

**PALNAC GEL
DICLOFENAC DIETHYLAMINE, LINSEED OIL, METHYL SALICYLATE &
MENTHOL GEL**

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

PALNAC GEL

**DICLOFENAC DIETHYLAMINE, LINSEED OIL, METHYL SALICYLATE &
MENTHOL GEL**

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each gm Contain:

Linseed oil BP 3.0 % w/w

Diclofenac Diethylamine BP..... 1.16% w/w

Eq. to Diclofenac Sodium 1.00 % w/w

Methyl Salicylate BP..... 10.0 % w/w

Menthol BP 5.0 % w/w

Preservative:

Benzyl Alcohol BP 1.0 %w/w

Gel Base Q.S.

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Qualitative & Quantitative Composition Formula:

Batch size: 750 kg

Sr. No.	Ingredients	Specification	Label Claim in %	Qty/gm (mg)	Qty/tube in gm	Qty/batch (kg)	Reason for inclusion
1	Diclofenac Diethylamine Eq. to. Diclofenac sodium	BP	1.16% w/w $\cong 1.0$ %w/w	11.60	0.348	8.7	Analgesic, Anti-inflammatory
2	Linseed Oil	BP	3.0% w/w	30.00	0.90	22.5	Emollient
3	Methyl Salicylate	BP	10.0% w/w	100.00	3.00	75	Counter-irritant
4	Menthol	BP	5.0% w/w	50.00	1.50	37.5	Topical antipruritic.
5	Benzyl alcohol	BP	1.0 %w/w	10.00	0.300	7.5	Preservative
6	Polysorbate 80	BP	--	10.00	0.300	7.5	Emulsifier
7	Butylated Hydroxy Toluene	BP	--	0.10	0.003	0.075	Preservative
8	Butylated Hydroxy Anisole	BP	--	0.11	0.0033	0.0825	Preservative
9	Polyoxyl 40 Hydrogenated castor oil	USP	--	40.00	1.20	30.0	Solubilizer agent.
10	Citric acid monohydrate	BP	--	0.10	0.0030	0.075	Buffering Agent
11	Disodium EDTA	BP	--	1.00	0.03	0.75	Chelating Agent
12	Carbopol 940	USP	--	14.00	0.420	10.5	Viscosity Agent
13	Isopropyl Alcohol	BP	--	40.00	1.200	30	Pharmaceutical Aid
14	Propylene glycol	BP	--	120.00	3.600	90	Humectant
15	Triethanolamine	BP	--	21.06	0.6318	15.795	Buffering Agent
16	Purified water	BP	--	q.s	q.s	q.s to 750 kg	Solvent

Where, BP – British Pharmacopoeia,
USP– United State Pharmacopoeia,
IH: In-House,
Q.S. – Quantity sufficient

Calculation:

Molecular weight of Diclofenac Diethylamine = 369.29

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A-590/591, TTC Ind. Area, MIDC Industrial Area, Mahape, Navi Mumbai, Maharashtra-400710. India.

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Molecular weight of Diclofenac sodium = 318.13

Mole. Wt of Diclofenac Diethylamine X L.C

Wt of Diclofenac Diethylamine = -----

Mole. Wt of Diclofenac sodium

369.29 X 1.0

= -----

318.13

= 1.16 %

- Molecular weight of Diclofenac Diethylamine is 369.29 mg equivalent to Molecular weight of Diclofenac sodium 318.13mg
- Therefore, 1.16 % of Diclofenac Diethylamine is equivalent to Molecular weight of Diclofenac sodium 1.0 %

3. Pharmaceutical form

Topical Gel

White smooth gel

4. Clinical Particulars

4.1 Therapeutic Indications:

Local treatment of inflammatory and degenerative forms of diseases of musculoskeletal system, which are accompanied by pain and swelling such as;

Rheumatoid arthritis, Ankylosing spondylitis, Acute podagric inflammation, Psoriatic and traumatic arthritis, Rheumatic damage to soft tissues (tendonitis, bursitis, myositis)

Other painful conditions like: Sprain, Strain, Lumbago, Sports injury, Muscular pain, Neck pain, Frozen shoulder, Wrist pain, Ankle sprain.

Pain in muscles and joints due to hard physical activity.

PALNAC 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)

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4.2 Posology and method of administration:

Linseed Oil, Diclofenac Diethylamine, Methyl Salicylate and Menthol Gel should be rubbed gently into the skin. Depending on the size of the affected site to be treated 2 - 4 gm. It should be applied 3 - 4 times daily and rubbed in lightly. After application, the hands should be washed unless they are the site being treated. Use in the elderly: The usual adult dosage may be used.

Linseed Oil, Diclofenac Diethylamine, Methyl Salicylate and Menthol Gel

may also be given to further treatment with other dosage forms of Ortofen or as prescribed by the physician.

Do not apply gel on broken skin.

Route of Administration: Topical

4.3 Contraindications

The use of PALNAC GEL is contraindicated in patients with a known hypersensitivity to diclofenac and/or any other active ingredient or excipient.

- PALNAC GEL 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.

- PALNAC GEL 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.

- PALNAC GEL is contra-indicated on broken or irritated skin.

4.4 Special warnings and precautions for use

Linseed Oil, Diclofenac Diethylamine, Methyl Salicylate and Menthol Gel should not be taken by mouth and should not be used under occlusive, airtight dressings. It should be applied only to intact skin surfaces and not to skin wounds or open injuries. It should not come in contact with eyes or mucous membranes.

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The safety of the concomitant use of sunscreens, cosmetics or other topical medications and Ortofen is unknown

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.

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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

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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, fulminant 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).

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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

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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 erythropoiesis. Patients

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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.

Special Precautions

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

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- 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 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 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.

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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

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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:

Pregnant Women

Teratogenic Effects – Pregnancy Category C

The safety of diclofenac gel has not been established during pregnancy. There are no well-controlled studies of diclofenac in pregnant women. Human and animal studies indicate that

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diclofenac crosses the placenta. In late pregnancy, as with other NSAIDs, diclofenac gel should be avoided because it may cause premature closure of the ductus arteriosus.

Studies in mice, rats, and rabbits in which diclofenac was administered orally throughout gestation revealed no evidence of teratogenicity despite the induction of maternal toxicity and foetal toxicity corresponding to a human equivalent dose approximately 4.5-, 2-, and 9-fold (mouse, rat, and rabbit, respectively) of the maximum human topical dose of diclofenac gel (based on bioavailability and body surface area comparison).

Non-Teratogenic Effects

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.

Labour and Delivery

In rat studies with oral NSAIDs, including diclofenac, as with other drugs known to inhibit prostaglandin synthesis, there is an increased incidence of dystocia and delayed parturition corresponding to a human equivalent dose approximately like the maximum recommended clinical dose (based on bioavailability and body surface area comparison). The effects of diclofenac gel on labour and delivery in pregnant women are unknown.

Lactating Women

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.

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

Females and Males of Reproductive Potential

Female Infertility

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.

Paediatric Patients

Safety and effectiveness in paediatric patients have not been established.

Geriatric Patients

Of the total number of subjects treated with diclofenac gel in clinical studies, 498 were 65 years of age and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, but greater sensitivity to the effect of NSAIDs in some older individuals cannot be ruled out. Diclofenac, as with any NSAID, is known to be substantially excreted by the kidneys, and the risk of toxic reactions to diclofenac gel may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using diclofenac gel in the elderly, and it may be useful to monitor renal function.

Renal Impairment

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

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recommended in patients with advanced renal disease. If diclofenac gel therapy is initiated, close monitoring of the patient's renal function is advisable.

Hepatic Impairment

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.

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).

4.7 Effects on the ability to drive and use machines

No evidence available

4.8 Undesirable effects:

Diclofenac Sodium

The following adverse reactions may happen:

- Cardiovascular thrombotic events
- GI bleeding, ulceration and perforation
- Hepatotoxicity
- Hypertension
- Heart failure and oedema
- Renal toxicity and hyperkalaemia

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- Anaphylactic reactions
- Serious skin reactions
- Haematologic toxicity

During clinical development, 913 patients were exposed to diclofenac sodium topical gel in randomised, double-blind, multicentre, vehicle-controlled, parallel-group studies in osteoarthritis of the superficial joints of the extremities. Of these, 513 patients received diclofenac sodium topical gel for osteoarthritis of the knee and 400 were treated for osteoarthritis of the hand. Additionally, 583 patients were exposed to diclofenac sodium topical gel in an uncontrolled, open-label, long-term safety trial in osteoarthritis of the knee. Of these, 355 patients were treated for osteoarthritis of 1 knee and 228 were treated for osteoarthritis of both knees. Duration of exposure ranged from 8 to 12 weeks for the placebo-controlled studies, and up to 12 months for the open-label safety trial.

Short-Term, Placebo-Controlled Trials

Adverse Reactions Observed in At Least 1% of Patients Treated with Diclofenac Gel

Non-serious adverse reactions that were reported during the short-term, placebo-controlled studies comparing diclofenac gel and placebo (vehicle gel) over study periods of 8–12 weeks (16 g per day), were application site reactions. These were the only adverse reactions that occurred in >1% of treated patients with a greater frequency in the diclofenac gel group (7%) than the placebo group (2%). Table 1 lists the types of application site reactions reported. Application site dermatitis was the most frequent type of application site reaction and was reported by 4% of patients treated with diclofenac gel, compared to 1% of placebo patients.

Table 1: Non-serious application site adverse reactions ($\geq 1\%$ diclofenac gel patients) – short-term controlled trials

	Diclofenac Gel N=913, N (%)	Placebo (vehicle) N=876, N (%)
Adverse Reaction [†]		

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Any application site reaction	62 (7)	19(2)
Application site dermatitis	32(4)	6(<1)
Application site pruritus	7(<1)	1(<1)
Application site erythema	6(<1)	3(<1)
Application site paraesthesia	5(<1)	3(<1)
Application site dryness	4(<1)	3(<1)
Application site vesicles	3(<1)	0
Application site irritation	2(<1)	0
Application site papules	1(<1)	0

†Preferred term according to MedDRA 9.1

In the placebo-controlled trials, the discontinuation rate due to adverse reactions was 5% for patients treated with diclofenac gel, and 3% for patients in the placebo group. Application-site reactions, including application-site dermatitis, were the most frequent reason for treatment discontinuation.

Long-term, Open-label, Safety Trial

In the open-label, long-term safety study, distribution of adverse reactions was similar to that in the placebo-controlled studies. In this study, where patients were treated for up to 1 year with up

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to 32 g per day of diclofenac gel, application site dermatitis was observed in 11% of patients. Adverse reactions that led to the discontinuation of the study drug were experienced in 12% of patients. The most common adverse reaction that led to discontinuation of the study was application-site dermatitis, which was experienced by 6% of patients.

Nicolau's syndrome, also known as livedo-like dermatitis or embolia cutis medicamentosa, is a rare complication reported following intramuscular diclofenac sodium injection.

Menthol and Methyl salicylate

PALNAC GEL contain Menthol and Methyl salicylate hence can cause convulsions.

4.9 Overdose

Diclofenac Sodium

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 following acute oral NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. GI bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur after an overdose.

In the event of oral ingestion resulting in significant systemic side effects, it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine.

The effect of dialysis or haemoperfusion in the elimination of diclofenac (99% protein-bound) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac. Supportive and symptomatic treatment should be

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given for complications such as renal failure, convulsions, GI irritation, and respiratory depression.

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.

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5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesic / Antipyretic / Anti-inflammatory

ATC code: M01AB55

Linseed Oil, Diclofenac Diethylamine, Methyl Salicylate and Menthol Gel is a multi-action topical gel for quick relief from pain, swelling & inflammation.

Diclofenac diethylamine is used topically as gel containing the equivalent to 1% of diclofenac sodium for local symptomatic relief of pain and inflammation. It is absorbed percutaneously.

A non-steroidal anti-inflammatory analgesic drug which inhibits prostaglandin synthesis by inhibition of cyclooxygenase (COX) thus reduces pain and inflammation.

Methyl Salicylate is a known anti-inflammatory agent. Methyl salicylate is a salicylic acid derivative that is an irritant to the skin and is used topically for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Menthol when applied to an affected area in gel form, menthol rapidly cools tendons and muscles.

Menthol primarily activates the cold-sensitive receptors in the skin. Menthol, after topical application, causes a feeling of coolness due to stimulation of 'cold' receptors by inhibiting Ca⁺⁺ currents of neuronal membranes.

Menthol is also a counter irritant and a mild analgesic.

Menthol is a vasodilator; it dilates blood vessels, produces a feeling of coolness and produces analgesia.

Linseed Oil is a very rich source of Alpha-linolenic Acid (ALA) (an essential fatty acid). Incorporation of ALA and its metabolites in cell membranes can affect membrane fluidity and may play a role in anti-inflammatory activity. Once ALA (which is different from arachidonic acid) is incorporated into cell membrane it produces eicosanoids (different types of chemicals than prostaglandins). The eicosanoids have anti-inflammatory properties.

Pharmacodynamic Properties

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

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

5.2 Pharmacokinetic properties

When applied topically, diclofenac sodium, methyl salicylate and linseed oil are absorbed and penetrate into the subcutaneous tissue, muscle tissue and joint capsule.

After cutaneous application of Diclofenac Sodium Gel a rapid onset of Diclofenac absorption can be observed leading to measurable plasma levels as early as 30 minutes. The achieved concentration of Diclofenac is about 50 times lower those achieved following oral administration of equivalent amounts of Diclofenac.

5.3 Pre-clinical Safety:

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr. No.	Ingredients	Specification
1.	Benzyl alcohol	BP
2.	Polysorbate 80	BP
3.	Butylated Hydroxy Toluene	BP
4.	Butylated Hydroxy Anisole	BP
5.	Polyoxyl 40 Hydrogenated castor oil	USP
6.	Citric acid monohydrate	BP
7.	Disodium EDTA	BP
8.	Carbopol 940	USP
9.	Isopropyl Alcohol	BP
10.	Propylene glycol	BP
11.	Triethanolamine	BP

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12.	Purified water	BP
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6.2 Incompatibilities

Not applicable,

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry Place, protect from sunlight.

6.5 Nature and contents of container

PALNAC GEL

30 gm Tube

30 gm of Aluminium Collapsible Tube is packed in carton along with pack insert.

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. Marketing Authorization Holder:

PAL PHARMACEUTICAL INDUSTRIES LTD.,

Plot 102 Maganda Road, Bompai

Industrial Area, Kano, Nigeria.

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9-Manufacturer Name:

GOPALDAS VISRAM & COMPANY LIMITED.

GOPALDAS VISRAM & CO. LTD.

A-590/591, TTC Ind. Area, MIDC Industrial Area, Mahape, Navi Mumbai, Maharashtra-400710. India.

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Plot No.A/590-591, T.T.C. INDUSTRIAL AREA, M.I.D.C.,

Mahape, Navi Mumbai - 400 710, India.

10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:



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