PRODUCT MONOGRAPH

VOLTAREN EMULGEL

Diclofenac diethylamine Gel, 11.6 mg/g (1.16% w/w)

VOLTAREN EMULGEL Back & Muscle Pain

Diclofenac diethylamine Gel, 11.6 mg/g (1.16% w/w)

VOLTAREN EMULGEL Joint Pain Extra Strength

Diclofenac diethylamine Gel, 23.2 mg/g (2.32% w/w)

VOLTAREN EMULGEL Extra Strength

Diclofenac diethylamine Gel, 23.2 mg/g (2.32% w/w)

Non-Steroidal Anti-inflammatory Drug (NSAID)
Analgesic agent for topical use

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VOLTAREN EMULGEL

Diclofenac diethylamine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Gel / 11.6 mg/g (1.16% w/w)	Propylene glycol. *For a complete listing see Dosage Forms, Composition and Packaging section.*
Topical	Gel/ 23.2 mg/g (2.32% w/w)	Butylhydroxytoluene, propylene glycol. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

VOLTAREN EMULGEL 1.16% and VOLTAREN EMULGEL Back & Muscle Pain 1.16%

Adults and adolescents aged 16 years and over:

VOLTAREN EMULGEL and VOLTAREN EMULGEL Back & Muscle Pain (diclofenac diethylamine gel) are indicated for:

- Relief of pain associated with recent (acute), localized muscle or joint injuries such as sprains, strains or sports injuries (*e.g*. ankle sprain, shoulder strain or back muscle pain). This is typically as an adjunct to other measures, such as rest, for the relief of discomfort associated with such injuries.

Geriatrics (> 65 years of age):
The usual adult dosage may be used.

Paediatrics (< 16 years of age):
Not for use in children under 16 years of age.

VOLTAREN EMULGEL Extra Strength 2.32% and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%

Adults between 18 to 65 years:

VOLTAREN EMULGEL Extra Strength 2.32% and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% (diclofenac diethylamine gel) are indicated for:

- Relief of pain associated with recent (acute), localized, minor muscle or joint injuries such as sprains, strains or sports injuries (*e.g*. ankle sprain, shoulder strain or back muscle pain). This is typically as an adjunct to other measures, such as rest, for the relief of discomfort associated with such injuries.

Geriatrics (> 65 years of age):
The safety and efficacy of VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% in adults over 65 have not been demonstrated and established.

Paediatrics (< 18 years of age):
The safety and efficacy of VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% in children under 18 have not been demonstrated and established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory agents.
- Concomitant use of other products containing diclofenac.
- Concomitant use of oral non-steroidal anti-inflammatory drugs (NSAIDs).
- During the last trimester of pregnancy

WARNINGS AND PRECAUTIONS

General
Diclofenac diethylamine gel is for topical use only and should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Discontinue the treatment if a skin rash develops after applying the product.

VOLTAREN EMULGEL can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.
Systemic availability of diclofenac diethylamine through percutaneous absorption is low compared with plasma levels obtained following ingestion of oral forms of diclofenac. Nevertheless, the possibility of systemic side effects cannot be completely excluded. Chances of this may be increased where Diclofenac diethylamine gel is applied to a relatively large area of skin and/or over an extended period of time (*e.g.,* especially if this goes beyond the maximum duration recommended for use).

Some possibility of gastro-intestinal bleeding in patients with a significant history of peptic ulceration has been reported in isolated cases in users of diclofenac diethylamine gel. Diclofenac diethylamine gel should therefore be used with caution by patients under medication for active peptic ulcers in the stomach or duodenum (*e.g*., proton pump inhibitors or histamine H_2 receptor antagonists). If the patient is uncertain, they should be advised to consult their doctor or pharmacist.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of bronchial asthma.

Asthma has been rarely reported in patients using topical NSAID preparations.

Local irritation, erythema, pruritus or dermatitis may occasionally occur with topical diclofenac diethylamine. Skin photosensitivity, desquamation, discoloration and bullous or vesicular eruptions have been reported in isolated cases. Patients should be warned against excessive exposure to sunlight in order to reduce the incidence of photosensitivity.

The following additional side effects have been observed with **oral** forms of diclofenac sodium.

Cardiovascular
Isolated cases: palpitation, chest pain, hypertension.

Gastrointestinal
Occasional: Epigastric pain, other gastro-intestinal disorders (*e.g.* nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).
Rare: Gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea.
In isolated cases: Lower gut disorders (*e.g.* non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Haematologic
In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Hepatic/Biliary/Pancreatic
Occasional: Elevation of serum aminotransferase enzymes (ALT, AST).
Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Immune
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of rare cases of anaphylactic/anaphylactoid systemic reactions including hypotension, and respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea. (See also "Skin").

Neurologic
Occasional: Headache, dizziness, or vertigo.
Rare: Drowsiness, tiredness.
In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing. Tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

Renal
In isolated cases: Acute renal failure, urinary abnormalities (*e.g*. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Sexual Function/Reproduction
Isolated cases: Impotence (association with diclofenac is doubtful).

Skin
Occasional: Rashes or skin eruptions.
Rare: Urticaria.
In isolated cases: Eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), photosensitivity reactions, erythroderma (exfoliative dermatitis), loss of hair, purpura including allergic purpura.

Special Populations

Pregnant Women:
Since no experience has been acquired with diclofenac diethylamine gel in pregnancy, it is not recommended for use in these circumstances.

It is contraindicated during the last trimester of pregnancy, owing to the possibility of uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus.

Animal data has shown an increased incidence of dystonia and delayed parturition when drug administration is continued into late pregnancy.

Nursing Women:
Since no experience has been acquired with diclofenac diethylamine gel in lactation, it is not recommended for use in these circumstances.

Following oral doses of 50 mg diclofenac administered every 8 hours, diclofenac passes into breast milk in quantities so small that no undesirable effects on the infant are to be expected.

VOLTAREN EMULGEL 1.16% and VOLTAREN EMULGEL Back & Muscle Pain 1.16%:

Geriatrics (> 65 years of age): No specific hazards are associated with geriatric use of diclofenac diethylamine gel.

Paediatrics (< 16 years of age): Not for use in children under 16 years of age.

VOLTAREN EMULGEL and VOLTAREN EMULGEL Back & Muscle Pain contain propylene glycol and benzyl benzoate, which may cause mild, localised skin irritation in some people.

VOLTAREN EMULGEL Extra Strength 2.32% and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%:

Geriatrics (> 65 years of age): The safety and efficacy of VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% in adults over 65 have not been demonstrated and established.

Paediatrics (< 18 years of age): The safety and efficacy of VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% in children under 18 have not been demonstrated and established.

VOLTAREN EMULGEL Extra Strength and VOLTAREN EMULGEL Joint Pain Extra Strength contain propylene glycol, which may cause mild, localised skin irritation in some people. It also contains butylhydroxytoluene, which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

Monitoring and Laboratory Tests
No monitoring parameters or laboratory tests are required to monitor response to therapy or possible adverse reactions.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse event incidence in the clinical studies was very low. The benign safety profile documented in the clinical studies is confirmed in the post-marketing experience in millions of patients worldwide. The adverse events occurring in studies were usually either moderate or mild.

Serious adverse events observed in all the studies, conducted over more than a decade, were very few in number and all unrelated to study treatment.

In post-marketing surveillance, approximately 90% of case reports are non-serious. Cutaneous adverse events, occurring mostly at the application site, constitute the most common symptoms reported. Serious adverse events associated with oral forms of diclofenac, including gastrointestinal bleeding, have been reported occasionally. No causal relationship has been established between diclofenac diethylamine gel and these systemic adverse events.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

VOLTAREN EMULGEL 1.16% Gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel:

The clinical data set includes data obtained in approximately 4926 patients with either the target indication of soft-tissue injuries (*e.g.* sprains, strains, bruises), osteoarthritis or soft-tissue rheumatism, 2728 of whom received VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), 1267 of whom received an active comparator, and 931 of whom received placebo. Patients were treated from 3-28 days as befitted the nature of the conditions under study.

Data from the safety population with the target indication investigated, who received short term exposure to VOLTAREN EMULGEL 1.16% gel in controlled trials and uncontrolled trials, confirm that a dose of 2-4 g of VOLTAREN EMULGEL 1.16% gel applied topically 3-4 times a day is safe and that the systemic adverse event profile observed for systemic NSAIDs is not seen with the topical formulation.

No subgroup analyses were performed. Long-term safety data from patients was not obtained in these studies as this is not relevant to a product intended for only short-term use up to 1 week.
The safety of VOLTAREN EMULGEL 1.16% gel was demonstrated in the safety population in clinical trials, which all showed that the incidence and type of rare or serious events resembles those of active controls or placebo.

The adverse events (AEs) whether or not drug related reported in 33 clinical trials are summarized in Table 1 (WHO-ART coding).

Table 1 - Adverse events (AEs) Reported in Clinical Trials (WHO-ART coding) with a Frequency of ≥1%			
	VOLTAREN EMULGEL1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) n= 2258 (100)	**<placebo> n= 633 (100)**	**Reference* n= 1112 (100)**
Local skin AEs	76 (3.4)	35 (5.5)	29 (2.6)
*Topical reference drugs (number of patients): felbinac (195), piroxicam (306), etofenamate (140), Mobilat containing adrenocortical extract, mucopolysaccharide, salicylic acid (113), Movelat containing mucopolysaccharide polysulphate, salicylic acid (78), ketoprofen (15), naproxen (15), benzydamine HCl (52), indomethacin (55), Dolobene containing dimethylsulfoxid heparin (39), monosalicylic acid (15-20). * Oral reference drug: ibuprofen (155)			

Similar percentages of local skin reactions including mostly itching, burning, erythema, local allergy and blistering were reported after both VOLTAREN EMULGEL 1.16% gel (3.4%) and placebo (5.5%). Most of the local AEs were mild to moderate. There were no reports of photosensitivity, although one case report referred to exposure to the sun. Approximately 0.3% of patients were withdrawn due to local skin AEs after applying VOLTAREN EMULGEL 1.16% gel or placebo.

In conclusion, the absolute numbers of reported adverse events were relatively small and there are no clinically significant differences in the incidence of adverse events in the VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), placebo and reference drug treatment groups. Most of the AEs are local, mild to moderate and reversible.

VOLTAREN EMULGEL Extra Strength 2.32% Gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel:

The key studies supporting the safety profile of VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) include two randomised, double-blind, placebo controlled trials. This dataset included 513 patients with acute lateral ankle sprain, 173 placebo, 91 VOLTAREN EMULGEL Extra Strength 2.32% gel once daily (o.d.), 169 twice per day (b.i.d.), and 80 three times per day (t.i.d.).

In the two double-blind placebo-controlled studies, topical exposure to VOLTAREN EMULGEL Extra Strength 2.32% gel was for up to 7 days. Skin and application site AEs are shown in Table 2.

Table 2 – Skin and application site AEs in double-blind, placebo-controlled studies

		VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel)		
	Placebo	o.d.	b.i.d.	t.i.d.
No. (%) of patients	N=173	N=91	N=169	N=80
General disorders & administration site conditions	2 (1.2)	0	0	1 (1.3)
Application site pain	1 (0.6)	0	0	0
Application site pruritus	0	0	0	1 (1.3)
Skin & subcutaneous tissue disorders	4 (2.3)	1 (1.1)	1 (0.6)	0
Dermatitis	1 (0.6)	0	0	0
Erythema	2 (1.2)	1 (1.1)	1 (0.6)	0
Pruritus	1 (0.6)	0	0	0
Skin exfoliation	1 (0.6)	0	0	0

The highest incidence of AEs at the application site occurred in the group using placebo gel. In the VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) groups, only two events were suspected of being drug related, severe erythema with b.i.d. administration and mild application site pruritus with t.i.d. administration. By contrast, in the placebo group, 4 AEs in the skin and subcutaneous tissue disorders system organ class (SOC) (skin exfoliation, 2 erythema, pruritus, all of mild severity) and 1 AE in the general disorders and administration site conditions SOC (moderate application site pain) were suspected of being treatment-related.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

VOLTAREN EMULGEL 1.16% Gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel

Digestive: Dyspepsia was observed in 0.58, 0.32, and 0.18% of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), Placebo, and Reference groups, respectively.

Body as a whole: Allergic events were observed in 0.04, 0.16, and 0.09% of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), Placebo, and Reference groups, respectively.

CNS: CNS events were observed in 0.09, 0.32, and 0.45% of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), Placebo, and Reference groups, respectively.

VOLTAREN EMULGEL Extra Strength 2.32% Gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel

Infections and infestations: rash pustular (very rare, <1/10,000)

Immune system disorders: hypersensitivity (including urticaria), angioedema (very rare, <1/10,000)

Respiratory, thoracic and mediastinal disorders: asthma (very rare, <1/10,000)

Skin and subcutaneous tissue disorders: dermatitis bullous (rare, ≥1/10,000 to <1/1,000), photosensitivity reaction (very rare, <1/10,000)

Abnormal Hematologic and Clinical Chemistry Findings

Clinical laboratory evaluations were not routinely performed in the studies undertaken for the indication of muscle and joint soft tissue injuries. The treatments were given for short periods only.

Post-Market Adverse Drug Reactions

Tabulated list of adverse reactions

The table includes adverse reactions from the clinical trials as well as from the post-marketing experience where causal relationship has been established.

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very rare: Rash pustular

Immune system disorders

Very Rare: Hypersensitivity (including urticaria), angioedema

Respiratory, thoracic and mediastinal disorders

Very Rare: Asthma

Skin and Subcutaneous tissue disorders

Common: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus

Rare: Dermatitis bullous

Very rare: Photosensitivity reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Canada Vigilance Program.

DRUG INTERACTIONS

Overview

No drug and substance interaction studies have been performed as part of the clinical development of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) and VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel).

From the pharmacokinetic point of view, diclofenac is extensively (>99.7%) protein bound, mainly to albumin (99.4%). Binding to serum albumin is characterised by 2 classes of binding sites: the high affinity sites are likely to be shared with benzodiazepines and the low affinity site with warfarin. Diclofenac does not modify other strongly protein bound drugs but may, *in vitro*, be displaced by salicylic acid (Davies and Anderson, 1997).

There is a considerable body of literature regarding interactions of oral NSAIDs, and diclofenac in particular, with other medicinal products. No interactions with other drugs are to be expected due to very low plasma levels observed after topical application of VOLTAREN EMULGEL.

Drug-Drug Interactions

No drug-drug interactions were noted in the clinical studies presented. Isolated interaction cases have been reported for topical VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) from the marketplace.

Only 22 cases of possible drug interactions with VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) over 200 million patients exposed have been made to the company world-wide safety database since first marketing:

- Twelve cases with oral anticoagulant therapy (3 with acenocoumarol, 3 with warfarin, 2 with phenprocoumon, 2 with fluindione, and 2 unknown).
- Four cases with blood pressure increase (with anti-hypertensive product of different classes).
- Three case with blood glucose increase (in insulin-dependent and in non-insulin dependent diabetes mellitus).
- One case of a psychiatric disorder (with concomitant ofloxacin use).
- One case of a rash and vascular bleeding associated with acetylsalicylic acid. The patient was also taking heparin and a topical herbal product containing camphor, methanol and ethanol.
- One case of gastric ulcer associated with concomitant acetylsalicylic acid use.

The customary drug-drug interactions between oral NSAIDs and anticoagulants, oral antidiabetic agents and certain other classes are usually based on the high protein-binding nature of the NSAID. With significantly lower amounts of active substance in circulation following topical application compared with after oral administration, such interactions may be predicted to be very unlikely with use of VOLTAREN EMULGEL.

No drug-drug interactions information was addressed for topical VOLTAREN EMULGEL Extra Strength 2.32% gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

VOLTAREN EMULGEL 1.16% and VOLTAREN EMULGEL Back & Muscle Pain 1.16%
Adults and adolescents 16 years and older:
VOLTAREN EMULGEL 1.16% gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel should be applied over the affected area 3 or 4 times daily. It should be rubbed gently into the skin.

The amount needed depends on the size of the painful area: 2 g to 4 g (1 g equals a strip approx. 2 cm long) of gel is sufficient to treat an area of about 400-800 cm^2. After application, the hands should be washed, unless they are the site being treated.

The duration of treatment depends on the natural course of healing, rest and also on clinical response. The gel should not be used for more than 7 days for muscle and joint injuries unless recommended by a doctor. Consumers should consult their doctor if the condition does not improve within 7 days, or if it gets worse.

VOLTAREN EMULGEL Extra Strength 2.32% and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%

Adults between 18 to 65 years:

- VOLTAREN EMULGEL Extra Strength 2.32% gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel should be applied over the affected area twice daily; 2 g in the morning and 2 g in the evening. The total dose should not exceed 4 g per day overall affected area. Applying a greater quantity of gel will not result in an increase of pain relief.

- The amount of VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% (2 g for each application) should be measured using the dosing card supplied in the drug product carton. For each application the gel should be squeezed from the tube and measured up to the 2 g line on the dosing card. Clean and dry the dosing card after each use. After application, the hands should be washed unless they are the site being treated.

The duration of treatment will depend on the response of the subject to the product, natural course of healing, time of the ankle injury, rest. The gel should not be used for more than 7 days for muscle and joint injuries unless recommended by a doctor. Consumers should consult their doctor if the condition does not improve within 7 days, or if it gets worse.

Missed Dose
If a dose of VOLTAREN EMULGEL is missed, it should be applied when the consumer remembers and then again at the next scheduled time. A double quantity should not be applied.

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

VOLTAREN EMULGEL 1.16% and VOLTAREN EMULGEL Back & Muscle Pain 1.16%

The low systemic absorption of topical diclofenac renders overdose very unlikely.
However undesirable effects, similar to those observed following an overdose of VOLTAREN tablets, can be expected if VOLTAREN EMULGEL 1.16% gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel is inadvertently ingested (1 unit of 100 g contains the equivalent of 1 g diclofenac sodium) and if VOLTAREN EMULGEL Extra Strength 2.32% gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel is inadvertently ingested (1 tube of 50 g contains the equivalent of 1 g diclofenac sodium), respectively.

In the event of accidental ingestion, resulting in significant systemic side effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory drugs should be used. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Management of overdosage with NSAIDs essentially consists of supportive and symptomatic measures. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

Twenty times the oral dose of 200 mg of diclofenac in overdose produced only somnolence with no signs of toxicity (AHFS Drug Information 1999). This would represent about 65 tubes of VOLTAREN EMULGEL. In case of accidental ingestion of one tube of product, the amount of diclofenac ingested would be less than one tablet of diclofenac 50 mg (which is the most common oral unit dose).

There are five cases of overdose in the paediatric population with VOLTAREN EMULGEL 1.16% gel listed on the company Safety Database. A 2-year-old girl swallowed a “soup spoonful”. Assuming that a spoon contains 15 ml (or grams) and that 100% of the dose was absorbed, the amount of available diclofenac would have been approximately 150 mg. No details of the other overdose are available. A 1-year-old girl and a 3-year-old boy were also reported to have swallowed unknown quantities of VOLTAREN EMULGEL 1.16% gel with no apparent adverse events. There are 2 cases of accidental topical exposure to VOLTAREN EMULGEL 1.16% gel in children, one to a 2-year-old boy and another to a 2-year-old child (gender not reported). No adverse events were reported in either case.

In the adult population, there is one case of an adult swallowing an unknown quantity of VOLTAREN in the database. No adverse events were reported. One report of a patient applying 1.5 tubes of

VOLTAREN EMULGEL 1.16% gel per day on his legs resulted in skin changes and "thin skin" (skin atrophy). Additionally, there is a consumer report of a patient with a history of cerebrovascular accident with left paralysis, hypertension, diabetes and epilepsy that used half a tube at the site of application in a single dose and experienced an increase in pain at the site. The database also includes a case report stated as serious where the patient became 'intoxicated', but there is no additional information.

The database contains a report of accidental exposure to haemorrhoids, resulting in a burning sensation. Finally, there were 3 consumer reports of accidental exposure in the eyes resulting in eye redness, eye discharge, eye irritation, and a feeling of increased intraocular pressure.

VOLTAREN EMULGEL Extra Strength 2.32% and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%

No over dosage information was assessed for VOLTAREN EMULGEL Extra Strength 2.32% or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Diclofenac is a well characterized, potent nonsteroidal anti-inflammatory drug (NSAID) with clinically proven anti-inflammatory, analgesic and antipyretic properties (Davies & Anderson 1997). NSAIDs, including diclofenac, reduce pain principally by inhibiting formation of prostaglandins, leukotrienes and free oxygen radicals.

All non-salicylate NSAIDs reversibly block cyclooxygenase activity, which is responsible for converting arachidonic acid to prostaglandins. Diclofenac is a potent, non-selective inhibitor of COX-1 and COX-2 (preferentially COX-2), which may underlie both its therapeutic efficacy and potential side effects (Giuliano & Warner 1999). In addition, diclofenac, when compared to NSAIDs such as ibuprofen, also blocks the lipoxygenase pathway of the arachidonic acid cascade, thereby inhibiting the formation of leukotriene B4 (LTB4), which is a known pain mediator and has been shown to stimulate pain receptors in the peripheral nerves. The inhibition of lipoxygenase also prevents the pro-inflammatory and gastrointestinal damaging effects of leukotrienes (Bertolini, Ottani & Sandrini 2001). Prostaglandins, along with thromboxanes and LTB4, are responsible for several inflammatory effects. The lipoxygenase inhibition produced by diclofenac may therefore play a significant role in its efficacy as an analgesic and anti-inflammatory agent (Amadio, Cummings & Amadio, 1993; Todd & Sorkin 1988).

Pharmacodynamics

Pharmacotherapeutic group: Topical products for joint and muscular pain. Anti- inflammatory preparations, non-steroids for topical use, ATC code: M02A A15.

As with other NSAIDs, the ability of diclofenac to inhibit prostaglandin synthesis is instrumental in the anti-inflammatory response. Data from *in vitro* studies show that most topical NSAIDs are able to

inhibit prostaglandin synthesis to a significant degree. In this respect, diclofenac has a high intrinsic activity, as demonstrated *in vitro* in human rheumatoid synovial microsomes (Dreiser 1994).

The pharmacodynamic properties of diclofenac have been demonstrated for each of the sodium, potassium and diethylamine salts administered either orally or topically in standard animal models of acute and chronic inflammation (Hiramatsu *et al* 1990, Kyuki *et al* 1983).

It has also been reported that topically applied diclofenac diethylamine 1.16% actively inhibited methyl nicotinate induced skin inflammation, which is known to involve prostaglandins and free arachidonic acid. Topical diclofenac was shown to exhibit a prolonged potent anti-inflammatory effect, even 48 hours after application (Duteil *et al* 1990).

The anti-inflammatory properties of VOLTAREN EMULGEL were demonstrated in two placebo-controlled, double-blind, randomized trials, one in healthy volunteers using the urate crystal induced inflammation model (NGB5) and the other in patients with chronic synovitis of the knee (NGB 8855). VOLTAREN EMULGEL proved to be superior to placebo in significantly reducing the diameter of erythema at 24 hours in study NGB 5 ($p<0.05$), and significantly reducing the thermal index in study NGB 8855 ($p<0.04$). Due to the small size of the studies, only objective parameters of erythema and thermal index could be evidenced.

Pharmacokinetics

Absorption: The quantity of diclofenac absorbed systemically from VOLTAREN EMULGEL is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. Absorption amounts to about 6% of the applied dose of diclofenac after topical application of 2.5 g VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) on 500 cm² skin, determined by the total renal elimination, compared with VOLTAREN tablets. A 10-hour occlusion leads to a 3-fold increase in the amount of diclofenac absorbed.

After topical application to approximately 400 cm^2 of skin, the extent of system exposure as determined by plasma concentration of VOLTAREN EMULGEL Extra Strength 2.32% gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel (2 applications/day) was equivalent to VOLTAREN EMULGEL 1.16% gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel (4 applications/day). The relative bioavailability of diclofenac (AUC ratio) for VOLTAREN EMULGEL Extra Strength 2.32% gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel *versus* tablet was 4.5% on day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapour permeable bandage.

Distribution: Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after topical administration of VOLTAREN EMULGEL to hand and knee joints. Maximum plasma concentrations are approximately 100 times lower than after oral administration of the same quantity of diclofenac. 99.7% of diclofenac is bound to serum proteins, mainly albumin (99.4%).

Metabolism: Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

Excretion: The total systemic clearance of diclofenac from plasma is 263 ± 56 ml/min. The terminal plasma half-life is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

Special Populations and Conditions

There are no gender differences in the pharmacokinetics of diclofenac. No safety or efficacy concerns relating to ethnicity have been identified from the marketplace. Davies and Anderson (1997) discuss the influence of age on diclofenac pharmacokinetics with relevance in the very young and elderly. Also, changes to the skin in the elderly will affect absorption in some patients. However, as plasma levels will be very low after topical application these factors are not a clinical concern. For similar reasons, any effect of hepatic or renal impairment on the pharmacokinetics of diclofenac is unlikely to be clinically significant. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

STORAGE AND STABILITY

VOLTAREN EMULGEL should be stored between 15 and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Aluminium (laminated) tube: There are no special handling instructions for VOLTAREN EMULGEL.

Dispenser: This is a pressurised container, it should be protected from direct sunlight and must not be pierced or burned even when empty.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VOLTAREN EMULGEL is a white to practically white, soft, homogenous, cream-like oil-in-water topical emulsion available in two strengths (diclofenac diethylamine 1.16% w/w and 2.32% w/w) and packaged in either:

VOLTAREN EMULGEL 1.16% Gel and VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel:

- An aluminium tube closed with a polypropylene screw cap, incorporating a point to pierce the aluminium sealing membrane before first use; or
- An aluminium laminated tube fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use; or

- A dispenser with a pressurized aluminium container (using nitrogen, which does not come in contact with the product) containing a multilayer pouch (low density polyethylene layer in contact with the product) with a high density polyethylene/titanium oxide valve and polyoxymethylene actuator and a plastic protective cap.

VOLTAREN EMULGEL 1.16% gel and VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel contain the following nonmedicinal ingredients: carbomer, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, perfume, propylene glycol, purified water.

Aluminium (laminated) tubes pack sizes: 30, 50, 100, and 150 g tubes.

Dispenser pack sizes: 75 and 100 mL dispensers (not marketed).

VOLTAREN EMULGEL Extra Strength 2.32% Gel and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel:

- An aluminium laminated tube fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.

Pack sizes: 30 and 100 g tubes in cartons with a dosing card.

VOLTAREN EMULGEL Extra Strength 2.32% gel and VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel contain the following nonmedicinal ingredients: butylhydroxytoluene, carbomers, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, oleyl alcohol, perfume, propylene glycol, purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

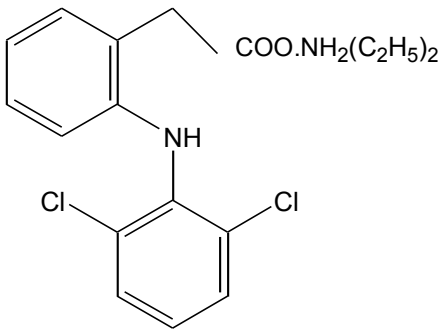
Drug Substance

Proper name: Diclofenac diethylamine

Chemical name: Diethylammonium{o-[(2,6-dichlorophenyl)-amino]-phenyl} acetate

Molecular formula and molecular mass: $C_{18}H_{22}Cl_2N_2O_2$, 369.3

Structural formula:



Physicochemical properties: Diclofenac diethylamine is a white to light beige crystalline powder. No polymorphic forms of diclofenac diethylamine have been observed. The solubility of diclofenac diethylamine in water is 15.8 g/L at a pH of 7.8 and a temperature of 18°C, 17.4 g/L at a pH of 7.6 and a temperature of 25°C, and 22.8 g/L at a pH of 7.6 and a temperature of 37°C. Diclofenac diethylamine has a pH range of 6.5-8.3 in a 1% solution in 10% ethanol. Diclofenac diethylamine has a pK_a value of 3.9 ± 0.2 in water at 25°C.

CLINICAL TRIALS

For the indication "pain in muscles and joints injuries", the studies NF 113 and D458 L7/D141 with VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) and study VOPO-P-307 with VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) are considered pivotal. Study demographics and trial design for these studies are presented in Table 5.

Study demographics and trial design

Table 5 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Pain in Muscle and Joint Injuries					
VOLTAREN EMULGEL 1.16% Gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel)					
NF113	Multicentre, parallel-group, randomised, double-blind, placebo-controlled Subjects had soft tissue trauma resulting in a minor sprain, dislocation, tear of muscle or tendon, or pulled muscle/ contusion	Gel was applied topically 4 times daily at a mean dose of 2.2 g (actual dose was determined by physician)	n=254	VOLTAREN: 34.1 (7-88) Placebo: 35.5 (12-84)	Men VOLTAREN: 72 (57%) Placebo: 83 (65%) Women VOLTAREN: 54 (43%) Placebo: 45 (35%)
D458 L7/D141	Single-centre parallel-group, randomised double-blind, placebo-controlled Subjects were soldiers with acutely sprained ankles	VOLTAREN EMULGEL or placebo was applied 3 times daily for up to 14 days	n= 80	VOLTAREN: 22.4 (19-29) Placebo: 22.2 (19-31)	All 80 subjects were male

Table 5 - Summary of patient demographics for clinical trials					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
VOLTAREN EMULGEL Extra Strength 2.32% Gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel)					
VOPO-P-307	Randomized, double-blind, 3-treatment arm, multi-centre, placebo-controlled, parallel group Subjects with acute ankle sprain	VOLTAREN EMULGEL Extra Strength 2.32% gel applied 3 times daily (t.i.d.) or twice daily (b.i.d.) for 7 days	n=162 ITT subjects* n=80 EMULGEL 2.32% gel b.i.d. n=82 placebo * all subjects who applied gel at least once n=139 PP subjects** n=71 EMULGEL 2.32% gel b.i.d. n=68 placebo ** applied gel twice a day for 7 days (included 6 subjects who did not apply the adequate quantity of gel)	VOLTAREN EMULGEL Extra Strength 2.32% gel t.i.d*.: 32.2 (18-81) b.i.d.: 30.9 (18-65) Placebo: 34.0 (17-66) * the t.i.d. subjects are not part of the efficacy analysis	Men VOLTAREN EMULGEL Extra Strength 2.32% gel t.i.d*.: 49 (61.3%) b.i.d.: 49 (61.3%) Placebo: 54 (65.9%) Women VOLTAREN EMULGEL Extra Strength 2.32% gel t.i.d*.: 31 (38.8%) b.i.d.: 31 (38.8%) Placebo: 28 (34.1%) * the t.i.d. subjects are not part of the efficacy analysis

Study results - Soft tissue trauma

VOLTAREN EMULGEL 1.16% Gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel

Study NF113

There was a significant difference in favour of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) for spontaneous pain on deliberate movement on day 7 with 44% (51) of the active treatment group having no pain, 43% (50) having only moderate pain and 13% (15) marked pain compared with 35% (41), 38% (44) and 24% (28) of the subjects in the placebo group respectively. Three (3) subjects (3%) of the placebo group had very marked pain at 7 days whereas no active treatment subject had marked pain (p=0.05 for day 7 evaluation) and similar results were found for pain on pressing, also on day 7 (p=0.02). The need for rescue medication was lower in the active treatment group, and of significantly shorter duration *i.e.,* those in the active treatment group stopped using rescue medication before those receiving placebo (p=0.02). The regression of haematoma was also faster in the active treatment group (p=0.04). These data concur with the investigator's general assessments rating the results on day 7 as 'excellent' in 64% of patients receiving active treatment and 52% in those receiving placebo.

Study D458 L7/D141

There was a significant difference for articular pain at rest and on movement (100 mm VAS) and joint swelling at days 3 and 4 in the VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) treated group compared to the placebo group ($p<0.001$). (The mean pain at rest (mornings) fell from 61.15 on the VAS to 24.13 by day 4 for the active treatment group compared to a fall from 53.33 at baseline to 29.71 on day 4 for the placebo treated group- $p<0.001$.) Patients withdrew as they got better and so by the 7th day, only those who had not yet healed still remained in the study. At this point there was no difference between active and placebo for joint swelling. Similar numbers of patients in each group required rescue analgesia. 60% of actively treated patients were able to stop using the gel before the 14th day as they were free of symptoms compared with 38% of the placebo group. Interruptions for inadequate efficacy occurred in the placebo group only (2 subjects). During the first 10 days of treatment, nearly twice as many active treatment patients became free of symptoms than the placebo treated group (n=17 and n=8 respectively, p value not given in final study report). This gives an indication of the effect of treatment on the natural time course for pain relief.

VOLTAREN EMULGEL Extra Strength 2.32% Gel or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel

Study VOPO-P-307 (ankle sprain)

In Study VOPO-P-307, 139 patients suffering from acute sprain of lateral ankle (mild to moderate) were randomized; 71 received VOLTAREN EMULGEL Extra Strength 2.32% (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32%) b.i.d. treatment and 68 the placebo. The dose regimen consisted of 2 g of gel (active or placebo) two times per day for 7 days. Six (6) subjects (2 subjects VOLTAREN EMULGEL Extra Strength and 4 Placebo subjects) did not apply the adequate quantity of gel but were included in the PP study. The primary efficacy variable was the Pain on Movement (POM) at Day 5. Pain on movement on a VAS scale was registered by the patient lying down while the investigator holding the injured ankle leg at 45° performed a gentle supination of the injured ankle to reach an angle of approx. 30°. All subjects included in the study had at baseline POM ≥50 mm on the 100 mm VAS scale. The secondary variables were POM at Day 3 and 8, and ankle pain at rest, tenderness, swelling and ankle joint function at Day 3, Day 5 and Day 8. Global assessment of benefit at Day 3, Day 5, and Day 8) and Global assessment of treatment benefit (Day 5 and Day 8) were also assessed.

At baseline, the mean POM values were similar for both groups (range: 75.4 to 76.5 mm); Pain on Movement (POM), 4 days after starting treatment (i.e. at Day 5), decreased to 26.5 mm in patients using VOLTAREN EMULGEL Extra Strength 2.32% gel and to 51.3 mm in the placebo group; in the VOLTAREN EMULGEL Extra Strength group, the decrease in mean POM from baseline corresponded to almost 50 mm on a 100 mm VAS, which was approximately twice the 25.2 mm decrease observed in the placebo group. VOLTAREN EMULGEL Extra Strength 2.32% gel was highly significantly superior in efficacy compared to placebo ($p<0.0001$).

In a post-hoc analysis, the overall population of subjects with Grade I or II ankle sprain (mild to moderate) were categorized as above or below a baseline POM score of 80 mm on VAS (28 subjects VOLTAREN EMULGEL Extra Strength group with POM mean baseline of 88.4 mm and 24 Placebo

subjects with POM mean baseline of 87.8 mm) or below a baseline POM score of 80 mm on a VAS (43 subjects VOLTAREN EMULGEL Extra Strength group with POM mean baseline of 67.1 mm and 44 Placebo subjects with POM mean of 70.2 mm). Efficacy was examined in each subgroup. Four days after starting treatment (i.e. Day 5), VOLTAREN EMULGEL Extra Strength 2.32% gel was statistically significantly better than placebo in reducing POM both in patients with baseline ≥80 mm (VOLTAREN EMULGEL Extra Strength 2.32% gel 56.5 mm; placebo 27.6 mm; $p<0.0001$), as well as patients with baseline pain <80 mm (VOLTAREN EMULGEL Extra Strength 2.32% gel 44.1 mm; placebo 23.6 mm; $p<0.0001$) at the primary efficacy endpoint.

Pain at rest, was also assessed; at baseline, the mean Pain at rest values were similar for both groups (range: 37.0 to 38.6 mm); 4 days after the treatment (i.e. at Day 5), the mean change from baseline was 28.3 mm for VOLTAREN EMULGEL Extra Strength 2.32% gel as compared to 21.8 mm for placebo.

Further evidence of the efficacy of VOLTAREN EMULGEL Extra Strength 2.32% gel is demonstrated by the median time to a 50% reduction in POM (i.e. reduction to 37.5 mm on VAS) from which was 4 days in the VOLTAREN EMULGEL Extra Strength 2.32% gel group, *versus* 8 days in the placebo group ($p<0.0001$). The median time to a VAS score of 30 mm or less for POM was similar 4 days in both active treatment groups, versus 8 days in the placebo group ($p<0.0001$). Thus, treatment with VOLTAREN EMULGEL Extra Strength 2.32% gel accelerated healing by 4 days.

VOLTAREN EMULGEL Extra Strength 2.32% gel was also effective in reducing swelling. At baseline the mean difference in swelling between the injured and contralateral ankle was similar for both groups (range 1.7-1.8 cm). Seven days after starting treatment, the mean difference in swelling between the injured and contralateral ankles was 0.4 cm for VOLTAREN EMULGEL Extra Strength 2.32% gel and 0.8 cm for placebo ($p<0.0001$).

Study VOPO-P-307 also assessed patient satisfaction with treatment for the pain of ankle sprain. On Day 5, (86%) of subjects who applied VOLTAREN EMULGEL Extra Strength 2.32% gel rated their treatment satisfaction as good, very good, or excellent (42.3%, 42.3%, and 1.4% respectively), compared with only (22%) of subjects in the placebo group (17.6%, 4.4% and 0% respectively) ($p<0.0001$).

VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) helps to relieve pain, decreases swelling, and improves patient mobility.

Comparative Bioavailability Studies

A single-centre, randomized, open-label, multiple-dose, crossover study was conducted in 38 male and female healthy volunteers to compare the extent of systemic exposure between VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) (2 applications/day) under non-occlusive and semi-occlusive conditions and VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) (4 applications/day) under non-occlusive conditions and oral diclofenac sodium 50 mg tablets t.i.d. Systemic exposure was determined after repeated topical application of 2 g of gel to approximately 400 cm^2 of skin on the same ankle, by measurement of plasma diclofenac concentrations. The comparative bioavailability results after topical treatment under non-occlusive conditions are presented in Table 6.

Table 6 - Summary Table of the Comparative Bioavailability Data				
Diclofenac (2 x 2 g 2.32% gel or 4 x 2 g 1.16% gel/day for 7 days, non-occlusive) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-24} (ng.h/mL)	67.9 74.6 (53.3)	62.4 68.7 (49.9)	108.4	92.9, 126.5
C_{max} (ng/mL)	4.6 5.4 (84.9)	4.6 5.7 (82.7)	98.8	81.7, 119.5
C_{min} (ng/mL)	1.6 1.8 (44.0)	1.5 1.6 (45.8)	109.9	90.8, 133.0
T_{max}§ (h)	13.8 (70.1)	16.2 (55.6)		

* VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel)
† VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel)
§ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Systemic absorption of diclofenac following topical application of VOLTAREN EMULGEL is about 6% of the administered dose and the peak plasma levels attained are 50 times (repeated doses) to 100 times (single dose) lower than those observed after an oral dose. Supportive of efficacy is adequate tissue concentrations of diclofenac in the targeted area after topical application. Overall, VOLTAREN EMULGEL can be expected to produce a direct anti-inflammatory and analgesic effect with significantly less AEs than after the oral administration of diclofenac.

Pharmacokinetics

Evidence in humans and animals with topical NSAIDs, including diclofenac, demonstrates lower plasma concentrations than with systemically administered NSAIDs, while drug concentrations in the soft tissues around the area of application are still of a magnitude considered sufficient to exert an anti-inflammatory response. Reviews of the therapeutic effectiveness and PK of diclofenac include Chlud & Wagener (1987, 1991), Chlud (1999), Grahame (1995), Davies & Anderson (1997), and Vaile & Davies (1998).

Percutaneous Absorption, Distribution, Metabolism, Excretion

Absorption of various NSAIDs, including diclofenac, occurs to a depth of at least 3-4 mm through the underlying dermis and subcutaneous tissue (Singh & Roberts 1994). At that level, uptake of drug from the dermal microcirculation into the systemic circulation occurs but the concentration of drug in

these layers is always higher than the plasma concentration. Although only a small proportion of the dose is absorbed, the skin acts as reservoir from which there is a sustained release of drug into underlying tissues (Dreiser 1994, Sioufi *et al* 1994). A recent multiple-dose, 7 day PK study (VOPO-PE-102) was conducted with VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) and VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel). On day 1, mean diclofenac plasma concentrations from the two topical treatments did not exceed the LLOQ (0.5 ng/mL) until at least 14 hours after the first dose, and steadily increased to 2-3 ng/ml after 24 hours. The reservoir function is important during the first day after application where the concentration of diclofenac in the stratum corneum is highest (Schaefer and Redelmeier 1996).

Mean trough values were similar over days 5 through 7, indicating that steady state was reached by Day 5 with mean diclofenac plasma concentrations of roughly 3 ng/ml. On Day 7, the mean plasma concentrations were low and the peak-to-trough fluctuation was modest. In contrast, after oral dosing, Day 7 mean plasma concentrations increased sharply and returned approximately to pre-dose levels within the 6-hour dose interval.

The data can be described by a linear one-compartment model with the absorption as the rate limiting factor, (i.e. flip-flop kinetics when absorption is considerably slower than disposition) which is often seen with topical formulations due to the persistence of the compound in the skin reservoir.

The concentration of the drug is higher in the dermis and subcutaneous tissue below the application site than at greater depths where the drug concentration becomes less than the corresponding plasma concentration. Thus, anti-inflammatory effects at deeper tissue levels may be influenced by both direct and systemic drug concentrations (Singh & Roberts 1994).

When VOLTAREN EMULGEL is applied topically, the amount of diclofenac absorbed through intact skin is proportional to the contact time and skin area covered and depends on the total topical dose and the hydration of the skin.

Systemic absorption amounts to approximately 3-7% of the dose of diclofenac after topical application of 2.5g VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) per 500 cm^2 skin, left for 12 hours on non-occluded skin (Riess *et al* 1986, Davies & Anderson 1997). Plasma drug concentrations are well below those observed after a standard oral or intramuscular dose and below the range at which systemic AEs usually occur. Maximum plasma concentrations of diclofenac after topical administration of VOLTAREN EMULGEL are between 50 (repeated dose) and 100 (single dose) times lower than after oral administration of VOLTAREN tablets (Riess *et al* 1986). The steady state is reached after 2 days of twice-daily administration and the low plasma levels remain in the same range over the full day indicating prolonged absorption from the application site (Sioufi *et al* 1994). Absorption of diclofenac through the skin can be increased by 3-10 times after application of an occlusive dressing.

Report 17727B-510.20-02-01-B describes a single and multiple dose (7 days), open, randomized, three-way cross-over, comparative bioavailability trial of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel), diclofenac enteric coated tablet and a diclofenac patch formulation that was in development in the Company, in 24 healthy volunteers. The main pharmacokinetic findings are summarized in Table 7.

Table 7 - Summary of pharmacokinetic data for Study NCH 17727B-510.20-02-01B		
Parameter	**VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) 4g (40 mg diclofenac-Na equivalent) t.i.d**	**VOLTAREN tablet 25 mg t.i.d**
After first administration (day 1)		
C_{max} (ng/ml)	5.36 (0.502 - 42.6)	370 (92.0 - 984)
t_{max} (h)	20.00 (10.00 - 23.95)	4.00 (1.00 - 18.00)
AUC_{0-24} (ng.h/ml)	43.6 (0.502 - 240)	1190 (231 - 3800)
After last morning administration (day 7)		
C_{max} (ng/ml)	12.0 (2.54 - 45.1)	380 (51.0 - 1330)
t_{max} (h)	18.00 (0.00 - 20.00)	4.00 (1.00 - 20.00)
AUC_{0-24} (ng.h/ml)	179 (51.8 - 332)	1360 (327 - 4690)
C_{min} (ng/ml)	4.07 (1.19 - 8.06)	2.11 (<0.5 - 4.79)
PTF (%)	95.0 (36.2 - 313)	664 (360 - 1250)
t_{max} values are median (range), other values are geometric means (range); N=24 for patch and gel, N=23 for the tablet		

As expected, these data demonstrate that the relative bioavailability of VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) *versus* tablets remained low (C_{max} <2% and 3% and AUC 4% and 13% respectively) after first and last administration.

A single-centre, randomized, open-label, multiple-dose, crossover study was conducted in 38 male and female healthy volunteers to compare the extent of systemic exposure between VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) (2 applications/day) under non-occlusive and semi-occlusive conditions and VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) (4 applications/day) under non-occlusive conditions and oral diclofenac sodium 50 mg tablets t.i.d. Systemic exposure was determined after repeated topical application of 2 g of gel to approximately 400 cm² of skin on the same ankle, by measurement of plasma diclofenac concentrations. The comparative bioavailability results after topical treatment under non-occlusive conditions are presented in Table 6. The relative bioavailability of diclofenac (AUC ratio) for VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) *versus* tablet was 4.5% on day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapour permeable bandage.

Table 8 - Summary of pharmacokinetic data for Study VOPO-PE-102		
Parameter	**VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) 2g (40 mg diclofenac-Na equivalent) b.i.d**	**VOLTAREN tablet 50 mg t.i.d**
After last morning administration (day 7)		
C_{max} (ng/ml)	4.6 (2.2-29.4)	1367 (88-4240)
t_{max} (h)	19.00 (00.00 – 24.00)	7.30 (01.00 – 24.00)

Table 8 - Summary of pharmacokinetic data for Study VOPO-PE-102		
Parameter	**VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) 2g (40 mg diclofenac-Na equivalent) b.i.d**	**VOLTAREN tablet 50 mg t.i.d**
AUC_{0-24} (ng.h/ml)	67.9 (38.2-255.2)	2830 (249-5955)
C_{min} (ng/ml)	1.6 (<LLQ-4.2)	3.5 (<LLQ-13.4)
PTF (%)	96 (45-327)	1156 (540-2644)
t_{max} values are median (range), other values are geometric means (range); N=38 for gel, N=38 for the tablet		

Diclofenac is extensively protein bound in plasma (>99.7%), mainly to albumin (99.4%) (Reiss *et al* 1978). The liver is the primary site of metabolism for diclofenac (Davies & Anderson 1997) to virtually inactive metabolites (Stierlin, Faigle & Colombi 1978, Stierlin *et al* 1979, Faigle *et al* 1988). The total systemic clearance of diclofenac from plasma is 263±56 ml/min (mean value ± SD). The terminal plasma half-life is 1 to 2 hours. Diclofenac and its metabolites are excreted mainly in urine (60%).

Diclofenac in target tissues

After topical administration of VOLTAREN EMULGEL to hand and knee joints in patients, diclofenac can be measured in the synovial tissue and synovial fluid with concentrations as high as 20 times the plasma concentration (Riess *et al* 1986). In study C.R.B. R8/1986 plasma concentrations of diclofenac recorded on the fourth day in 7 patients ranged from 6 to 52 ng/ml with one extreme value of 698 ng/ml. In synovial fluid, the concentrations of diclofenac ranged from 119 to larger than 3320 ng/ml and in synovial tissue ranged from 131 to 1740 ng/ml. In the other patient study T13/1987 diclofenac could not be detected in plasma samples. In synovial fluid from knee joints the diclofenac concentrations were in the range of 6.5-22.1 ng/g sample. These patient studies confirm that topically applied diclofenac will reach the target tissues (soft tissue/joint) at sufficient concentrations to exert a therapeutic response. Relevant publications include Radermacher *et al* (1991), Gondolph-Zink & Gronwald (1996), Day *et al* (1999), Kurowski & Dunky (1992), Chlud & Wagener (1987, 1991), Chlud (1999), Dreiser (1994), and Giuliano & Warner (1999).

Drug and substance interactions

The customary drug-drug interactions between oral NSAIDs and anticoagulants and oral antidiabetic agents, for example, are usually consequent to the high protein-binding of the NSAID. With a significantly lower amount of active substance in circulation following topical application than after oral administration, such interactions may be predicted to be very unlikely with VOLTAREN EMULGEL.

Pharmacokinetics in special patient populations

There are no gender differences in the pharmacokinetics of diclofenac. No safety or efficacy concerns relating to ethnicity have been identified from the marketplace. Davies and Anderson (1997) discuss the influence of age on diclofenac pharmacokinetics with relevance in the very young and elderly. Also, changes to the skin in the elderly will affect absorption in some patients. However, as plasma levels will be very low after topical application these factors are not a clinical concern. For similar reasons, any effect of hepatic or renal impairment on the pharmacokinetics of diclofenac is unlikely to be clinically significant. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Pharmacodynamics

Pharmacodynamics studies - anti-inflammatory activity

As with other NSAIDs, the ability of diclofenac to inhibit prostaglandin synthesis is instrumental in the anti-inflammatory response. Data from *in vitro* studies show that most topical NSAIDs are able to inhibit prostaglandin synthesis to a significant degree. In this respect, diclofenac has a high intrinsic activity, as demonstrated *in vitro* in human rheumatoid synovial microsomes (Dreiser 1994).

Prostaglandins, along with thromboxanes and leukotriene B4 (LTB4), are responsible for several inflammatory effects such as vasodilatation, increased vascular permeability, hyperalgesia and increased platelet aggregation. Free oxygen radicals, also mediators of inflammation, are by-products of prostaglandin synthesis. Diclofenac non-specifically inhibits the cyclo-oxygenase pathway with a subsequent reduction in prostaglandin, prostacyclin and thromboxane production. Although non specific, diclofenac inhibits preferentially COX-2 pathway (Giuliano & Warner 1999). The production of leukotrienes is also decreased following the administration of diclofenac, suggesting an inhibitory effect on the lipoxygenase pathway with direct impact on LTB4 and inhibition of pain (Amadio, Cummings & Amadio 1993).

The pharmacodynamic properties of diclofenac have been demonstrated for each of the sodium, potassium and diethylamine salts administered either orally or topically in standard animal models of acute and chronic inflammation (Hiramatsu *et al* 1990, Kyuki *et al* 1983).

It has also been reported that topically applied diclofenac diethylamine 1.16% actively inhibited methyl nicotinate induced skin inflammation, which is known to involve prostaglandins and free arachidonic acid. Topical diclofenac was shown to exhibit a prolonged potent anti-inflammatory effect, even 48 hours after application (Duteil *et al* 1990).

The anti-inflammatory properties of VOLTAREN EMULGEL were demonstrated in two placebo-controlled, double-blind, randomized trials (refer to Table 9), one in healthy volunteers using the urate crystal induced inflammation model (NGB5) and the other in patients with chronic synovitis of the knee (NGB 8855). VOLTAREN EMULGEL proved to be superior to placebo in significantly reducing the diameter of erythema at 24 hours in study NGB 5 ($p<0.05$), and significantly reducing the thermal index in study NGB 8855 ($p<0.04$). Due to the small size of the studies, only objective parameters of erythema and thermal index could be evidenced.

Table 9 - Summary of Studies NGB 5 and NGB 8855					
Study Investigator Country	**Regimen Design Comparator**	**Condition**	**Population**	**Criteria**	**Efficacy**
NGB 5 P.A. Dieppe UK	5 applications in 48 hours (every 12 hr) DB, CO Placebo	Urate crystal induced inflammation Model	Total: 19 (healthy volunteers) Age range: 18-50 years	Lesion diameter, tenderness, intensity of erythema, subject and investigator preference.	**VE *vs*. Placebo**: significantly reduced erythema diameter at 24 hours. Investigator's and volunteer's preference at 48 hours ($p<0.05$).
NGB 8855 B. Hazelman UK	3/day up to 7 days DB, CO Placebo	Mild to moderate chronic synovitis of knee	Total: 13 Male: 38% Mean age: 55 years Age range: 13-82 years	Thermal index, tenderness, pain on passive movement, swelling, rescue medication.	**VE *vs*. Placebo**: reduced thermal index ($p<0.04$).

Duteil, *et al* (1990) compared the potency of VOLTAREN EMULGEL with that of five other topical NSAIDs (indomethacin, ibuprofen, phenylbutazone, bufexamac and niflumic acid) and three topical corticosteroids (clobetasol, hydrocortisone and hydrocortisone butyrate) in healthy volunteers. Four hours after a single application of each drug to the forearm, inhibition of methyl-nicotinate induced inflammation was greatest with VOLTAREN EMULGEL and indomethacin cream (84% and 85%, respectively, relative to a control vehicle). VOLTAREN EMULGEL demonstrated the most sustained anti-inflammatory effect, providing 75% inhibition when re-tested 48 hours after application.

Pharmacodynamics studies - analgesic activity

Interestingly, diclofenac also blocks the lipoxygenase pathway of the arachidonic cascade, thereby inhibiting the formation of LTB4 which is known to be a pain mediator stimulating the pain receptors in the peripheral sensory nerves (Martin, *et al* 1988). Inhibition of lipoxygenase also decreases the formation of the slow-reacting substance of anaphylaxis (composed of leukotriene C4, D4 and E4).

In animals, using the Randall and Sellito's test, VOLTAREN EMULGEL has been shown to increase the pain threshold after a single subcutaneous injection of yeast suspension (Kyuki *et al* 1983).

TOXICOLOGY

VOLTAREN EMULGEL 1.16% Gel or VOLTAREN EMULGEL Back & Muscle Pain 1.16% Gel

The toxicology of VOLTAREN EMULGEL 11.6 mg/g gel (or VOLTAREN EMULGEL Back & Muscle Pain 11.6 mg/g gel) was investigated in a series of *in vivo* studies, including acute and three-month repeat dose toxicity, but concentrating particularly on potential local tolerance and photo-safety issues, as outlined in Table 10 below.

Table 10 – VOLTAREN EMULGEL 11.6 mg/g Gel (or VOLTAREN EMULGEL Back & Muscle Pain 11.6 mg/g Gel) Toxicology Program

Study type and duration	Route of administration	Species	Compound administered
Single–dose toxicity	Topical, occluded	Rat	VOLTAREN EMULGEL 11.6 mg/g Gel
Single–dose toxicity	Oral	Rat	Diclofenac diethylamine
Repeat-dose toxicity: 3 months	Topical, occluded	Rabbit	VOLTAREN EMULGEL 11.6 mg/g Gel
Local tolerance / photo-safety			
Phototoxicity, single dose	Topical	Mouse	VOLTAREN EMULGEL 11.6 mg/g Gel
Phototoxicity, single dose	Topical	Guinea pig	VOLTAREN EMULGEL 11.6 mg/g Gel
Photo-allergenicity	Topical	Guinea pig	VOLTAREN EMULGEL 11.6 mg/g Gel
Skin sensitization	Topical, occluded	Guinea pig	VOLTAREN EMULGEL 11.6 mg/g Gel
Skin irritation, 5 days	Topical, occluded	Rabbit	VOLTAREN EMULGEL 11.6 mg/g Gel
Skin irritation, 5 days	Topical, occluded	Rabbit	VOLTAREN EMULGEL 11.6 mg/g Gel
Eye irritation, single dose	Ocular	Rabbit	VOLTAREN EMULGEL 11.6 mg/g Gel

VOLTAREN EMULGEL 11.6 mg/g gel (or VOLTAREN EMULGEL Back & Muscle Pain 11.6 mg/g gel) was generally well tolerated. The acute toxicity of diclofenac diethylamine was essentially the same as that of diclofenac sodium when expressed in terms of the base. There was no evidence of any significant local irritancy, unexpected toxicity or of any photo-safety concerns.

There have been no other studies specifically designed to investigate toxicity of the drug substance, diclofenac diethylamine, or of the drug product, VOLTAREN EMULGEL 11.6 mg/g gel (or VOLTAREN EMULGEL Back & Muscle Pain 11.6 mg/g gel). The non-clinical toxicology of diclofenac sodium is directly relevant to diclofenac diethylamine and is summarized below.

Single dose experiments in mice, rats, rabbits and dogs indicate an acute intravenous LD_{50} in the region of 100 mg/kg and an oral LD_{50} nearer 200 mg/kg with little evidence to suggest any significant influence of age or sex on the outcome. An oral study in baboons suggests significantly greater tolerance with a probable LD_{50} of more than 600 mg/kg. Death following intravenous administration was usually attributed to respiratory or cardiac failure, those following oral administration to gastrointestinal problems.

Repeat dose oral gavage studies of up to 6 months duration in rats indicate a no observed adverse effect level (NOAEL) of 1 to 2 mg/kg/day. A similar result was obtained in a one-month mouse study by dietary administration. At doses greater than 4 mg/kg/day, deaths were common and usually associated with mild anaemia, neutrophilia, disturbance of plasma proteins, increased extramedullary haematopoiesis and, most prominently, ulceration of the gastrointestinal tract with accompanying

peritonitis. These latter were commonly associated with hypertrophy or reactive hyperplasia of the mesenteric lymph nodes.

In a series of baboon studies, similar changes were apparent with deaths consistently seen within 3 months of treatment at 20 mg/kg/day or more. In a 1-year study, 5 of 14 animals treated at 15 mg/kg/day had died by 8.5 months when this dosage was reduced to 10 mg/kg/day. Both constipation and diarrhoea were apparent and there was a high incidence of skin ulcers the severity of which was treatment-related. In both three-month studies, but not in the one-year study, there was evidence of nephropathy at the high dose with increased blood urea nitrogen and disturbance of plasma electrolytes in one study. In the one-year study only and at the high dose only (where 13 of 14 animals died despite a dosage reduction) adrenal cortical hyperplasia was noted in several animals. Other changes seen in baboons were essentially similar to those in rats and the deaths were all associated with gastrointestinal changes. Gastrointestinal changes were seen at the lowest dosages studied in baboons (around 3-5 mg/kg/day) but were generally considered to reflect an exacerbation of pre-existing conditions rather than a primary effect of treatment with diclofenac.

The potential genetic toxicology of diclofenac sodium has been studied in a wide variety of *in vitro* and *in vivo* studies. Most of these studies were carried out many years ago and include:

- Ames tests of the drug, of urine and bile concentrates, and of the major hydroxy-metabolites of diclofenac.
- *In vitro* mammalian cell mutation studies of diclofenac sodium and its hydroxy-metabolites.
- *In vivo* chromosome aberration and nucleus anomaly tests in Chinese hamsters after both short-term treatment and repeated administration for 12 weeks.
- Metaphase analyses of spermatogonia and spermatocytes following five administrations.
- A dominant lethal study in mice.

None of these studies gave any indication of a positive outcome. Recently fully GLP compliant *in vitro* photo-mutagenicity and photo-chromosome aberration studies have been carried out. The photo-mutagenicity study (Ames test) was also negative. Chromosome aberrations were seen in the other study at 25 µg/ml and with 16 minutes of UV radiation. These conditions were associated with a reduced mitotic index and the apparently positive result is attributed to cytotoxicity. No chromosome aberrations were seen at lower doses of UV or at lower concentrations of diclofenac. An additional conventional *in vivo* GLP compliant chromosome aberration study has also been completed with diclofenac sodium and was also negative.

One mouse and two rat carcinogenicity studies have been conducted. Exposure levels, as judged from plasma concentration data obtained during the more recent of these studies, were 12-45 ng/g in mice at the NOAEL (0.3 mg/kg/day) and 10-48 ng/ml in rats at the lowest dosage (0.25 mg/kg/day). In all 3 studies there was a dosage-related increase in mortality at 1 and 2 mg/kg/day with only isolated animals surviving at the high dose. Most deaths were associated with gastrointestinal ulceration and peritonitis. There were few changes that could be ascribed to treatment at lower dosages (0.1 to 0.5 mg/kg/day) and there was no treatment-related increase in the incidences of benign or malignant tumours in any of these studies.

Reproduction toxicity has been assessed in a series of pre-ICH design studies, including Segment I and III studies in rats and a variety of Segment II studies in mice, rats and rabbits. Almost all studies included treatment at toxic dosages and death of the dams, usually attributed to peritonitis, was a

common finding. Treatment with diclofenac sodium in the Segment I and III studies was generally associated with a slight increase in gestation and occasional dystocia resulting in increased peri-natal mortality. Even discounting this, there was usually an increase in embryo-foetal and/or perinatal losses. Birth weight was reduced. Foetal changes extended to the lowest dosage examined, 2 mg/kg/day, in both studies. Other than deaths associated with dystocia, post-natal survival was not affected.

In the Segment II studies in mice, there was no clear effect of treatment at 2 or 4 mg/kg/day when given orally, even when administered through days 0-17 of gestation. Reductions in foetal numbers and reduced ossification at higher dosages were associated with severe maternal toxicity. In oral rat studies a similar picture emerged. There were some minor contradictory findings at 4 mg/kg/day but none at 2 mg/kg/day and clear effects at higher dosages, including reduced ossification, that were attributed to maternal toxicity. An intramuscular study indicated no changes in the foetuses at 10 mg/kg/day, despite maternal sedation and local injection site responses. In a GLP compliant subcutaneous rat study, however, minimally reduced ossification was identified at 1.2 mg/kg/day; 0.4 mg/kg/day was a NOAEL. In an oral rabbit Segment II study, 5 mg/kg/day was a clear NOAEL, changes at 10 mg/kg/day included increased embryonic and foetal resorptions and reduced foetal ossification in three foetuses. An intramuscular rabbit study identified 3 mg/kg/day as the NOAEL with increased abortions and dead foetuses, reduced number of fully formed foetuses and reduced ossification, and reduced foetal viability at higher dosages, associated with maternal toxicity.

VOLTAREN EMULGEL Extra Strength 2.32% Gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel)

The toxicology of VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) was investigated in a series of *in vivo* studies. The studies shown in Table 11 concentrated particularly on potential local tolerance, sensitisation and photo-safety issues.

Table 11 – VOLTAREN EMULGEL Extra Strength 2.32% Gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% Gel) Toxicology Program

Study type and duration	Route of administration	Species	Compound administered
7-Day repeated skin irritation in rabbits	Topical with 25 mg/cm^2 test product VOLTAREN EMULGEL 23.2 mg/g and with 50 mg/cm^2 VOLTAREN EMULGEL 11.6 mg/g Gel (occlusive condition for 4 and 18 hours)	Rabbits	VOLTAREN EMULGEL 23.2 mg/g Gel VOLTAREN EMULGEL 11.6 mg/g Gel
Cumulative 28 days skin irritation study in rabbits	Topical with 25 mg/cm^2 test product VOLTAREN EMULGEL 23.2 mg/g and with 50 mg/cm^2 VOLTAREN EMULGEL 11.6 mg/g Gel (occlusive condition for 4 hours)	Rabbits	VOLTAREN EMULGEL 23.2 mg/g Gel VOLTAREN EMULGEL 11.6 mg/g Gel
Cumulative 90 days local tolerance	Topical with 10 mg/cm^2 and 20mg/cm^2 test product	Rabbits	VOLTAREN EMULGEL 23.2 mg/g Gel
Sensitisation test using Maximisation (Magnusson and Kligman) Protocol	Topical with 0.25 mg/15 cm^2 of test product at 100%, 50%, and 25%	Albino guinea-pigs	VOLTAREN EMULGEL 23.2 mg/g Gel
Photosensitisation test	Topical with 3.8 mg/cm^2 test product	Albino guinea-pigs	VOLTAREN EMULGEL 23.2 mg/g Gel

Topical treatment with VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) appeared to be well tolerated. Although treatment with VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) yielded slightly higher irritation indices than with the marketed VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) (possibly due to the increased potency of active ingredient), the irritation observed were considered as slight. All the erythemas found with VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) and VOLTAREN EMULGEL 1.16% gel (or VOLTAREN EMULGEL Back & Muscle Pain 1.16% gel) were barely perceptible and transient. In addition, VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) was well tolerated in 28-day and 90-day cumulative irritation studies. VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) was neither sensitising nor photosensitising in guinea pigs. These results indicate that VOLTAREN EMULGEL Extra Strength 2.32% gel (or VOLTAREN EMULGEL Joint Pain Extra Strength 2.32% gel) is likely to be well tolerated.

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PART III: CONSUMER INFORMATION

Voltaren Emulgel/
Voltaren Emulgel Back & Muscle Pain
Diclofenac diethylamine gel 11.6 mg/g (1.16%)

Voltaren Emulgel Extra Strength/
Voltaren Emulgel Joint Pain Extra Strength
Diclofenac diethylamine gel 23.2 mg/g (2.32%)

This leaflet is part III of a three-part "Product Monograph" published when **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength.
Read all of this leaflet carefully before you start using this medicine because it contains important information for you,

- Keep this leaflet. You may need to read it again.
- Contact your doctor or pharmacist if you have any questions about the drug or need more information or advice.

ABOUT THIS MEDICATION

What the medication is used for:

Voltaren Emulgel, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength

- For the relief of aches and pain associated with acute, localized minor muscle or joint injuries such as sprains, strains or sports injuries (*e.g*. sprain of ankle, strain of shoulder or back muscles). Rest may also be helpful to assist the relief of associated discomfort.

What it does:
Voltaren Emulgel, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength are specially formulated for rubbing into the skin to relieve acute pain affecting the joints and muscles. The active substance, diclofenac, is one of the groups of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) that work within the body by blocking the production of particular substances, called prostaglandins, which are involved in the development of pain and inflammation.

When it should not be used:

- If you are currently taking diclofenac or any other over-the-counter or prescription oral non-steroidal anti-inflammatory drug (NSAID) which are used to treat pain, fever or inflammation, such as ibuprofen, acetylsalicylic acid (ASA) or naproxen. If you are not sure, ask your doctor or pharmacist.
- If in the past you have had allergic reactions to diclofenac or any other NSAIDs such as ibuprofen, ASA or naproxen.
- If you have attacks of asthma, urticaria (hives), or acute rhinitis (nasal inflammation, irritation or stuffy nose that lasts less than 6 weeks), swelling of the face or tongue, runny nose after taking ASA or other NSAIDs
- If you are allergic to any of the nonmedicinal ingredients in the gel (see list of nonmedicinal ingredients).
- If you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery.
- If you are breast-feeding.

If any of these applies to you, do not use this medicine. If you are not sure, ask your doctor or pharmacist.

What the medicinal ingredient is:
Diclofenac diethylamine

What the nonmedicinal ingredients are:
Voltaren Emulgel 1.16% gel and **Voltaren Emulgel** Back & Muscle Pain 1.16% gel contain the following nonmedicinal ingredients: Carbomer, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, perfume (containing benzyl benzoate), propylene glycol, purified water.

Voltaren Emulgel Extra Strength 2.32% gel and **Voltaren Emulgel** Joint Pain Extra Strength 2.32% gel contain the following nonmedicinal ingredients: butylhydroxytoluene, carbomers, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, oleyl alcohol, perfume, propylene glycol, purified water.

Propylene glycol and benzyl benzoate, may cause mild localized skin irritation in some people.

Butylhydroxytoluene may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

What dosage forms it comes in:
Voltaren Emulgel 1.16% gel and **Voltaren Emulgel** Back & Muscle Pain 1.16% gel come in tubes of 20g, 30g, 50g, 100g, 120g and 150g.

Voltaren Emulgel Extra Strength 2.32% gel and **Voltaren Emulgel** Joint Pain Extra Strength 2.32% gel come in tubes of 30g and 100g in a carton with a dosing card.

The gel is white, cooling, non-greasy, non-staining, cream-like.

WARNINGS AND PRECAUTIONS

BEFORE you use **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength talk to your doctor or pharmacist if:

- You have a history of stomach ulcers or take medication for such gastrointestinal disorders.

- You are pregnant or think you may be pregnant or are planning to have a baby.
- You are taking, or have recently taken, any other medicines, including Over the Counter drugs.

Voltaren Emulgel and **Voltaren Emulgel** Back & Muscle Pain are not intended for use in children under the age of 16.

Voltaren Emulgel Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength are not intended for use in children under the age of 18.

Do not apply to cuts or open wounds or to skin that has a rash or eczema. Discontinue the treatment if a skin rash develops after applying the product.

Avoid applying on large areas of skin or for a longer than approved duration of use, unless under medical advice.

A brace or wrap commonly used for injuries like sprains can be used but do not wrap the skin with an airtight (plastic) or occlusive dressing when using **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength.

In very rare cases, your skin may be more sensitive to sunlight while using this product. Use caution during sun exposure or when using tanning booths/sun lamps. Possible signs are sunburn with itching, swelling and blistering.

Be careful not to get it in your eyes. If this happens, rinse your eyes well with clean water and tell a doctor or a pharmacist.

Voltaren Emulgel, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength are for EXTERNAL USE ONLY.

Do not use it in the mouth, vaginal or anal areas.

Never swallow it.

INTERACTIONS WITH THIS MEDICATION

Check with your doctor or pharmacist if you are taking any other NSAIDs (e.g. ibuprofen, acetylsalicylic acid or naproxen) or anticoagulants (blood thinners), high blood pressure medication, oral anti-diabetic agents, fluoroquinolone antibiotics (*i.e.*, ofloxacin) or are taking medication for peptic ulcers, gastroesophageal disease or to control excess acidity. If you suspect a drug interaction, notify your doctor or pharmacist.

PROPER USE OF THIS MEDICATION

Usual dose:

Voltaren Emulgel and **Voltaren Emulgel** Back & Muscle Pain:
For adults and adolescents 16 years and older:

- Apply gel 3 to 4 times a day.
- The amount needed will vary depending upon the size of the painful or swollen area: 2 g to 4 g (1 g equals a strip approximately 2 cm long) gel will be sufficient to cover a 400 to 800 cm^2 area.

Voltaren Emulgel Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength:
For adults between 18 to 65 years:

- Apply 2 g of gel 2 times a day (morning and evening) on the painful area.
- The amount of gel applied (2 g for each application) should be measured using the dosing card supplied in the product carton. For each application the gel should be squeezed from the tube and measured up to the 2 g line on the dosing card. Clean and dry the dosing card after each use.
- Do not use more than 4 g per day.

Voltaren Emulgel, Voltaren Emulgel Back & Muscle Pain, **Voltaren Emulgel** Extra Strength and **Voltaren Emulgel** Joint Pain Extra Strength:

- Tubes: before first use, unscrew and remove the cap. Use the reverse side of the cap to remove the seal from the tube.
- Gently squeeze out a small amount of gel from the tube and apply to the painful or swollen area, slowly rubbing into the skin. You may notice a slight cooling effect when you rub the gel in.
- Wash your hands after rubbing in **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength or **Voltaren Emulgel** Joint Pain Extra Strength to avoid accidental contact with the mouth and eyes, unless of course they are the site being treated.

The gel should not be used for more than 7 days for muscle and joint injuries unless recommended by a doctor. Talk to your doctor if your condition does not improve within 7 days, or if it gets worse.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you use more gel than you should wipe off the surplus gel with a tissue.
If you or a child accidentally swallows the gel, contact your doctor immediately.

Missed Dose:
If you miss applying **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength or **Voltaren Emulgel** Joint Pain Extra Strength at the correct time, apply it when you remember and then next apply it at the usual time. Do not apply a double quantity.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Itching, reddening or slight irritation of the skin are common after use of **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength or **Voltaren Emulgel** Joint Pain Extra Strength. These symptoms are usually mild, passing and harmless. If you are concerned, tell a doctor or pharmacist. Discontinue the treatment if a skin rash develops after applying the product.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist
Some rare and very rare side effects might be serious	Skin rash with blisters; hives	✓	✓
	Wheezing, shortness of breath or feeling of tightness in the chest (asthma)	✓	✓
	Swelling of the face, lips, tongue or throat	✓	✓
Common	Skin rash, itching, reddening or smarting of the skin	✓	✓
Very rare side effects	The skin may be more sensitive to the sun. Possible signs are sunburn with itching, swelling and blistering	✓	✓

This is not a complete list of side effects. For any unexpected effects while taking **Voltaren Emulgel**, **Voltaren Emulgel** Back & Muscle Pain, **Voltaren Emulgel** Extra Strength or **Voltaren Emulgel** Joint Pain Extra Strength, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 30°C.
Should not be stored after the expiry date shown on the carton and tube.
Do not use after the expiry date stated on the label.
Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

Online at MedEffect;
By calling 1-866-234-2345 (toll-free);
By completing a Consumer Side Effect Reporting Form and sending it by:

Fax to 1-866-678-6789 (toll-free), or
Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be received by contacting the sponsor, GlaxoSmithKline Consumer Healthcare Inc., at: 1-888-788-8181
www.voltaren.ca

This leaflet was prepared by GlaxoSmithKline Consumer Healthcare Inc.

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