Voltaren Emulgel Forte 2%

1 NAME OF THE MEDICINAL PRODUCT
Voltaren Emulgel Forte 2%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One gram of Voltaren Emulgel Forte 2% contains 23.2 mg of diclofenac diethylamine, which corresponds to 20 mg of diclofenac sodium.

Excipients:
Propylene glycol (50 mg/g gel)
Butyl hydroxytoluene (0.2 mg/g gel).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gel
White to practically white, soft, homogeneous, cream-like gel.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Local treatment of pain, inflammation and swelling in adults and adolescents aged 12 years and over due to:
• Soft tissue injuries: pain and inflammation and swelling in trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises and/or backache (e.g. sports injuries).
• Localized forms of soft tissue rheumatism such as tendonitis (e.g. tennis elbow), bursitis.
• By physician's order - pain caused by osteoarthrosis of the peripheral joints, as of the knee or fingers.
The gel should not be used for more than 14 days

4.2 Posology and method of administration
Adults and adolescents aged 12 years and over:
Voltaren Emulgel Forte 2% provides lasting pain relief of up to 12 hours (applied 2 times daily - morning and evening). It should be rubbed gently into the skin at the affected area.

The amount needed depends on the size of the painful area: 2 g to 4 g (a quantity ranging in size from a cherry to a walnut) of gel is sufficient to treat an area of about 400-800 cm². After application, the hands should be washed, unless they are the site being treated. The duration of treatment depends on the indication and clinical response. The gel should not to be used for more than 14 days for soft-tissue injuries or soft tissue rheumatism, or 21 days for arthritis pain, unless recommended by a doctor.

When used without medical prescription, patients should consult their doctor if the condition does not improve within 7 days, or if it gets worse.

Paediatric patients (under 12 years of age) Voltaren Emulgel Forte 2% is not recommended for use in children below 12 years of age, due to insufficient data on efficacy and safety for this age group.

Elderly patients (over 65 years of age)
The usual adult dosage may be used.

4.3 Contraindications

- Patients with or without chronic asthma in whom asthma, angioedema, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.
- Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Hypersensitivity to any other ingredient of the gel.
- During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

The possibility of experiencing systemic adverse events (those associated with the use of systemic forms of diclofenac) from application of this medicine cannot be excluded if the preparation is used at higher dosage/large amounts over large areas of skin and/or over a prolonged period (see the product information of systemic forms of diclofenac e.g. oral or injection for systemic adverse reactions).

Concomitant use of systemic NSAIDs should be cautioned since the possibility of an increase in incidence of untoward effects, particularly systemic side effects, cannot be ruled out.

This medicine should be applied only to intact, non-diseased skin, and not to skin wounds or open injuries. It should not be used with occlusion. It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Patients with a history of, or active peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases.

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

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

Patients should be warned against excessive exposure to sunlight in order to reduce the incidence of photosensitivity.

Information concerning excipients

This medicine contains propylene glycol, which may cause mild, localised skin irritation in some people. It also contains butylhydroxytoluene which may cause local

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

Instruct patients not to smoke or go near naked flames – risk of severe burns. Fabric (clothing, bedding, dressings, etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

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. There are no known interactions with Voltaren Emulgel Forte 2% but for a list of interactions known with oral diclofenac the SPCs for oral dosage forms should be consulted.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available on the use of topical formulations of diclofenac and its effects on fertility in humans.

Pregnancy

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.

Rarely, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after 20 weeks gestation in pregnancy may cause fetal renal dysfunction leading to oligohydramnios.

These effects are seen after days to weeks of treatment. Although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

The use of NSAIDs after week 20 of gestation should be restricted. If the benefit of NSAID treatment is considered greater than the risk, limit use to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of amniotic fluid if NSAID treatment of this medicine at the full treatment dosage extends beyond five days. Discontinue the NSAID if oligohydramnios occurs.

Lactation
Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of this medicine 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, this medicine should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7 Effects on ability to drive and use machines
This medicine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Undesirable effects include mild and passing skin reactions at the site of application. In very rare instances, allergic reactions may occur.
Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very rare: Rash pustular
Immune system disorders
Very rare: Hypersensitivity (including urticaria), angioedema
Respiratory, thoracic and mediastinal disorders

Very rare: Asthma
Skin and subcutaneous tissue disorders
Common: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus.
Rare: Dermatitis bullous.
Very rare: Photosensitivity reaction
Not known: Desquamation, skin discolouration

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
Additionally, please also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose
Signs and symptoms
The low systemic absorption of topical diclofenac renders overdose very unlikely. However undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if this medicine is inadvertently ingested (e.g. 1 tube of 50 g contains the equivalent of 1 g diclofenac sodium.)

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

In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used. The use of activated charcoal should be considered especially within a short time (within one hour) of ingestion of a toxic dose.

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

Mechanism of action and pharmacodynamic effects: Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Diclofenac exerts its therapeutic effects primarily through inhibition of prostaglandin synthesis by cyclo-oxygenase 2 (COX-2).

This medicine is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, this medicine relieves pain, decreases swelling, and shortens the time to return to normal function. In one ankle sprain study (VOPO-P-307), this medicine significantly decreased pain on movement scores verus placebo treated subjects within three days of starting treatment, including a subject of patients with severe pain. In addition treatment this medicine also significantly improved ankle joint function within 3 days of beginning treatment.

Due to an aqueous-alcoholic base the gel also 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. After topical application to approximately 400 cm^2 of skin, the extent of systemic exposure as determined by plasma concentration of this medicine (2 applications/day) was equivalent to diclofenac 1.16% (4 applications/day). The relative bioavailability of diclofenac (AUC ratio) for this medicine versus tablet was 4.5% on day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapour permeable bandage.

Distribution

Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after application of topical diclofenac to hand and knee joints. Maximum plasma concentrations were 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%).

From the skin and underlying tissue, diclofenac penetrates inflamed areas, preferentially distributing to and persisting in deep inflamed tissues (such as joints) rather than in the bloodstream. Diclofenac 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
This medicine was well tolerated in a variety of studies. There was no potential for phototoxicity and diclofenac-containing gel caused no skin sensitisation or irritation.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Purified water
Isopropyl alcohol
Propylene glycol
Cocoyl caprylocaprate
Liquid paraffin
Macrogol cetostearyl ether
Carbomers
Diethylamine
Oleyl alcohol
Perfume eucalyptus sting
Butylhydroxytoluene
Oleyl alcohol
Perfume eucalyptus sting

6.2 Incompatibilities
Non stated.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials
Period after opening 36 months.

6.4 Special precautions for storage
Store below 25°C.
This medicine should be kept out of sight and reach of the children.

6.5 Nature and contents of container

For the screw cap:
Aluminium laminated tube [low density polyethylene / aluminium / high density polyethylene (internal layer)] fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.

For the flip-top cap:
Aluminium laminated tube [low density polyethylene / aluminium / high density polyethylene (internal layer)] fitted with a high-density polyethylene shoulder. The tube is closed with a snapped-on flip-top cap made of polypropylene and thermoplastic elastomer lid. The flip-top cap has polypropylene tamper evident tabs located on each side of the cap.

Pack sizes: 50, 100, 150 grams
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
None.

7 MARKETING AUTHORISATION HOLDER
GSK CONSUMER HEALTHCARE, ISRAEL LTD
P.O.B 3256, PETACH TIKVA, 4951038, ISRAEL

8 MANUFACTURER
GLAXO SMITH KLINE CONSUMER HEALTHCARE S.A.
ROUTE DE L'ETRAZ 2, CH-1260 NYON, SWITZERLAND

9 MARKETING AUTHORISATION NUMBER(S)
152-63-33919-00

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