any visit.

Study conclusions
There was no evidence of sensitisation potential following the repeated application of diclofenac DEA 2.32% gel and only a low cumulative skin irritation potential was observed with diclofenac DEA 2.32% gel after repeated 48 hour (72 hour on weekends) occlusive applications over 3 weeks.

It is agreed that, given the conditions of the sensitisation and irritation test significantly exaggerate the conditions which apply in normal use, the observed absence of sensitisation and the low cumulative irritation effect can be taken to indicate that diclofenac DEA 2.32% gel should be a well-tolerated product with no skin sensitisation or clinically significant cumulative irritation potential.

Study VOPO-P-103
A randomised, single (evaluator) blind, single centre, intra-individual comparison study evaluating the phototoxic potential of Voltaren 2.32% gel after single application and UV exposure in healthy male and female volunteers

Methods
The study included four phases (also see Table 22 below):

- Screening
- Determination of Minimal UV-induced Erythema Dose (MED). The MED was defined as the dose of UVA+B that produced the first perceptible, unambiguous redness reaction with clearly defined borders 22-24 h after irradiation (a score of 1 on the scale described on the scale shown in Table 55.
- Treatment phase - single 24 h application of study drug on Day 1, evaluation of the irritation potential on Day 2 (after removal of test drug) followed by UV irradiation.
- Evaluation of the phototoxic potential after irradiation - from Days 2 to 4 or 5 (if a reaction at Day 5 seen)

Table 22: Study Design

Screening	Drug application	Irradiation	← Evaluation →	
	Drug application to skin / Irradiation for MED determination	MED determination / Drug removal / Irritation evaluation / Irradiation and evaluation	Test site evaluation	Test site evaluation / End of study
Days -14 - -1	Day 1	Day 2	Day 3	Day 4 and/or 5
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5-6

- **Study participants and inclusion/exclusion criteria**

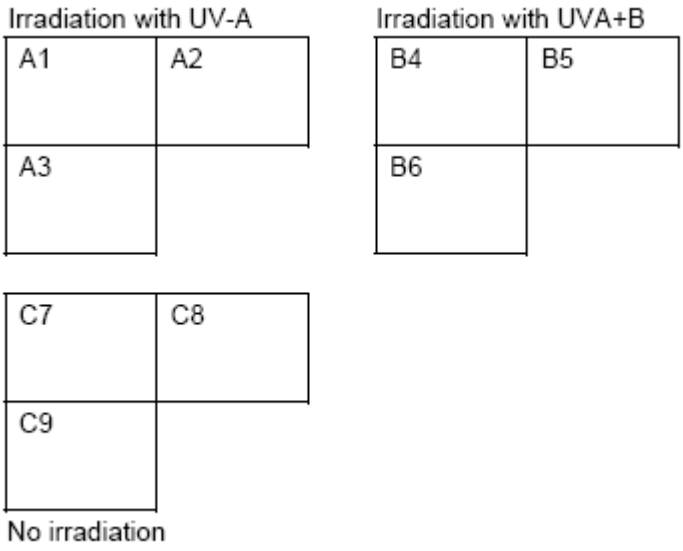
These were healthy male and female aged 18-55 years subjects fulfilling standard entry requirements.

- **Treatments**

The investigational medicinal products (IMPs) were Diclofenac DEA 2.32% gel and vehicle (identical to Diclofenac DEA 2.32% gel without the active ingredient) and a blank control. A vehicle gel was included in the study to help differentiate between possible phototoxicity due to the active ingredient (phototoxic reaction observed with diclofenac gel only) and phototoxicity due to the inactive ingredients (phototoxicity in response to both active and vehicle gels).

On the back of each subject, a raster was drawn up delineating areas (A, B, and C). Each area was divided in three sites, each of which defined the localisation of the Finn Chambers: A 1,2, 3; B 4, 5, 6; C 7, 8 and 9 (See Figure 2).

Figure 2: Test Site Irradiation



Sites A 1-3 were dosed as per randomisation schedule. 0.2ml of the test drug or vehicle may applied in Extra Large Finn Chambers fixed onto the skin using medical tape and left in place for 24 hours. Sites B 4-6 and C 7-9 were dosed in identical fashion to (A 1-3). Area A was irradiated with 5 J/cm2 UVA. Area B was exposed to 75% of the MED of UVA+B radiation determined for each subject. Area C was a non-irradiated control.

Subjects were instructed to keep the treated area dry and avoid exposure to sunlight.

UVA/UVA+B test site irradiation

On Day 2, the Finn Chambers were removed, and excess test material removed with gauze. After approximately 30 minutes the area was irradiated with a solar simulator. One application site was irradiated with 5 J/cm2 UVA, one was exposed to 5% of the pre-determined MED and one acted as a non-irradiated control.

Determination of Minimal UV-induced Erythema Dose (MED)
Day 1 – six pre-designated areas on the subject's upper right buttock were sequentially irradiated with incremental doses of UVA+B; action was taken to ensure that each of the 6 areas was irradiated only once. These areas were separated by approximately 1 cm.

The UVA+B doses for MED determination were based on the skin phototype but doses could be adapted if deemed necessary by the investigator.

Table 23 below provides the erythema scale (5-point scale) for MED determination.

Table 23: Erythema Scale for MED determination (5-point scale)

Score	Description
0	No visible reaction and / or erythema
0.5	Barely perceptible, erythema with no clearly defined border
1	Minimal erythema (i.e., the first perceptible, unambiguous redness reaction with clearly defined borders)
2	Moderate, clearly defined erythema and edema
3	Severe / strong erythema with edema and blistering

- **Objectives**

Primary

- To assess the phototoxic potential of diclofenac DEA 2.32% gel and vehicle gel after a single application to the skin of healthy subjects with ultraviolet (UV) exposure.

Secondary

-To assess the irritation potential of diclofenac DEA 2.32% gel after single dose without UV exposure.
-To evaluate overall safety.

- **Endpoints**

For each subject, both the phototoxic reaction score (PtRS) and the photoirritation intensity were determined separately for both test drugs (active and vehicle) and both types of UV (UVA and UVA+B).

Evaluation of Phototoxicity and Irritation Potential
Phototoxicity potential was evaluated on Days 2-4 (and 5 if needed) by grading erythema on a 5-point scale (Table 24) and recording other local reactions (present or absent).

Table 24: Evaluating phototoxicity potential and irritation potential

Erythema reaction score (ERS) (5-point scale):

- No erythema: 0
- Erythema barely visible: 0.5
- Mild erythema: 1
- Moderate erythema: 2
- Severe erythema: 3

Irritation potential was evaluated on Day 2 only, prior to irradiation, by grading irritation reactions on the following 6-point scale:

Irritation potential (6-point scale):

- No reaction 0
- Slight reddening 0.5
- Clear evidence of redness 1
- Redness + edema or papules 2
- With the addition of blisters 3
- Large blisters 4

- **Phototoxicity reaction.** This was diagnosed when the erythema reaction score on the treated and irradiated area was higher than that observed on treated but non-irradiated area and higher than that observed on non-treated but irradiated area (1978). The numerical value of the phototoxic reaction score (PtRS) was defined as the lower of the two differences.

- **Photoirritation intensity.** This was pre-defined as the highest phototoxic reaction score (PtRS) observed at any time after irradiation (10 minutes, 24 or 48 hours and 72 hours, if applicable). For each subject, both the PtRS and the photoirritation intensity were determined separately for both test drugs (active and vehicle) and both types of UV (UVA and UVA+B).

Safety assessments

Safety was assessed by recording all adverse events (AEs) and serious adverse events (SAEs) including their severity and relationship to study drug as well as physical examination and vital signs.

Results

All 35 randomised subjects completed the study and were therefore included in all the data sets: phototoxic potential, irritation potential and safety.

- **Outcomes and estimation**
  - **Phototoxicity potential evaluation**

Erythema reactions

Skin evaluations were performed at 0.17, 24 and 48 hours after UV exposure and the distribution of the erythema reaction scores is summarised in Tables 25-28.

Table 25: Distribution of erythema scores at 0.17h

	No Irradiation (N=35)			UVA (N=35)			UVA+B (N=35)		
Erythema Scores	DDEA	Veh	Blank	DDEA	Veh	Blank	DDEA	Veh	Blank
No erythema	29	32	33	27	32	33	22	25	26
Erythema barely visible	6	3	2	8	3	2	13	10	9

Table 26: Distribution of erythema scores at 24 h

	No Irradiation (N=35)			UVA (N=35)			UVA+B (N=35)		
Erythema Scores	DDEA	Veh	Blank	DDEA	Veh	Blank	DDEA	Veh	Blank
No erythema	26	34	35	22	33	35	12	-	1
Erythema barely visible	9	1	-	13	2	-	19	8	8
Mild erythema	-	-	-	-	-	-	4	27	26

Table 27: Distribution of erythema scores at 48 h

	No Irradiation (N=35)			UVA (N=35)			UVA+B (N=35)		
Erythema Scores	DDEA	Veh	Blank	DDEA	Veh	Blank	DDEA	Veh	Blank
No erythema	32	35	35	32	35	35	27	4	7
Erythema barely visible	3	-	-	3	-	-	8	12	14
Mild erythema	-	-	-	-	-	-	-	19	14

Table 28: Distribution of Maximum erythema scores

	No Irradiation (N=35)			UVA (N=35)			UVA+B (N=35)		
Erythema Scores	DDEA	Veh	Blank	DDEA	Veh	Blank	DDEA	Veh	Blank
No erythema	23	31	33	20	30	33	12	-	1
Erythema barely visible	12	4	2	15	5	2	19	8	8
Mild erythema	-	-	-	-	-	-	4	27	26

Only a few subjects showed barely visible erythema without irradiation. The frequency of barely visible erythema was higher on skin treated with diclofenac DEA 2.32% gel (DDEA) at all time points, with the greatest frequency at 24 hours after irradiation. After UVA irradiation there was a slightly increased frequency of barely visible erythema on skin treated with diclofenac DEA 2.32% gel particularly at 24 hours. Results with UVA irradiation were very similar to results without irradiation. Mild erythema occurred after irradiation with UVA+B at 24 hours and 48-hour with a higher frequency with vehicle and blank than diclofenac. The highest frequency was observed at 24 hours. The observation of mild erythema on untreated and irradiated areas suggests that some subjects may have been irradiated with doses near their individual MED.

Potential phototoxic reactions (PtRS)

The distribution of the PtRS is summarised by treatment at each time point, for each irradiation category, in Table 29.

Table 29: Distribution of phototoxic reaction scores

Phototoxic	UVA (N=35)						UVA+B (N=35)					
Reaction	0.17 h		24 h		48 h		0.17 h		24 h		48 h	
Scores	DDEA	Veh	DDEA	Veh	DDEA	Veh	DDEA	Veh	DDEA	Veh	DDEA	Veh
-1	-	-	-	-	-	-	-	-	7	-	10	-
-0.5	3	3	3	-	2	-	4	5	21	1	18	-
0	29	31	25	34	31	35	27	27	5	31	6	28
0.5	3	1	7	1	2	-	4	3	2	3	1	6
1	-	-	-	-	-	-	-	-	-	-	-	1

At all time points, the majority of subjects showed a PtRS of 0 or below with either active or vehicle treatment and for both types of UV irradiation (UVA and UVA+B) at all time points.

For UVA, peak PtRS values were seen 24-hour after irradiation; 7 of the 35 subjects scored 0.5 at the DDEA site.

For UVA+B, peak PtRS values were seen 48 hours after irradiation; 6 of the 35 subjects scored 0.5 at the vehicle site, one subject scored 0.5 at the DDEA site and one subject scored 1 at the vehicle site.

The distribution of the photoirritation intensities is summarised for each irradiation category by treatment in Table 30:

Table 30: Distribution of photoirritation intensity

Photoirritation	UVA (N=35)		UVA+B (N=35)	
Intensity	DDEA	Veh	DDEA	Veh
-0.5	-	-	2	-
0	24	33	27	23
0.5	11	2	6	11
1	-	-	-	1

The results are consistent with those seen for the PtRS scores. The most frequent photoirritation intensity score was 0. Roughly one third of subjects had a photoirritation score of >0 after UVA exposure with DDEA and after UVA+B exposure with vehicle.

- **Irritation potential evaluation**

Before dosing, there was no evidence of irritation at any application site for any subject. The distribution of the irritation scores at 0.25-0.5 hour after removal of the Finn Chambers is summarised for each irradiation category by treatment in Table 31.

Table 31: Distribution of irritation scores at 0.25-0.5 hour

	No Irradiation (N=35)			UVA (N=35)			UVA+B (N=35)		
Irritation Scores	DDEA	Veh	Blank	DDEA	Veh	Blank	DDEA	Veh	Blank
No reaction (0)	30	33	34	29	31	33	28	34	33
Slight reddening (0.5)	5	2	1	6	4	2	7	1	2

Slight reddening was seen more frequently with DDEA, less frequently with vehicle and rarely without treatment. These results are consistent with the reactions observed on non-irradiated areas at 0.17, 24, and 48 hours after irradiation and suggest the absence of any irritation potential for diclofenac DEA 2.32% gel in normal use. (Other local reactions, mainly mild erythema on plaster sites were observed in five subjects).

The overall conclusion from the study was that single applications of diclofenac DEA 2.32% and vehicle gel to the skin of healthy subjects followed by UV exposure (UVA and UVA+B) were well tolerated. The distribution of maximum erythema score (Table 64) shows that mild erythema was observed on blank untreated but irradiated (0.75 MED UVA+B) areas in 26 out of 35 subjects indicating that the UVA+B doses received on the back were higher than the local MED. The applicant considers a possible explanation of this overexposure is the known variation in MED according to body site (1966; 1979; 1984).

In terms of phototoxic potential, the majority of subjects showed a PtRS of 0 or lower, after either active or vehicle gel for both types of UV irradiation (UVA and UVA+B) at all time points. The applicant has commented that the clinical relevance of the few observed phototoxicity reactions is questionable in view of the higher than MED doses of UVA+B delivered on the back and there is little evidence of phototoxicity potential with diclofenac DEA 2.32% gel in normal use.

Regarding the irritation potential, few subjects showed slight reddening 22-24 hours after 24 hours occluded exposure to diclofenac DEA 2.32% gel or to vehicle.

Overall conclusions on clinical safety

Diclofenac gel is a well-established product and no new safety concerns have been identified, even with this product (diclofenac DEA 2.32% gel), which is twice the strength of the currently licensed Voltarol gel.

The steady-state pharmacokinetic study VOPO-PE-102 has confirmed that, under both non-occluded and semi-occluded conditions, there is negligible systemic absorption from the proposed 2.32% DDEA gel.

In addition, it can be concluded from the specific safety studies, VOPO-P-103 and VOPO-P-105, that diclofenac DEA 2.32% gel does not cause skin sensitisation, have clinically important cumulative irritation potential or induce photosensitisation.

Based on the above, together with the overall adverse event reporting/absence of any other safety concerns, there are considered to be no emergent safety concerns in relation to the proposed 2.32% DDEA gel.

IV.6 Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

These applications were received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force; a Risk Management Plan was approved for these applications. The reference product has been in use for many years and the safety profile of the diclofenac is well-established.

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted, from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflets (PILs) has been performed on the basis of a bridging report making reference to the PIL for the Voltarol 1.16% Emulgel product (P and GSL legal status). The bridging report is acceptable.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable.

The benefit-risk evaluation for DDEA 2.32% can be considered favourable, and the new formulation approvable for both over the counter (legal status P and GSL) Marketing Authorisations in the proposed indications.

The grant of Marketing Authorisations is recommended.

RECLASSIFICATION ANNEX

Annex 1

Prescription Only Medicine to Pharmacy Reclassification

Voltarol Extra Strength Emulgel P 2.32% Gel /Voltarol Extra Strength Emulgel P 2.32% Gel

Diclofenac diethylamine

PL 00030/0444

Pharmacy to General Sales List Reclassification

Voltarol 12 Hour Emulgel 2.32% Gel/Voltarol Extra Strength Emulgel 2.32% Gel

Diclofenac Diethylamine

PL 00030/0447

Novartis Consumer Health UK Limited, trading as Novartis Consumer Health

Approval date: 20 March 2013

TABLE OF CONTENTS FOR THE ANNEX

1 Introduction

Voltarol 12 Hour Emulgel P 2.32% Gel/Voltarol Extra Strength Emulgel P 2.32% Gel (PL 00030/0444) will hereafter be referred to as 'Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P'.

Voltarol 12 Hour Emulgel 2.32% Gel/Voltarol Extra Strength Emulgel 2.32% Gel (PL 00030/04447) will hereafter be referred to as 'Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel'.

Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P can be used for the local symptomatic relief of pain and inflammation in: trauma of the tendons, ligaments, muscles and joints e.g. due to sprains, strains and bruises; localised forms of soft tissue rheumatism and for the relief of pain of non-serious arthritic conditions in adults and children aged 14 years and over.

Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel can be used for the local symptomatic relief of pain and inflammation in: trauma of the tendons, ligaments, muscles and joints e.g. due to sprains, strains and bruises; localised forms of soft tissue rheumatism in adults and children aged 14 years and over but not for the relief of pain of non-serious arthritic conditions.

100 grams of each product contains 2.32 grams of the active ingredient diclofenac diethylamine.

The licence holder[1], Novartis Consumer Health UK Limited, trading as Novartis Consumer Health, applied to make available as a Pharmacy (P) medicine, Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P in pack size of 100g. Pharmacy medicines can be sold without prescription from Pharmacies by or under the supervision of a pharmacist.

In addition, the licence holder applied to make available as a General Sales List (GSL) Medicine, Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel in a pack size of 50g. General Sales List medicines can be sold without prescription from general retail outlets.

The Medicines and Healthcare Products Regulatory Agency (MHRA) considers Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P in a 100g pack size sufficiently safe to be sold from pharmacies and Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel in a 50g pack size sufficiently safe to be sold on general sale. This report outlines the evidence that the MHRA reviewed and which led to the decision to approve these applications.

2 Background

Diclofenac diethylamine reduces substances in the body that cause pain and swelling and therefore acts to relieve pain and reduce inflammation (it is a non-steroidal anti-inflammatory drug [NSAID]).

Pharmacy medicines can be sold or supplied without prescription only from pharmacies, by or under the supervision of a pharmacist. General Sales List medicines can be sold or supplied without prescription in other retail outlets other than pharmacies by someone who is not a pharmacist.

3 Proposed Terms of Reclassification

Novartis Consumer Health Ltd (the applicant) proposed the following conditions for P and GSL supply of the two products:

[1] A licence holder or marketing authorisation holder is the company with legal authorisation to make the medicine available to patients.

PL number	**PL 00030/0444**	**PL 00030/0447**
Legal status	P	GSL
Invented Name	- Voltarol 12 Hour Emulgel P - Voltarol Extra Strength Emulgel P	- Voltarol 12 Hour Emulgel - Voltarol Extra Strength Emulgel
INN and strength	Diclofenac diethylamine 2.32% w/w	Diclofenac diethylamine 2.32% w/w
Indications	For the local symptomatic relief of pain and inflammation in: - trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises - localised forms of soft tissue rheumatism For the relief of pain of non-serious arthritic conditions.	For the local symptomatic relief of pain and inflammation in: - trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises - localised forms of soft tissue rheumatism
Age	Adults and children aged 14 years and over.	Adults and children aged 14 years and over
Treatment period	Do not use for more than 14 days unless recommended by a doctor	For a maximum period of 7 days
Maximum strength	2.32%w/w	2.32%w/w
Maximum pack size	100g	50g
Maximum dose	4g	4g
Maximum daily dose	8g	8g

Products containing diclofenac diethylamine for topical use (applied to the skin have previously been authorised as P and GSL medicines under the following circumstances:

	P	**GSL**
Indications	For local symptomatic relief of pain and inflammation in trauma of the tendons, ligaments, muscles and joints and in localised forms of soft tissue rheumatism. For relief of pain of non-serious arthritic conditions.	For local symptomatic relief of pain and inflammation in trauma of the tendons, ligaments, muscles and joints e.g. due to sprains, strains and bruises and in localised forms of soft tissue rheumatism.
Age	For use in adults and children not less than 12 years	For use in adults and children aged 12 years or over
Treatment period	Do not use for more than 14 days unless recommended by a doctor	For a maximum period of 7 days
Maximum strength	1.16%w/w	1.16%w/w
Maximum pack size	100g	50g
Maximum dose	4g	4g
Maximum daily dose	16g	16g

The applicant justified this reclassification on the basis that although the products were twice as strong as P and GSL diclofenac gel products already authorised, the proposed indications, maximum daily dose of diclofenac, and duration of treatment were intended to be broadly in line with those of the existing P and GSL diclofenac gel products.

4. Criteria for P classification

To be reclassified from Prescription Only Medicine (POM) to P, a medicine must:

- Be unlikely to be a direct or indirect danger to human health when used without the supervision of a doctor, even if used correctly
- Be generally used correctly (i.e. not frequently or to a wide extent used incorrectly)
- Not contain substances or preparations of substances where the activity of the product or its side effects require further investigation
- Not normally be prescribed by a doctor for injection (parenteral administration)

These criteria are set out in the Human Medicines Regulations 2012, Regulation 62(3).

5 Criterion for General Sales List classification

Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), General Sales List is appropriate for medicines that can, with reasonable safety, be sold or supplied by someone other than a pharmacist.

The term “with reasonable safety” has been defined as: “where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

6 Assessment of suitability for pharmacy availability for Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P

The MHRA assessed the application for Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P against the criteria for classification as a Prescription Only Medicine, as stated in section 4.

6.1 Direct danger

Direct danger means that a danger may be present if the product causes adverse reactions that are important.

The applicant demonstrated that when used correctly the overall amount of diclofenac in the body and the highest concentration in the blood was comparable to that of the lower strength gel that was already classified as P and GSL.

The currently approved pack size of the 1.16% gel classified as P (100g) represents just over 6 day’s treatment at the maximum approved daily dosage. The proposed P pack size for Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P (100g) would provide 12.5 days’ treatment at the maximum approved daily dosage. Although this represents a twofold increase compared with the currently-approved product, it was considered that the pack size was reasonable, given the maximum duration of treatment,

Therefore, reclassification of this product to P was not considered to be a direct danger.

6.2 Indirect danger

Indirect danger to human health, even when the product is used correctly, could occur where treatment might mask or hide an underlying condition requiring medical attention and supervision.

The conditions for which the product is to be used, the population of people it is intended to be used by, and the proposed length of treatment are the same as for the 1.16% gel which is already approved as a P product. Therefore, reclassification of this product to P was not considered to be an

indirect danger.

6.3 Incorrect use – frequently and to a very wide extent

The 2.32% gel is to be used twice daily compared to the already authorised 1.16% gel which can be used up four times daily. Therefore, consideration was given the risk of a patient who is used to using the lower strength gel using the 2.32% gel four times daily by mistake.

It was decided that if this did happen, it was unlikely to present a danger to health as the amount of diclofenac that entered the blood stream was very much lower than that of diclofenac tablets in strengths and dosages that were available as P medicines.

In addition, it was considered that the risk of confusion could be minimised by clear information on the label and patient leaflet ensuring clear differentiation from the lower strength gel and clear information about the twice daily dosage.

It was concluded therefore that this product did not meet this POM criterion.

6.4 Activity and/or adverse reactions require further investigation

Given the well-characterised safety and efficacy profile of diclofenac gel, it was decided this POM criterion did not apply.

6.5 Is normally prescribed as an injection

This product is a gel to be applied to the skin. Therefore, this POM criterion did not apply.

7 Assessment of suitability for General Sales List availability for Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel

As with the P product outlined in section 6 above Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel was considered not to meet the POM criteria.

The MHRA assessed the application for Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel against the General Sales List criterion, as stated in section 5.

The product differed from the currently authorised GSL medicine in two respects – the strength (2.32% compared to 1.16%) and the number of days treatment in the pack (just over 6 days compared to just over 3 days). It was considered that as the pack size was not greater than the amount that could be used at maximum dose within the maximum duration of treatment, and with appropriate warnings on the label and leaflet the product could be sold without the supervision of a pharmacist without the risk of hazard to health.

It was therefore considered that this product met the GSL criterion.

8 Advice from the Commission on Human Medicines

As part of the application for new Marketing Authorisations for these two products, the Commission on Human Medicines advised in favour of the Pharmacy availability of Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P pack size 100g and the GSL availability of Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel pack size 50g.

9 Conclusion

The MHRA has taken the decision to approve the application to reclassify Voltarol 12 Hour Emulgel P/Voltarol Extra Strength Emulgel P pack size 100g from POM to P and to reclassify Voltarol 12 Hour Emulgel/Voltarol Extra Strength Emulgel pack size 50g to GSL under the terms set out in section 3 above.

Medicines and Healthcare products Regulatory Agency
February 2019

Voltarol 12 Hour Emulgel P 2.32% Gel/ Voltarol Extra Strength Emulgel P 2.32% Gel

Voltarol 12 Hour Emulgel 2.32% Gel/ Voltarol Extra Strength Emulgel 2.32% Gel

(Diclofenac diethylamine)

PL 00030/0444 and 0447

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

Date submitted	Application type	Scope	Outcome