1. NAME OF THE MEDICINAL PRODUCT

JAWADICLO GEL

(Diclofenac Diethylamine eq. to Diclofenac sodium 1.16 % w/w, Methyl Salicylate 10.0 % w/w, Linseed oil 3.0 % w/w and Menthol 5.0 % w/w Gel)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac Diethylamine BP

Eq. to Diclofenac Sodium 1.16%w/w

Methyl Salicylate BP 10%w/w

Linseed oil BP 3.0%w/w

Menthol BP 5.0%w/w

Preservative

Benzyl Alcohol BP 1.0%w/w

Gel Base q.s

3. PHARMACEUTICAL FORM

Topical dosage form- Gel

A white gel with a strong menthol odour and a smooth texture gel packed in a 20G collapsible tube with aluminium seal and a screw cap

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For local symptomatic relief of pain and inflammation in:

- Trauma of the tendons, ligaments, muscle and joints e.g. due to sprains, strains and bruises.
- Localized forms of soft tissue rheumatism.

It is recommended that treatment should be reviewed after 14 days in these indications. These indications should be not warrant treatment for more than 6 weeks.

- For the symptomatic treatment of osteoarthritis of superficial joints such as a knee.
- In the symptomatic treatment of osteoarthritis, therapy should be reviewed after 4 weeks.

4.2 Posology and method of administration

Posology

Topical application

Adults*: JAWADICLO GEL should be rubbed gently into the skin. Depending on the size of the affected site to be treated 2-4g (a circular shaped mass approximately 2.0-2.5cm in diameter) should be applied 3-4 times daily. After application, the hands should be washed unless they are the site being treated.

Elderly: The usual adult dose may be used.

Children and adolescents below 14 years: There are insufficient data on efficacy and safety available for children and adolescents below 14 years of age (see also contraindications section 4.3). In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

* It is recommended that treatment be reviewed after 14 days. These indications should not warrant treatment for more than 6 weeks.

4.4 Contraindications:

Hypersensitivity to diclofenac or to any of the excipients contained in the gel .

Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).

During the last trimester of pregnancy.

Use in patients hypersensitive to propylene glycol or isopropanol or other components of the gel base.

The use in children and adolescents aged less than 14 years is contraindicated.

4.5 Special warnings and precautions for use:

The possibility of systemic adverse events from application of JAWADICLO GEL cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the product information on systemic forms of diclofenac).

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

JAWADICLO GEL can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

JAWADICLO GEL should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should not be ingested.

Side effects include itching, reddening or smarting of the skin or skin rash. Photosensitivity reactions have been observed in isolated cases.

Asthma has been rarely reported in patients using topical non steroidal anti-inflammatory drugs (NSAID) preparations.

Application over extensive areas for prolonged periods or application in excess of recommended dosage may give rise

to systemic effects. These include gastrointestinal disturbances and bleeding, irritability, fluid retention, rash, hepatitis, renal dysfunction, anaphylaxis and rarely blood dyscrasias, bronchospasm and erythema multiforme.

This product should only be used with great caution in patients with a history of peptic ulcer, gastrointestinal bleeding, hepatic or renal insufficiency, or bleeding diathesis, or intestinal inflammation. Circulating levels of the active drug substance are low but the theoretical risk in these patients should be considered.

Information concerning excipients

JAWADICLO GEL contains propylene glycol, which may cause mild, localised skin irritation in some people.

4.5 Interaction with other medicinal products and other forms of interaction

Since systemic absorption of diclofenac from topical application is very low, such interactions are very unlikely. However, the following interactions occur with oral forms of JAWADICLO GEL:

Lithium and digoxin: JAWADICLO GEL may increase plasma levels of lithium or digoxin.

Anticoagulants: Although clinical investigations do not appear to indicate that JAWADICLO GEL has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Ant diabetic agents: Clinical studies have shown that JAWADICLO GEL can be given together with oral anti diabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Ciclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including JAWADICLO GEL. This might be mediated through combined renal anti-prostaglandin effects of both the NSAID and ciclosporin.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the non-steroidal anti-inflammatory drugs.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other NSAIDs and steroids: Co-administration of JAWADICLO GEL with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although the clinical significance is unknown.

Diuretics: Various NSAIDs are liable to inhibit the activity of diuretics. Concomitant treatment with potassium sparing diuretics may be associated with increased serum potassium levels; hence serum potassium should be monitored.

4.6 Paediatric population

Children and adolescents below 14 years: There are insufficient data on efficacy and safety available for children and adolescents below 14 years of age (see also contraindications section 4.3). In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

* It is recommended that treatment be reviewed after 14 days. These indications should not warrant treatment for more than 6 weeks.

4.7 Interaction with other medicinal products and other forms of interaction
Contraindications of concomitant use

Since systemic absorption of diclofenac from topical application is very low, such interactions are very unlikely. However, the following interactions occur with oral forms of **JAWADICLO GEL**:

Lithium and digoxin: JAWADICLO GEL may increase plasma levels of lithium or digoxin.

Anticoagulants: Although clinical investigations do not appear to indicate that JAWADICLO GEL has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Ant diabetic agents: Clinical studies have shown that JAWADICLO GEL can be given together with oral anti diabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Ciclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including JAWADICLO GEL. This might be mediated through combined renal anti-prostaglandin effects of both the NSAID and ciclosporin.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the non-steroidal anti-inflammatory drugs.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other NSAIDs and steroids: Co-administration of JAWADICLO GEL with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although the clinical significance is unknown.

Diuretics: Various NSAIDs are liable to inhibit the activity of diuretics. Concomitant treatment with potassium sparing diuretics may be associated with increased serum potassium levels; hence serum potassium should be monitored.

4.8 Additional information on special populations

4.9 Fertility, Pregnancy and lactation

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including

cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic Period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. 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. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of JAWADICLO GEL1.16% no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional. Under this circumstance, JAWADICLO GEL should not be applied on the breasts of nursing mothers, nor elsewhere on large

4.10 Effects on ability to drive and use machines

Patients, who experience dizziness or other central nervous system disturbances, including visual disturbances, while Taking NSAIDs should refrain from driving or operating machinery.

4.11 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following

Convention: 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), not known: cannot be estimated

from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Hypertension

Infections and infestations: Very rare:	Rash pustular.
Immune system disorders: Very rare:	Hypersensitivity (including urticaria), Angioneurotic oedema
Respiratory, Thoracic and mediastinal disorders Very rare:	Asthma
Skin and subcutaneous tissue disorders Common: Rare: Very rare:	Dermatitis (including contact dermatitis), Rash, Erythema, Eczema, Pruritus. Dermatitis bullous. Photosensitivity reaction

JAWADICLO GEL is usually well tolerated. Itching, reddening or smarting of the skin, or skin rash, commonly occurs. Photosensitivity reactions have very rarely been observed.
Systemic absorption of JAWADICLO GEL is low compared with plasma levels obtained following oral forms of Docofast. However, where JAWADICLO GEL is applied to a relatively large area of skin and over a prolonged period, the possibility of systemic side effects cannot be completely excluded.
Asthma has very rarely been reported in patients using topical NSAID preparations.

4.12 Overdose

The low systemic absorption of topical diclofenac renders over dosage very unlikely. However, undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if topical diclofenac is inadvertently ingested (1 tube of 100g contains the equivalent of 1000mg diclofenac sodium). In the event of accidental ingestion, resulting in significant systemic side-effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory drugs should be used. Gastric

decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Management of over dosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from over dosage JAWADICLO GEL. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mode of action:

Diclofenac is a non-steroidal anti-inflammatory (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac.

JAWADICLO GEL is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, JAWADICLO GEL relieves pain, decreases swelling, and shortens the time to return to normal function.

Clinical data have demonstrated that JAWADICLO GEL reduces acute pain one hour after initial application ($p < 0.0001$ versus placebo gel). Ninety-four percent (94%) of patients responded to JAWADICLO GEL after 2 days of treatment versus 8% with placebo gel ($p < 0.0001$). Resolution of both pain and functional impairment were achieved after 4 days of treatment with JAWADICLO GEL ($p < 0.0001$ versus placebo gel).

Due to an aqueous-alcoholic base it exerts a soothing and cooling effect.

5.2 Pharmacokinetic properties

Absorption

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. Absorption amounts to about 6 % of the applied dose of diclofenac after topical application of 2.5 g JAWADICLO GEL on 500 cm^2 skin, determined by reference to the total renal elimination,

compared with docofast tablets. A 10-hour occlusion leads to a three-fold increase in the amount of diclofenac absorbed.

Distribution

Diclofenac concentrations have been measured from plasma; synovial tissue and synovial fluid after topical administration of JAWADICLO 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 there, diclofenac preferentially distributes and persists in deep inflamed tissues, such as the joint, where it is found in concentrations up to 20 times higher than in plasma.

Biotransformation

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

Elimination

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

Characteristics in patients

No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits. Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

JAWADICLO GEL was well tolerated in a variety of studies. There was no potential for photo toxicity and diclofenac-containing gel caused no skin sensitization.

6. Pharmaceutical particulars

6.1 List of excipients

Benzyl Alcohol

Propylene Glycol

Liquid Paraffin

Isopropyl Alcohol

Disodium EDTA

Cremophor RH-40

Butylated Hydroxyl Toluene (BHT)

White Soft Paraffin (Pet. Jelly)

Carbomer 940

Purified Water

Sodium Hydroxide Pellets

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Protect from heat

Keep out of the reach and sight of children.

Store in a cool dry place

6.5 Nature and contents of container

A white gel with a strong menthol odour and a smooth texture gel packed in a 20G collapsible tube with aluminium seal and a screw cap

6.6 Special precautions for disposal and other handling

No special requirements

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

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