1.1 Name of the medicinal product: DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL

1.2 Qualitative and quantitative composition:

Composition: -
- Diclofenac Diethylamine BP 1.16%W/W eq. to Diclofenac Sodium BP (1.0 % W/W)
- Linseed Oil (Olium Lini) (Containing predominantly alpha Linolenic Acid) BP (3.0 % W/W)
- Methyl Salicylate BP (10.0 % W/W)
- Menthol BP (5.0 % W/W)
- Benzyl Alcohol BP (1.0 % W/W)
- Gel Base (- QS)

Sr. No.	Ingredients	Specifi - cation	Label Claim w/w	Over- ages added (In %)	Quantity in % w/w	Reason for Function
1.	Linseed oil	BP	3.00%	NA	3.00%	Medicament
2.	Diclofenac Diethylamine eq.to Diclofenac Sodium	BP	1.16% 1.00%	5%	1.218%	Medicament
3.	Methyl Salicylate	BP	10.00%	NA	10.00%	Medicament
4.	Menthol	BP	5.00%	NA	5.00%	Medicament
5.	Benzyl Alcohol	BP	1.00%	NA	1.00%	Preservative
6.	Propylene Glycol	BP	NA	NA	4.00%	Solvent
7.	Isopropyl alcohol	BP	NA	NA	3.00%	Solvent
8.	Diethanolamine	USP	NA	NA	1.00%	Alkalizing agent; Emulsifying agent
9.	Acrypol 940	USP	NA	NA	1.00%	Thickening agent
10.	Sodium Methyl Hydroxybenzoate	BP	NA	NA	0.100%	Preservative
11.	Sodium Propyl Hydroxybenzoate	BP	NA	NA	0.050%	Preservative
12.	Disodium Edetate	BP	NA	NA	0.020%	Preservative
13.	Cetomacrogol 1000	IH	NA	NA	1.000%	Emollient
14.	Light Liquid Paraffin	BP	NA	NA	4.000%	Emollient
15.	Creshmer RH 40	IH	NA	NA	0.700%	Emulsifying agent
16.	Chlorocresol	BP	NA	NA	0.100%	Preservative
17.	Butylated Hydroxytoluene	BP	NA	NA	0.050%	Preservative
18.	Purified Water	IH	NA	NA	64.800%	Vehicle

1.3 Pharmaceutical form: Gel

Description: White coloured gel.

1.4 Clinical Particulars

1.3.1.4.1 Therapeutic indications

DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL is indicated for the treatment of pain, swelling and inflammation due to musculo-skeletal disorders (such as sprains, strains, tendonitis, bursitis, hand, neck, shoulder pain, sciatica, muscle stiffness, joint pain, backache and lunage).

4.2 Posology and method of administration

Route: Topical

Method of administration

Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. If you purchased this product without a prescription, follow these directions closely.

DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL is for external use only.

Do not put gel in mouth or swallow it.

If the gel is swallowed accidentally, tell your doctor straight away or contact the accident and emergency department of your nearest hospital. If you accidentally get gel in your eyes or mouth, wash immediately with water and contact your doctor.

4.3 Contraindications

- The use of **DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL** is contraindicated in patients with a known hypersensitivity to diclofenac and/or any other active ingredient or excipient.
- It should not be administered in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) or salicylate idiosyncrasy. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- It is contraindicated in the setting of Coronary Artery Bypass Grafting (CABG) surgery.
- Product can cause convulsions. Contraindicated in infants below 2 years of age. Caution must be exercised when older children are treated. Avoid direct application into nostrils.
- **DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL** is contra-indicated on broken or irritated skin.

4.4 Special warnings and precautions for use

Precautions

Showering/bathing should be avoided for at least 1 hour after the application.

Patient should wash his/her hands after use, unless the hands are the treated joint. If diclofenac gel is applied to the hand(s) for treatment; patient should not wash the treated hand(s) for at least 1 hour after the application.

DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL should not be applied to open wounds.

Contact of diclofenac gel with eyes and mucous membranes should be avoided.

External heat and/or occlusive dressings should not be applied to treated joints.

Exposure of the treated joint(s) to sunlight should be avoided.

DICLOFENAC SODIUM, METHYL SALICYLATE, LINSEED OIL & MENTHOL GEL should not be used concomitantly with sunscreens, cosmetics, lotions, moisturizers, insect repellents, or other topical medications on the same skin sites has not been evaluated.

Concomitant use of diclofenac gel with oral NSAIDs has not been evaluated, and may increase adverse NSAIDs effects.

Wearing of clothing or gloves should be avoided for at least 10 minutes after applying diclofenac gel.

This product is contraindicated in infants below 2 years of age. Caution must be exercised when older children are treated.

Topical analgesic preparations containing methyl salicylate should be used with caution in patients at increased risk of developing salicylate adverse effects. This product contains methyl salicylate and when applied or rub on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joint pains may increase the chances of

bleeding. Children suffering from flu, chickenpox, or fever should avoid using this product because salicylates may induce Reyes Syndrome.

Warnings:

Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase (COX)-2 selective and non-selective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimise the potential risk for an adverse CV event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAIDs use. The concurrent use of aspirin and NSAIDs such as diclofenac does increase the risk of serious gastrointestinal (GI) events. Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

GI Effects – Risk of GI Ulceration, Bleeding and Perforation

NSAIDs, including diclofenac, can cause serious GI events, including bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for 1 year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared with patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAIDs therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and, therefore, special care should be taken in treating this population.

To minimise the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during diclofenac therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e. more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2–6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e. more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared with other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in

all trials who developed marked transaminase elevations.
In post-marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Post-marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulfilment hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.
Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and post-marketing experiences, transaminases should be monitored within 4–8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.
If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, abdominal pain, diarrhoea, dark urine, etc.), diclofenac sodium should be discontinued immediately.
To minimise the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and 'flu-like' symptoms), and the appropriate action patients should take if these signs and symptoms appear. To minimise the potential risk for an adverse liver-related event in patients treated with diclofenac sodium, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g. antibiotics, anti-epileptics).

Hypertension

NSAIDs, including diclofenac gel, can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including diclofenac gel, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac gel and throughout the course of therapy.

Congestive Heart Failure and Oedema

Fluid retention and oedema have been observed in some patients treated with NSAIDs, including diclofenac gel. Diclofenac gel should be used with caution in patients with fluid retention or heart failure.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state. No information is available from controlled clinical studies regarding the use of diclofenac gel in patients with advanced renal disease. Therefore, treatment with diclofenac gel is not recommended in patients with advanced renal disease. If diclofenac gel therapy is initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac gel. Diclofenac gel should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including diclofenac gel, can cause serious skin adverse events such as, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations, and the use of the drug should be discontinued at the first appearance of skin rash or any other signs of hypersensitivity. Diclofenac gel should not be applied to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of

the drug. Diclofenac gel should not be allowed to come into contact with the eyes or with mucous membranes. The effect of diclofenac gel under occlusive dressings has not been evaluated, and should be avoided.

Pregnancy

As with other NSAIDs, diclofenac gel should be avoided in late pregnancy, because it may cause premature closure of the ductus arteriosus.

Corticosteroid Treatment

Diclofenac gel cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Inflammation

The pharmacological activity of diclofenac in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed non-infectious, painful conditions.

Haematological Effects

Anaemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoeisis. Patients on long-term treatment with NSAIDs, including diclofenac gel, should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients being treated with diclofenac gel, who may be adversely affected by alteration in platelet function, such as those with coagulation disorders or patients receiving anticoagulants should be carefully monitored.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, diclofenac gel should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Sun Exposure

Patients should minimize or avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in an earlier onset of ultraviolet light induced skin tumours. The potential effects of diclofenac gel on skin response to ultraviolet damage in humans are not known.

Eye Exposure

Contact of diclofenac gel with eyes and mucosa, although not studied, should be avoided. Patients should be advised that if eye contact occurs, they should immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin

When diclofenac is administered with aspirin, the binding of diclofenac to protein is reduced, although the clearance of free diclofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Anticoagulants

The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

ACE Inhibitors

NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. The response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should

be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs, including diclofenac and lithium, are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs, including diclofenac, are administered concomitantly with methotrexate.

Cyclosporine

Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity. Caution should be used when diclofenac is administered concomitantly with cyclosporine.

Oral NSAIDs

Specific interaction studies of diclofenac gel and oral NSAIDs were not performed. Also, the clinical trials of diclofenac gel prohibited concomitant use of oral NSAIDS. There is systemic exposure to diclofenac following normal use of diclofenac gel, up to 6% of the systemic levels of a single oral dose of diclofenac sodium. Therefore, concomitant administration of diclofenac gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.

Topical Treatments

Concomitant use of diclofenac gel with other topical products, including topical medications, sunscreens, lotions, moisturisers and cosmetics, on the same skin site has not been tested and should be avoided because of the potential to alter local tolerability and absorption.

Warfarin

This product contains methyl salicylate and when applied or rubbed on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joints pains may increase the chances of bleeding.

4.6 Pregnancy and Lactation

Pregnancy:

The use of diclofenac, as with other NSAIDs, is associated with the adverse foetal cardiovascular effect of premature closure of the ductus arteriosus.

Safety for use of menthol and methyl salicylate in pregnancy has not been established; therefore, the potential benefit of the product should be weighed against the possible risks to the mother and child.

Lactation:

It is not known whether diclofenac is excreted in human milk; however, studies in animals detected diclofenac in the milk after oral administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac gel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility:

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including diclofenac sodium topical gel, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including diclofenac sodium topical gel, in women who have difficulties conceiving or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

The following adverse reactions may happen:

· Cardiovascular thrombotic events
· GI bleeding, ulceration and perforation
· Hepatotoxicity
· Hypertension
· Renal toxicity and hyperkalaemia
· Serious skin reactions
· Haematologic toxicity

Headache, dizziness, nausea and vomiting, skin irritation, contact dermatitis, rash, itching, redness or swelling, burning or stinging sensation may occur.

May cause hypersensitivity/allergic reactions in some individuals with sensitive skin

4.9 Overdose

Diclofenac diethylamine

There has been no experience of overdose with diclofenac gel.

No events of accidental ingestion have been reported with diclofenac gel. Effects like those observed after an overdose of diclofenac tablets can be expected if substantial amounts of diclofenac gel are ingested.

Symptoms of methyl salicylate overdose:

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage.

Symptoms of more severe intoxication or of acute poisoning following overdose include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis.

Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur.

Symptoms of menthol overdose

Ingestion of significant quantities is reported to cause symptom: severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma; instant collapse in infants after the local application of menthol to their nostrils.

Seizures may be the first clinical sign of severe toxicity of camphor; however, seizures are usually self-limited. Severe toxicity of camphor can result in delirium, visual hallucinations, cerebral edema, and status epilepticus. Systemic toxicity may include hypotension, tachycardia, respiratory failure, and death.

Treatment

The stomach should be emptied by gastric lavage or administration of oral activated charcoal Fluid and electrolyte management is the mainstay of treatment with the immediate aim of correction of acidosis, hyperpyrexia, hypokalaemia and dehydration if present. Any convulsions must be controlled first through supportive care including anticonvulsant therapy.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action:

The mechanism of action of diclofenac is similar to that of other NSAIDs. Diclofenac inhibits the enzyme, COX, an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacyclin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.

Menthol dilates the blood vessels causing a sensation of coldness, followed by an analgesic effect. Menthol also acts as a penetration enhancer, increasing the penetration of drugs when applied on the skin, to give a faster onset of action.

Methyl salicylate is a salicylic acid derivative. Salicylates inhibit cyclooxygenase, thereby reducing the formation of prostaglandins, and cause platelet dysfunction. Methyl salicylate is used topically as a counter-irritant. Upon application, it is absorbed through the skin and is applied for the relief of pain in rheumatic conditions and painful muscle or joints.

Pharmacodynamic Effects

Diclofenac, the active component of RELAXDON has anti-inflammatory, anti-nociception, and antipyretic effects. Menthol dilates the blood vessels causing a sensation of coldness, followed by an analgesic

effect. Salicylates inhibit cyclooxygenase, thereby reducing the formation of prostaglandins, and cause platelet dysfunction.

5.2 Pharmacokinetic properties

Diclofenac Sodium

The pharmacokinetics of diclofenac gel were assessed in healthy volunteers following repeated applications during 7 days of diclofenac gel to one knee (4 × 4 g per day) or to two knees and two hands (4 × 12 g per day) versus the recommended oral dose of diclofenac sodium for the treatment of osteoarthritis (3 × 50 mg per day). A summary of the pharmacokinetic parameters is presented in Table 2.

Treatment	**C_{max} (ng/mL) Mean ± SD % of Oral (CI)**	**t_{max} (hr) Median (range)**	**AUC_{024} (ng•h/mL) Mean ± SD % of Oral (CI)**
Diclofenac gel 4 × 4 g per day (=160 mg diclofenac sodium per day)	15 ± 7.3 0.6%(0.5–0.7)	14 (0–24)	233 ± 128 5.8% (5–6.7)
Diclofenac gel 4 × 12 g per day (=480 mg diclofenac sodium per day)	53.8 ± 32 2.2% (1.9–2.6)	10 (0–24)	807 ± 478 19.7% (17–22.8)
Diclofenac sodium tablets, orally 3 × 50 mg per day (=150 mg diclofenac sodium per day)	2270 ± 778 100%	6.5 (1–14)	3,890 ± 1710 100%
C_{max} = maximum plasma concentration; t_{max} = time of C_{max}; $AUC_{0–24}$ = area under the concentration-time curve; SD = standard deviation; CI = confidence interval			

Systemic exposure (area under the concentration-time curve) and maximum plasma concentrations of diclofenac are significantly lower with diclofenac gel than with comparable oral treatment of diclofenac sodium.

Systemic exposure with recommended use of diclofenac gel (4 × 4 g per day applied to one knee) is on average 17 times lower than with oral treatment. (Basis: treatment with diclofenac gel of one knee, 4 times a day versus 50 mg, 3 times a day of oral diclofenac tablets). The amount of diclofenac sodium that is systemically absorbed from diclofenac gel is on average 6% of the systemic exposure from an oral form of diclofenac sodium.

The average peak plasma concentration with recommended use of diclofenac gel (4 × 4 g per day applied to one knee) is 158 times lower than with the oral treatment.

The pharmacokinetics of innovator diclofenac gel has been tested under conditions of moderate heat (application of a heat patch for 15 minutes prior to gel application) and of moderate exercise (first gel application followed by a 20-minute treadmill exercise). No clinically relevant differences of systemic absorption and of tolerability were found between applications of diclofenac gel (4 × 4 g per day on one knee) with and under the conditions tested. However, the pharmacokinetics of diclofenac gel was not tested under the condition of heat application following gel application. Therefore, concurrent use of diclofenac gel and heat is not recommended.

Linseed Oil

The absorption of linseed oil is proportional to the surface area involved, duration of exposure, concentration and skin integrity. Absorption characteristics of linseed oil vary with the dose, formulation and route of administration. Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin or application to large areas of skin

Methyl salicylate

May be absorbed through intact skin. The absorption of topical salicylates is proportional to the surface area involved, duration of exposure, concentration and skin integrity. Absorption characteristics of salicylates vary with the dose, formulation and route of administration. Percutaneous absorption is

enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin or application to large areas of skin

Both the rate and extent of absorption increases after repeated application; increasing the bioavailability. Methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application. At therapeutic levels, the half-life of salicylates is 2-4 hours. As salicylate level increase into the toxic range, the half-life can be greater than 18 hours.

Menthol

After absorption, menthol is excreted in the urine and bile as a glucuronide.

5.3 Preclinical safety data

None stated.

6 Pharmaceutical particulars

6.1 List of excipients

Benzyl Alcohol, Propylene Glycol, Isopropyl alcohol, Diethanolamine, Acrypol 940, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, Disodium Edetate, Cetomacrogol 1000, Light Liquid Paraffin, Creshmer RH 40, Chlorocresol, Butylated Hydroxytoluene and Purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

- Store at a temperature below 30° C.
- Do not freeze, Protect from direct sunlight.
- Keep all medicines out of the reach of children.
- Avoid contact with eyes.
- Keep the tube tightly close after use.

6.5 Nature and contents of container

Primary packing : 30 gm of cream filled in lami tube.

Secondary packing: Such one lami tube is packed in a carton along with leaflet.

Tertiary packing: 10 Cartons are packed in a shrink. Such 50 shrinks are packed in 5 ply shipper. Shippers to be sealed with BOPP tape.

6.6 Special precautions for disposal and other handling

None

7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. PRIYA PHARMACEUTICAL NIG. LTD.** No. C-1, Airport Road, 2F, Kano State, Nigeria.
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. ASTAMED HEALTHCARE (I) PVT. LTD.** Plot No. 2 & 3, Phase II, Genesis Ind. Complex, Kolgaon, Dist. Thane, Tal. Palghar, 401404 Maharashtra State, India
Contact person's phone number	+91 9920633632/ +91 9967364363
Contact person's email	nayan.thakkar@astamed.com