Product Monograph

Including Patient Medication Information

PAIN RELIEF GEL Extra Strength

Diclofenac Diethylamine Gel, For Topical Use,

23.2 mg/g (2.32% w/w) Taro Standard

ATC Code: M02A A15 Anti-inflammatory preparations, non-steroids for topical use

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	02/ 2025

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults between 18 to 65 years:

Pain Relief Gel Extra Strength (diclofenac diethylamine gel 2.32% w/w) is indicated for:

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Patients with or without chronic asthma in whom attacks of asthma, angioedema, 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
- Following coronary artery bypass grafting surgery

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- See 4.2 Recommended Dose and Dosage Adjustment

4.2 Recommended Dose and Dosage Adjustment

Adults between 18 to 65 years:

- Pain Relief Gel Extra Strength 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 over all affected areas. Applying a greater quantity of gel will not result in an increase of pain relief.

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. If the condition does not improve or worsens within 7 days of starting treatment, patient should consult their doctor to exclude an alternative underlying cause of pain.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

For Topical Use Only.

The amount of Pain Relief Gel Extra Strength (2 g for each application) should be measured using the dosing guide supplied with the product.

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 wiped with a tissue and then washed. The tissue should be thrown in the trash after use. Patients should wait until the gel dries before showering or bathing.

4.5 Missed Dose

If a dose of Pain Relief Gel Extra Strength 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.

5 OVERDOSAGE

The low systemic absorption of topical diclofenac renders overdose very unlikely. However undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if Pain Relief Gel Extra Strength is ingested (1 tube of 100 g contains the equivalent of 2 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. Further management should be as clinically indicated, or as recommended by the regional Poison Control Centre.

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.

There are 173 worldwide cases of overdose with diclofenac diethylamine gel in the GlaxoSmithKline safety database. Fifty concern patients of age up to 18 years; 78 concern the adult and elderly population, and 45 concern patients of unspecified age.

In the paediatric population, no adverse event was reported in 39 out of 50 cases; 5 out of 11 cases with clinical adverse events (with patient's age ranging from 5 months to 11 years) reported listed skin reactions after topical application (e.g. rash, urticaria, erythema). Other adverse events reported were burning sensation; skin disorder, alopecia, thermal burn, decreased appetite, thyroid disorder, headache, diarrhoea, nausea, skin reaction, erythema (in this medically confirmed case, the causal relationship with diclofenac diethylamine gel was assessed as unlikely); vomiting, headache and dizziness; inflammation; eye swelling, nasal inflammation and eye inflammation in two children who accidentally received a small amount of gel near the eyes; nausea and feeling abnormal.

There were no cases of accidental ingestion. A 19-month-old child accidentally ran her lips around an opened tube, but no adverse events were reported.

In the adult population, out of 78 cases, 24 reported clinical adverse events after topical application: e.g. skin reactions (rash, burning sensation, skin exfoliation, eczema, erythema, dermatitis), hypersensitivity symptoms (e.g. swollen tongue, dyspnoea), peripheral swelling, feeling hot, gastrointestinal reactions (e.g. epigastric discomfort in a case with co-suspect celecoxib; abdominal pain upper, vomiting), hypotension (case confounded by concomitant medications), events related to the underlying condition (e.g. pain, arthralgia, chondropathy). A 79-year-old polymedicated patient with a medical history of hypertension, type 2 diabetes mellitus, and respiratory disease developed acute renal failure after using two full tubes of 120 grams in a 10-day period. Angina pectoris occurred in a 46-year-old polymedicated (not further specified) male patient treated with diclofenac free acid for nearly 20 years with a dose of 2 tablets 3 times a day (overdose) in addition to recently started diclofenac diethylamine. A 78-year-old patient treated with fluindione developed haematoma after application of excessive amounts (a tube of 100 ml in 4 days) of diclofenac diethylamine gel.

In the population of unspecified age, out of 45 cases, only 16 cases reported clinical adverse events after topical application: e.g. skin reactions (e.g. application site pruritus, skin irritation, rash), sensory loss, burning sensation, peripheral swelling, gastritis in a patient with a history of stress-induced gastritis, poisoning (not further specified). In one case, a female patient developed unspecified circulatory system complaints, dizziness and nausea after applying too

much product, summarized as misuse of 2 x 150 g per week. Final outcome was complete recovery. A female consumer wanted to commit suicide with diclofenac diethylamine gel; no other adverse event than suicide attempt was reported. In another case, a male patient with an unspecified renal disorder developed comatose state and possible renal failure after use of the product regularly and continuously for more than one year over a large area of skin including the back, the shoulder and the legs. The patient used about 2 tubes every three weeks. In another case, a female patient with alcohol and narcotic addiction used the product to get intoxicated. Diclofenac diethylamine gel was heated, and the vapours were being aspirated with a specific syringe. The content was injected into the mouth or the ear to achieve intoxication from the alcohol that had been extracted from the process. No adverse event other than alcohol poisoning and drug abuse was reported.

There was one case of ingestion: An elderly female patient accidentally swallowed diclofenac diethylamine gel 25g but most of it was not absorbed because the patient spontaneously vomited most of the drug. No further adverse event occurred.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Gel, 23.2 mg/g diclofenac diethylamine (2.32% w/w)	Butylhydroxytoluene, carbomer homopolymer Type C, cocoyl caprylocaprate, diethylamine, fragrance, isopropyl alcohol, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylene glycol, purified water.

This product contains mineral oil (see 7 WARNINGS AND PRECAUTIONS).

Pain Relief Gel Extra Strength is a white to practically white, soft, homogenous, cream-like gel.

It is packaged in 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 g and 100 g tubes in cartons with a dosing card.

7 WARNINGS AND PRECAUTIONS

General

Diclofenac diethylamine gel 2.32% w/w 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 used with occlusion. It should not be allowed to come into contact with the eyes, or mucous membranes, and should never be taken by mouth.

Pain Relief Gel Extra Strength contains 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. For a complete list of non-medicinal ingredients see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

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

Pain Relief Gel Extra Strength can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

Patients should be instructed to be cautious when smoking or near open flames due to risk of severe burns. Pain Relief Gel Extra Strength contains mineral oil which is potentially flammable when it builds up on fabric (clothing, bedding, dressings etc.). Washing clothing and bedding may reduce product build up but not totally remove it.

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 2.32% w/w 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).

Gastrointestinal

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 2.32% w/w 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.

Monitoring and Laboratory Tests

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

Respiratory

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.

Skin

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 side effects have been observed with oral forms of diclofenac sodium.

Cardiac and Vascular disorders
Uncommon: myocardial infarction, cardiac failure, palpitations, angina, arrhythmias, chest pain.
Very rare: hypertension, vasculitis.

Ear and labyrinth disorders
Common: vertigo.
Very rare: hearing impaired, tinnitus.

Eye disorders
Very rare: visual impairment (blurred vision, diplopia).

Gastrointestinal disorders
Very common: nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Uncommon: gastritis, gastrointestinal hemorrhage, hemorrhagic diarrhea, melena, hematemesis, gastric and intestinal ulcerations (with or without bleeding or perforation).
Very rare: lower gut disorders (including haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's disease), intestinal diaphragm disease, hyperacidity, stomatitis, glossitis, coated tongue, esophageal lesions, constipation, pancreatitis.

Haematologic
Very rare: thrombocytopenia, leukopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia, anemia secondary to gastrointestinal bleeding.

Hepatic

Common: elevations (≥3 times the upper normal limit) of serum aminotransferase enzymes (SGPT or ALT, SGOT or AST).
Uncommon: liver function disorders including hepatitis, hepatic necrosis, hepatic failure, jaundice.
Very rare: hepatitis fulminant.

Immune system disorders
Uncommon: hypersensitivity anaphylactic / anaphylactoid systemic reactions (including hypotension and shock).
Very rare: angioedema (including face edema).

Nervous system disorders
Common: dizziness, headache.
Uncommon: somnolence, malaise, impaired concentration, tiredness.
Very rare: sensory disturbances including paraesthesia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage), dysgeusia.

Psychiatric disorders
Very rare: disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Renal and urinary disorders
Uncommon: edema (facial, general, peripheral).
Very rare: acute kidney injury (acute renal failure), nephrotic syndrome, urinary abnormalities (*e.g*. haematuria and proteinuria), tubulointerstitial nephritis, renal papillary necrosis.

Respiratory disorders
Uncommon: asthma (including dyspnea).
Very rare: pneumonitis.

Skin and subcutaneous disorders
Common: rash, pruritus.
Uncommon: urticaria.
Very rare: bullous dermatitis, erythema, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), alopecia, photosensitivity reactions, purpura, Henoch-Schonlein purpura.

7.1 Special Populations

7.1.1 Pregnancy

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.

If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible and consult your doctor.

7.1.2 Breast-feeding

It is not known whether topical diclofenac is excreted in breast milk. However, studies in animals detected diclofenac in milk after oral administration. Precaution should be exercised because many drugs are excreted in human milk.

Diclofenac should only be used during lactation if the expected benefit justifies the potential risk to the newborn. If there are compelling reasons for using it, it should not be applied to the breasts nor should it be used at a higher dosage or for a longer period of time than recommended. Nursing women should consult their doctor before using the product.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

The key studies supporting the safety profile of diclofenac diethylamine gel 2.32% w/w include two randomised, double-blind, placebo controlled trials. This dataset included 513 patients with acute lateral ankle sprain, 173 placebo, 91 diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w was for up to 7 days. Skin and application site AEs are shown in Table 1.

Table 1 – Skin and application site AEs in double-blind, placebo-controlled studies

		Diclofenac diethylamine gel 2.32 w/w)		
No. (%) of patients	**Placebo N=173**	**o.d. N=91**	**b.i.d. N=169**	**t.i.d. 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 diclofenac diethylamine gel 2.32% w/w 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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

No clinical efficacy and safety pediatric studies have been conducted for diclofenac diethylamine 2.32% w/w.

8.3 Less Common Clinical Trial Adverse Reactions

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)

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

No clinical efficacy and safety pediatric studies have been conducted for diclofenac diethylamine 2.32% w/w.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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.

8.5 Post-Market Adverse Reactions

List of adverse reactions

The list 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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug and substance interaction studies have been performed as part of the clinical development of diclofenac diethylamine gel 23.2 mg/g / 2.32% w/w).

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.

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 diclofenac diethylamine gel 2.32% w/w.

9.4 Drug-Drug Interactions

No drug-drug interactions were noted in the clinical studies presented. Isolated interaction cases have been reported for topical diclofenac diethylamine gel from the marketplace.

Eighty-six worldwide cases of possible drug interactions with diclofenac diethylamine gel over

more than 4 billion patients treatment courses have been entered to the GlaxoSmithKline company world-wide safety database since first marketing:

In 64 cases, a possible interaction between diclofenac diethylamine gel and only one other interacting drug was reported:

- Twenty cases with other anti-inflammatory medications (diclofenac, ibuprofen, acetylsalicylic acid, naproxen, piroxicam, celecoxib, and an unknown anti-inflammatory medication); clinical adverse events reported were e.g. pain, arthralgia, somnolence, gastrointestinal haemorrhage, gastric ulcer, haemorrhoids, diarrhoea, renal failure, hypertension, tachycardia, rash).
- Twenty-four cases with oral anticoagulant therapy (acenocoumarol, warfarin, phenprocoumon, fluindione, clopidogrel, and an unknown anticoagulant); only 2 cases did not report any clinical adverse event. The most frequently reported clinical adverse events were haemorrhages (in five cases, e.g. gastrointestinal haemorrhage, epistaxis, gingival bleeding) and international normalized ratio increased (6 cases). Other adverse events reported included renal failure, prothrombin level decreased.
- Six cases with anti-hypertensives (with an unknown anti-hypertensive, candesartan, losartan, lisinopril, captopril, valsartan; clinical adverse events reported were e.g. blood pressure increased, acute kidney injury).
- Three cases of psychiatric disorders (3 cases of confusional state with rivastigmine).
- Five cases with unspecified medications (with clinical adverse events such as dermatitis allergic, skin irritation, renal disorder).
- Two cases of gastrointestinal haemorrhage associated with fluoxetine.
- One case of headache associated with pantoprazole.
- One case of toxicity to lithium associated with lithium.
- One case of erythema and urticaria associated with heat therapy.
- One case of renal disorder associated with torasemide.

In the remaining twenty-two cases, there were more than one possibly interacting medication, with no particular drugs and adverse events pattern identified.

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 Pain Relief Gel Extra Strength (diclofenac diethylamine gel 2.32% w/w).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Diclofenac is a well characterized, potent nonsteroidal anti-inflammatory drug (NSAID) with clinically proven anti-inflammatory, analgesic and antipyretic properties. 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. 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. 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.

Systemic absorption of diclofenac following topical application of diclofenac diethylamine gel 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, diclofenac diethylamine gel can be expected to produce a direct anti-inflammatory and analgesic effect with significantly less AEs than after the oral administration of diclofenac.

10.2 Pharmacodynamics

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

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.

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.

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. 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.

It has also been reported that topically applied diclofenac diethylamine 1.16% w/w 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.

The anti-inflammatory properties of diclofenac diethylamine gel 1.16% w/w were demonstrated in two placebo-controlled, double-blind, randomized trials (refer to Table 2), one in healthy volunteers using the urate crystal induced inflammation model (NGB 5) and the other in patients with chronic synovitis of the knee (NGB 8855). Diclofenac diethylamine gel 1.16% w/w (DDG) 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 2 - 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.	**DDG *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.	**DDG *vs*. Placebo**: reduced thermal index ($p<0.04$).

The potency of diclofenac diethylamine gel 1.16% w/w was compared 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 diclofenac diethylamine gel 1.16% w/w and indomethacin cream (84% and 85%, respectively, relative to a control vehicle). Diclofenac diethylamine gel 1.16% w/w demonstrated the most sustained anti-inflammatory effect, providing 75% inhibition when re-tested 48 hours after application.

10.3 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.

Percutaneous Absorption, Distribution, Metabolism, Excretion

Absorption: Absorption of various NSAIDs, including diclofenac, occurs to a depth of at least 3-4 mm through the underlying dermis and subcutaneous tissue. 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.

The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. After topical application to approximately 400 cm^2 of skin, the extent of system exposure as determined by plasma concentration of diclofenac diethylamine gel 2.32% w/w (2 applications/day) was equivalent to diclofenac diethylamine gel 1.16% w/w (4 applications/day). The relative bioavailability of diclofenac (AUC ratio) for diclofenac diethylamine gel 2.32% w/w 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 a diclofenac diethylamine gel 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%).

Diclofenac accumulates in the skin which acts as reservoir from where there is a sustained release of drug into underlying tissues. From the skin and underlying tissue, diclofenac preferentially distributes and persists in deep inflamed tissues (such as the joint), rather than in the bloodstream. Diclofenac is found in tissues at concentrations up to 20 times higher than in plasma.

Metabolism: Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, and mainly single and multiple hydroxylations, most of which are converted to glucuronide conjugates (hydroxyl-gluconates). The main metabolite is 4-hydroxy-diclofenac (30%-40%). All the metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination: The total systemic clearance of diclofenac from plasma is 263 $\pm$ 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.

A recent multiple-dose, 7 day PK study (VOPO-PE-102) was conducted with diclofenac diethylamine gel 1.16% w/w and diclofenac diethylamine gel 2.32% w/w. 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.

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.

When diclofenac diethylamine gel 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 diclofenac diethylamine gel 1.16% w/w per 500 cm^2 skin, left for 12 hours on non-occluded skin. 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 diclofenac diethylamine gel 1.16% w/w are between 50 (repeated dose) and 100 (single dose) times lower than after oral administration of diclofenac tablets. 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. Absorption of diclofenac through the skin can be increased by 3-10 times after application of an occlusive dressing.

<u>Diclofenac in target tissues</u>
After topical administration of diclofenac diethylamine gel 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. 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.

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. Publications have discussed 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.

11 STORAGE, STABILITY AND DISPOSAL

Pain Relief Gel Extra Strength (diclofenac diethylamine gel 2.32% w/w) should be stored between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for Pain Relief Gel Extra Strength.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

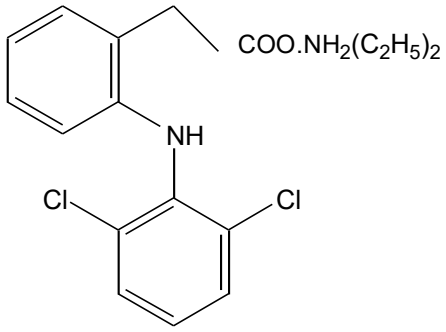
Drug Substance

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.

14 CLINICAL TRIALS

For the indication "ankle sprains", the study VOPO-P-307 with diclofenac diethylamine gel 2.32% w/w is considered pivotal. Study demographics and trial design for these studies are presented in Table 3.

14.1 Trial Design and Study Demographics

Table 3 - Summary of patient demographics for clinical trials					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Sex**
Diclofenac diethylamine gel 2.32% w/w					
VOPO-P-307	Randomized, double-blind, 3-treatment arm, multi-centre, placebo-controlled, parallel group Subjects with acute ankle sprain	Diclofenac diethylamine gel 2.32% w/w applied 3 times daily (t.i.d.) or twice daily (b.i.d.) for 7 days	n=162 ITT subjects* n=80 Diclofenac diethylamine gel 2.32% w/w b.i.d. n=82 placebo * all subjects who applied gel at least once n=139 PP subjects** n=71 Diclofenac diethylamine gel 2.32% w/w 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)	Diclofenac diethylamine gel 2.32% w/w) 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	<u>Men</u> Diclofenac diethylamine gel 2.32% w/w t.i.d*.: 49 (61.3%) b.i.d.: 49 (61.3%) Placebo: 54 (65.9%) <u>Women</u> Diclofenac diethylamine gel 2.32% w/w 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

14.2 Study Results

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 diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w 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 Visual Analogue Scale (VAS) 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 diclofenac diethylamine gel 2.32% w/w and to 51.3 mm in the placebo group; in the diclofenac diethylamine gel 2.32% w/w 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. Diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w 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), diclofenac diethylamine gel 2.32% w/w gel was statistically significantly better than placebo in reducing POM both in patients with baseline ≥80 mm (diclofenac diethylamine gel 2.32% w/w) 56.5 mm; placebo 27.6 mm; $p<0.0001$), as well as patients with baseline pain <80 mm (diclofenac diethylamine gel 2.32% w/w) 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 diclofenac diethylamine gel 2.32% w/w as compared to 21.8 mm for placebo.

Further evidence of the efficacy of diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w accelerated healing by 4 days.

Diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w 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 diclofenac diethylamine gel 2.32% w/w) 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) ($p<0.0001$).

Diclofenac diethylamine gel 2.32% w/w helps to relieve pain, decreases swelling, and improves patient mobility.

14.3 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 diclofenac diethylamine gel 2.32% w/w (2 applications/day) under non-occlusive and semi-occlusive conditions and diclofenac diethylamine gel 1.16% w/w (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 4.

Table 4 - 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)		

* diclofenac diethylamine gel 2.32% w/w

† diclofenac diethylamine gel 1.16% w/w

§ Expressed as the arithmetic mean (CV%) only

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 diclofenac diethylamine gel 1.16% w/w, diclofenac enteric coated tablet and a diclofenac patch formulation that was in development in GlaxoSmithKline, in 24 healthy volunteers. The main pharmacokinetic findings are summarized in Table 5.

Table 5 - Summary of pharmacokinetic data for Study NCH 17727B-510.20-02-01B		
Parameter	**Diclofenac diethylamine gel 1.16% w/w 4g (40 mg Diclofenac-Na equivalent) t.i.d.**	**Diclofenac Na 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 diclofenac diethylamine gel 1.16% w/w *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 diclofenac diethylamine gel 2.32% w/w (2 applications/day) under non-occlusive and semi-occlusive conditions and diclofenac diethylamine gel 1.16% w/w (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 diclofenac diethylamine gel 2.32% w/w *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 6 - Summary of pharmacokinetic data for Study VOPO-PE-102

Parameter	**Diclofenac diethylamine gel 2.32% w/w 2g (40 mg Diclofenac-Na equivalent) b.i.d.**	**Diclofenac Na 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)
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%). The liver is the primary site of metabolism for diclofenac to virtually inactive metabolites. 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%).

Bioequivalence Study with Clinical End Point

A multi-center, double-blind, randomized, placebo-controlled, parallel-group study, comparing Pain Relief Gel Extra Strength (Diclofenac diethylamine gel, 2.32%) (Taro Pharmaceuticals Inc.)

to VOLTAREN EMULGEL Extra Strength (Diclofenac Diethylamine Gel, 2.32%) (Canadian Reference Product) and both active treatments to a placebo control in subjects with acute sprain of lateral ankle, was conducted at 8 clinical sites in India.

Following 5 consecutive days twice daily (morning and evening) treatment, the Test (Pain Relief Gel Extra Strength) was determined to be bioequivalent to the Reference (VOLTAREN EMULGEL Extra Strength) in the treatment of acute sprain of lateral ankle. In the PP population, the 90% CIs for the ratio of Test-to-Reference were contained within the interval (0.80, 1.25) for the primary endpoint of mean change from Baseline to Day 5 in POM on VAS.

In the mITT population, the Test and Reference products were each shown to be statistically superior ($p<0.0001$) to Placebo vehicle for the primary endpoint.

Summary of Efficacy Analysis Results

Primary Efficacy Parameter: Change from Baseline to Day 5 in POM on VAS			
Parameter	**Test**	**Reference**	**Vehicle**
Per Protocol Population			
N	81	83	
LS Mean	-44.98	-42.33	
LS Mean Ratio	1.06		
90% CI Test/Reference	(0.99, 1.14)		
Modified Intent-to-Treat Population			
N	92	92	46
LS Mean[a]	-42.74		-21.98
LS Mean[b]		-41.53	-22.46
LS Mean Difference to Vehicle	-20.76	-19.06	
p-value vs Vehicle	<0.0001	<0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; LS = least square; POM = pain on movement; VAS = Visual Analog Scale

a. The LS Means from ANCOVA model on Test and Vehicle subjects only.
b. The LS Means from ANCOVA model on Reference and Vehicle subjects only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The toxicology of diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w 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 7 below.

Table 7 – Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w Toxicology Program

Study type and duration	Route of administration	Species	Compound administered
Single–dose toxicity	Topical, occluded	Rat	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Single-dose toxicity	Oral	Rat	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Repeat-dose toxicity: 3 months	Topical, occluded	Rabbit	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Local tolerance / photo-safety			
Phototoxicity, single dose	Topical	Mouse	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Phototoxicity, single dose	Topical	Guinea pig	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Photo-allergenicity	Topical	Guinea pig	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Skin sensitization	Topical, occluded	Guinea pig	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Skin irritation, 5 days	Topical, occluded	Rabbit	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Skin irritation, 5 days	Topical, occluded	Rabbit	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w
Eye irritation, single dose	Ocular	Rabbit	Diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w

Diclofenac diethylamine gel 11.6 mg/g / 1.16% w/w 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, diclofenac diethylamine gel 11.6 mg/g/ 1.16% w/w. 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.

Carcinogenicity: 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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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.

16.1.2 Comparative Toxicology

The toxicology of diclofenac diethylamine gel 2.32% w/w was investigated in a series of *in vivo* studies. The studies shown in Table 8 concentrated particularly on potential local tolerance, sensitisation and photo-safety issues.

Table 8 – Diclofenac diethylamine gel 23.2 mg/g/ 2.32% w/w 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 diclofenac diethylamine gel 23.2 mg/g and with 50 mg/cm2 diclofenac diethylamine gel 11.6 mg/g (occlusive condition for 4 and 18 hours)	Rabbits	Diclofenac diethylamine gel 23.2 mg/g Diclofenac diethylamine gel 11.6 mg/g
Cumulative 28 days skin irritation study in rabbits	Topical with 25 mg/cm^2 test product diclofenac diethylamine gel 23.2 mg/g and with 50 mg/cm^2 diclofenac diethylamine gel 11.6 mg/g (occlusive condition for 4 hours)	Rabbits	Diclofenac diethylamine gel 23.2 mg/g Diclofenac diethylamine gel 11.6 mg/g
Cumulative 90 days local tolerance	Topical with 10 mg/cm^2 and 20mg/cm^2 test product	Rabbits	Diclofenac diethylamine gel 23.2 mg/g
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	Diclofenac diethylamine gel 23.2 mg/g
Photosensitisation test	Topical with 3.8 mg/cm^2 test product	Albino guinea-pigs	Diclofenac diethylamine gel 23.2 mg/g

Topical treatment with diclofenac diethylamine gel 2.32% w/w appeared to be well tolerated.

Although treatment with diclofenac diethylamine gel 2.32% w/w yielded slightly higher irritation indices than with the marketed diclofenac diethylamine gel 1.16% w/w (possibly due to the increased potency of active ingredient), the irritation observed were considered as slight. All the erythemas found with diclofenac diethylamine gel 2.32% w/w and diclofenac diethylamine gel 1.16% w/w were barely perceptible and transient. In addition, diclofenac diethylamine gel 2.32% w/w was well tolerated in 28-day and 90-day cumulative irritation studies. Diclofenac diethylamine gel 2.32% w/w was neither sensitising nor photosensitising in guinea pigs. These results indicate that diclofenac diethylamine gel 2.32% w/w is likely to be well tolerated.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Voltaren Emulgel / Voltaren Emulgel Back and Muscle Pain / Voltaren Emulgel Joint Pain Regular Strength, diclofenac diethylamine 11.6mg/g (1.16% w/w), submission control 270680, Product Monograph, Haleon Canada ULC

2. Voltaren Emulgel Extra Strength/ Voltaren Emulgel Joint Pain Extra Strength, diclofenac diethylamine 23.2 mg/g (2.32% w/w), submission control 302636, March 30, 2026, Product Monograph, Haleon Canada ULC

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PAIN RELIEF GEL EXTRA STRENGTH

Diclofenac diethylamine gel 23.2 mg/g (2.32% w/w) Taro Standard

This patient medication information is written for the person who will be taking **Pain Relief Gel Extra Strength**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Pain Relief Gel Extra Strength**, talk to a healthcare professional.

What Pain Relief Gel Extra Strength is used for:

- For the relief of pain associated with recent (acute), localized 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.

How Pain Relief Gel Extra Strength works:

Pain Relief Gel Extra Strength is 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.

The ingredients in Pain Relief Gel Extra Strength are:

Medicinal ingredients: diclofenac diethylamine.

Non-medicinal ingredients: butylhydroxytoluene, carbomer homopolymer Type C, cocoyl caprylocaprate, diethylamine, fragrance, isopropyl alcohol, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylene glycol, purified water.

Propylene glycol 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.

Pain Relief Gel Extra Strength comes in the following dosage forms:

Pain Relief Gel Extra Strength 2.32% w/w gel comes in tubes of 30 g and 100 g in a carton with a

dosing card.

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

Do not use Pain Relief Gel Extra Strength 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.
- In the past you have had allergic reactions to diclofenac or any other NSAIDs such as ibuprofen, ASA or naproxen.
- 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.
- You are allergic to any of the nonmedicinal ingredients in the gel (see list of non-medicinal ingredients).
- You are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery.
- You are about to have or after heart surgery.

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Pain Relief Gel Extra Strength. Talk about any health conditions or problems you may have, including if you:

- Have a history of stomach ulcers or take medication for such gastrointestinal disorders.
- Are pregnant, or think you may be pregnant, or are planning to have a baby or are breast feeding.
- Are taking, or have recently taken, any other medicines, including Over the Counter drugs.

Other warnings you should know about:

Pain Relief Gel Extra Strength is <u>not intended</u> 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.

Do not use more than directed or for a longer than approved duration of use, unless under medical advice. Avoid applying on large areas of the skin.

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 Pain Relief Gel 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.

Do not smoke or go near open flames due to risk of severe burns. This product contains mineral oil which is potentially flammable when it builds up on fabric and may not be totally removed by washing.

Wash your hands after use. 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.

Pain Relief Gel Extra Strength is for EXTERNAL USE ONLY.

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

Never swallow it.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Pain Relief Gel Extra Strength:

- 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.

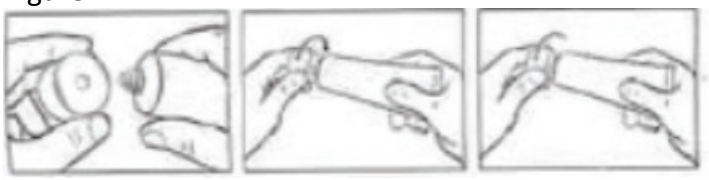
How to take Pain Relief Gel Extra Strength:

- To remove the security seal before first use, remove the cap off the tube. (see figure 1)
- Firmly insert the star-shaped groove located on the reverse side of the cap into the star-shaped security seal of the tube. (see figure 1)
- Firmly turn the cap to remove the security seal from the tube. (see figure 1)
- Measure the amount of the gel using the dosing card and then gently apply to the affected area, slowly rubbing into the skin. You may notice a slight cooling effect when you rub the gel in.
- After use, place the cap back on the tube and store in an upright position. (see figure 1)
- After application wipe your hands with a tissue and then wash to avoid accidental contact with the mouth and eyes. The tissue should be thrown in the trash after use.

- Wait until Pain Relief Gel Extra Strength dries before showering or bathing.

Do not throw away any medicines via wastewater (e.g. toilet or sink). Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

Figure 1:



Usual dose:

For adults between 18 to 65 years (extra strength):

- Apply 2 g of gel 2 times a day (morning and evening) on the affected 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.

Use no more than is required for the shortest period of time needed. 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:

If you dispense more gel than needed, wipe off the surplus gel with a tissue.

If you or a child swallows the gel, contact your doctor immediately.

If you think you, or a person you are caring for, have taken too much Pain Relief Gel Extra Strength, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Missed Dose:

If you miss applying Pain Relief Gel 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.

Possible side effects from using Pain Relief Gel Extra Strength:

These are not all the possible side effects you may have when taking Pain Relief Gel Extra Strength. If you experience any side effects not listed here, tell your healthcare professional.

Itching, reddening or slight irritation of the skin are common after use of Pain Relief Gel 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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Skin rash, itching, reddening or smarting of the skin		✓	✓
RARE **Some rare and very rare side effects might be serious**			
Skin rash with blisters; hives		✓	✓
Swelling of the face, lips, tongue or throat		✓	✓
Wheezing, shortness of breath or feeling of tightness in the chest (asthma)		✓	✓
VERY RARE			
The skin may be more sensitive to the sun. Possible signs are sunburn with itching, swelling and blistering		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

Store between 15°C and 30°C.

Pain Relief Gel Extra Strength should not be stored or used after the expiry date shown on the label.

Keep out of reach and sight of children.

If you want more information about Pain Relief Gel Extra Strength:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by calling 1-800-268-1975.

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