Module 1.3.1

Approval Professional Information

VOLTAREN EMULGEL 12 HOUR

SCHEDULING STATUS:

S1

1. NAME OF THE MEDICINE

Voltaren Emulgel 12 hour (2 % gel)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Diethylamine-{-o-[2,6-dichlorophenyl)-amino]-phenyl}-acetate.

1 g of Voltaren Emulgel 12 Hour contains 23,2 mg of the active substance diclofenac diethylamine, which corresponds to 20 mg diclofenac sodium.

Excipients: Propylene glycol (50 mg/g gel), Buthylhydroxytoluene (0.2 mg/g gel), Isopropyl alcohol (175 mg/g gel)

Anti-oxidant: Buthylhydroxytoluene (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

For the local symptomatic relief of pain and inflammation in:

- trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment.

Method of administration

For the flip-top cap:
Use a finger, thumb, side of your hand or even edge of a table against the underside of the cap lid to open the flip-top cap easily. Tamper evident tabs located on each side of the flip-top cap will break when the cap is opened for the first time. Before first use check if the tamper evident tabs are not broken.

For the screw cap:
To remove the seal before first use, unscrew and remove the cap. Use the reverse side of the cap to insert, twist and remove the seal from the tube.

Adults and children 14 years and over: The gel should be rubbed gently into the skin. Depending on the size of the affected site to be treated, 2 - 4 g (a circular shaped mass approximately 2,0 – 2,5 cm in diameter) should be applied 2 times a day (preferably morning and evening). The maximum daily dose is 8 g. Therefore, the maximum weekly dose is 56 g.

After application, the hands should be washed unless they are the site being treated.

If symptoms do not improve by day 7, or if they worsen within the first 7 days, a consultation with a doctor is recommended. Do not use for more than 14 days unless recommended by a doctor.

Use in the elderly: The usual adult dosage may be used.

Children and adolescents: There are insufficient data on efficacy and safety available for the 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.

4.3 Contraindications

Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

Hypersensitivity to any other ingredient of the gel.

Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

Concomitant use of other products containing diclofenac.

Concomitant use of oral NSAIDs.

Voltaren Emulgel should not be used by patients with porphyria.

During the last trimester of pregnancy.

Heart failure.

History of gastrointestinal bleeding or perforation (PUBs) related to previous NSAIDs.

Active or history of recurrent ulcer/haemorrhage/perforations.

4.4 Special warnings and precautions for use

The possibility of systemic adverse events from application of Voltaren Emulgel 12 Hour cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the professional information on systemic forms of diclofenac).

Voltaren Emulgel 12 Hour 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.

Keep out of the sight and reach of children.

Patients should be instructed to be cautious when smoking or near naked flames due to risk of severe burns. Voltaren Emulgel 12 Hour contains paraffin which is potentially flammable when it builds up on fabric

(clothing, bedding, dressings etc.). Washing clothing and bedding may reduce product build up but not totally remove it.

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 medicines 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.

Information concerning excipients:

Voltaren Emulgel 12 Hour contains propylene glycol, which may cause 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.

Warnings that should be taken into consideration with systemically absorbed Voltaren

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with Voltaren therapy. In view of Voltaren's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBss) which may be fatal.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of Voltaren in patients with a history of ulcers, and in the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving Voltaren, treatment with Voltaren should be stopped.

Voltaren should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis. Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Serous skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with the oral administration of Voltaren. Voltaren Emulgel 12 Hour gel should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

4.5 Interaction with other medicinal products and other forms of interaction

Systemic absorption of diclofenac from topical application is very low and no medicine interactions during treatment with Voltaren Emulgel 12 Hour have been reported, but the following have been observed with oral forms of diclofenac or other NSAIDs.

Lithium and digoxin: Diclofenac may increase plasma concentrations of lithium and digoxin.

Anticoagulants: Although clinical investigations do not appear to indicate that Voltaren Emulgel 12 Hour 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 medicines, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Antidiabetic medicines: Clinical studies have shown that Voltaren Emulgel 12 Hour can be given together with oral antidiabetic medicines 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 medicines.

Ciclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDs, including diclofenac. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

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 NSAID.

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 Voltaren Emulgel 12 Hour with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

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.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Anti-hypertensives: Concomitant use of NSAIDs with antihypertensive medicines (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Interactions as experienced with systemically absorbed Voltaren

When given concomitantly with lithium, non-steroidal anti-rheumatic medicines raise the concentration of lithium in the blood.

The bioavailability of Voltaren is reduced by acetylsalicylic acid and that of acetylsalicylic acid by Voltaren, when the two medicines are administered together.

The use of two or more NSAIDs concomitantly could result in an increase in side effects.

Concomitant administration of corticosteroids with Voltaren increases the risk of gastrointestinal ulceration or bleeding (PUBs).

Voltaren may enhance the effects of anti-coagulants such as warfarin when co-administered with Voltaren.

Anti-platelet agents and selective serontonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Fertility

Treatment with Voltaren Emulgel 12 Hour is unlikely to have an adverse effect on fertility because the systemic exposure to diclofenac after application of Voltaren Emulgel 12 Hour is low.

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/foetal 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-foetal 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 oligohydroamniosis;

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.

Regular use of non-steroidal anti-inflammatory medicines during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Lactation

Diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Voltaren Emulgel 12 Hour, 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, Voltaren Emulgel 12 Hour 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

Voltaren Emulgel 12 Hour 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.

Each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations:

Less frequent: Rash pustular

Immune system disorders:

Less frequent: Hypersensitivity (including urticaria), angioedema

Respiratory, thoracic and mediastinal disorders:

Less frequent: Asthma

Skin and subcutaneous tissue disorders:

Frequent: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus.

Less frequent: Dermatitis bullous, photosensitivity reaction

The following additional side-effects have been observed with oral forms of diclofenac.

Gastro-intestinal disorders:

Less frequent: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

Gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea.

Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Nervous System Disorders:

Less frequent: Headache, dizziness, or vertigo, drowsiness, tiredness, disturbances of sensation, paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing. Tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

Skin and Subcutaneous Tissue Disorders:

Less frequent: Rashes or skin eruptions, urticaria, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), photosensitivity reactions, erythroderma (exfoliative dermatitis), loss of hair, purpura including allergic purpura.

Renal and Urinary Disorders:

Less frequent: Acute renal failure, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Hepatobiliary Disorders:

Less Frequent: Elevation of serum aminotransferase enzymes (ALT, AST), liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood and Lymphatic System Disorders:

Less frequent: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Immune System Disorders:

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of rare cases of anaphylactic/anaphylactoid systemic reactions including hypotension, and respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea. (See also “Skin and Subcutaneous Tissue Disorders”).

General Disorders and Administration Site Conditions:

Less frequent: Oedema, chest pain

Cardiac Disorders:

Less frequent: Palpitation.

Vascular Disorders:

Less frequent: Hypertension.

Reproductive System and Breast Disorders:

Less frequent: Impotence (association with diclofenac is doubtful).

Side effects experienced with systemically absorbed Voltaren

Cardiac disorders

Less frequent: Cardiac failure, hypertension.

Frequency unknown: Oedema.

Gastrointestinal disorders

Frequent: Peptic ulcers, perforation or gastrointestinal bleeding (sometimes fatal), nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Skin and subcutaneous tissue disorders:

Less frequent: Bullous reactions including Stevens-Johnson syndrome.

Frequency unknown: Toxic epidermal necrolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The low systemic absorption of topical diclofenac renders overdose very unlikely.

Undesirable effects, similar to those observed following an overdose of Voltaren tablets, can be expected if Voltaren Emulgel 12 Hour is inadvertently ingested (e.g. 1 tube of 50 g contains the equivalent of 1 g diclofenac sodium.).

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 of ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacological classification: A.3.1 Antirheumatic (anti-inflammatory agents)

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

Voltaren Emulgel 12 Hour is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic origin, Voltaren Emulgel 12 Hour relieved pain, decreased swelling, and shortened the time to return to normal function. In one ankle sprain study (VOPO-P-307), Voltaren Emulgel 12 Hour significantly decreased pain on movement scores versus placebo treated subjects within three days of starting treatment. In addition, treatment with Voltaren Emulgel 12 Hour also significantly improved ankle joint function within 3 days of beginning treatment.

Due to an aqueous-alcoholic base the gel also exerts a 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 cm2 of skin, the extent of systemic exposure as determined by plasma concentration of Voltaren Emulgel 12 Hour (2 applications/day) was equivalent to diclofenac 1.16 % gel (4 applications/day).

The relative bioavailability of diclofenac (AUC ratio) for Voltaren Emulgel 12 Hour 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 %).

Diclofenac penetrates inflamed areas, preferentially distributing to and persisting in deep inflamed tissues such as joints, 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

Voltaren Emulgel 12 Hour 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

Butylhydroxytoluene

Carbomers

Cocoyl caprylocaprate

Diethylamine

Isopropyl alcohol

Liquid paraffin

Macrogol cetostearyl ether

Oleyl alcohol

Propylene glycol

Perfume eucalyptus sting

Purified water

6.2 Incompatibilities

None stated.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

All presentations: Store at or below 30 °C.

Voltaren Emulgel 12 Hour should be kept out of sight and reach of children.

6.5 Nature and contents of container

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.

30 g and 50 g Laminated aluminium tube with white cap

100 g Laminated aluminium tube with white cap or Laminated aluminium tube with white triangular cap

Pack sizes: 50g and 100g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 HOLDER OF CERTIFICATE OF REGISTRATION

GlaxoSmithKline Consumer Healthcare South Africa (Pty) Limited

39 Hawkins avenue

Epping Industria 1

Cape Town

7460

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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