## 1. Name of the medicinal product

Zortafen Cream

2. Qualitative and quantitative composition

1 g of cream contains diclofenac as 23.2 mg diclofenac diethylamine corresponding to 20 mg of diclofenac sodium.

**Excipient(s) with known effect**

1 g of cream contains 54 mg of propylene glycol (E1520), 0.2 mg butylhydroxytoluene (E321) and 1 mg fragrance (contains 0.15 mg benzyl alchohol (E1519), citral, citronellol, coumarin, eugenol, farnesol, geraniol, d-limonene, linalool).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

cream

White to almost white, homogeneous cream

4. Clinical particulars

4.1 Therapeutic indications

**For adults and adolescents aged 14 years and over**

For the short-term local, symptomatic treatment of mild to moderate pain in acute strains, sprains or contusions following blunt trauma.

4.2 Posology and method of administration

**Posology**

*Adults and adolescents aged 14 years and over:*

The occurrence of undesirable effects can be minimized by using the lowest possible dose for the shortest duration of treatment necessary to relieve symptoms.

Zortafen cream is used 2 times a day (preferably morning and evening).

Depending on the size of the affected site to be treated, a cherry to walnut size quantity is required, corresponding to 1 - 4 g of cream (23.2 - 92.8 mg diclofenac, diethylamine salt) corresponding to 20 - 80 mg diclofenac sodium This is sufficient to treat of an area of 400 – 800 $cm^2$.

The maximum daily dose is 8 g of cream corresponding to 185.6 mg of diclofenac, diethylamine (corresponding to 160 mg diclofenac sodium).

The duration of use depends on the symptoms and the underlying disease. Zortafen cream should not be used longer than 1 week without medical advice.

If symptoms worsen or do not improve after 3 - 5 days, a doctor should be consulted.

**Special patient groups**

*Elderly patients*:

No special dose adjustment is required. Because of the potential undesirable effect profile, elderly people should be carefully monitored.

*Patient with renal impairment*:

No dose reduction is required in patients with renal impairment

*Patient with hepatic impairment*:

No dose reduction is required in patients with hepatic impairment.

*Children and adolescents (under 14 years):*

There are insufficient data on efficacy and safety in children and adolescents under 14 years of age (see section 4.3)

**Method of administration**

For cutaneous use.

The cream is applied to the affected parts of the body thinly and gently rubbed into the skin. Afterwards, the hands should be wiped with a paper towel and then washed, unless the hands are the area to be treated.

If too much cream is accidentally applied, the excess cream should be wiped with a paper towel.

The paper towel should be disposed in the household waste to prevent unused product reaching the aquatic environment.

Before applying a bandage (see section 4.4) the cream should be left to dry for a few minutes on the skin.

4.3 Contraindications
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- patients with a history of hypersensitivity reactions, such as asthma, bronchospasmus, urticaria, acute rhinitis or angioedema in response to acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs).

- on open injuries, inflammations or infections of the skin as well as on eczema or mucous membranes;

- in the third trimester of pregnancy (see section 4.6);

- in children and adolescents under 14 years of age.

4.4 Special warnings and precautions for use
The possibility of systemic undesirable effects from application of topical diclofenac cannot be excluded if the preparation is used on large areas of skin and over a prolonged period. The cream should therefore be used with caution by patients with reduced renal function, reduced heart

function or reduced liver function as well as patients with active peptic ulcers in the stomach or duodenum.

Zortafen cream must only be applied to intact, not diseased or injured skin. Eyes and mucous membranes must not come into contact with the medicinal product and it must not be taken orally.

Topical diclofenac may be used with a non-occlusive bandage but not with an airtight occlusive dressing (see section 5.2).

If symptoms worsen or do not improve after 3 - 5 days, a doctor should be consulted.

Patients suffering from asthma, hay fever, swelling of nasal mucous membranes (so called nasal polyps) or chronic obstructive pulmonary disease, chronic respiratory infections (particularly associated with hay fever-like symptoms), and patients with hypersensitivity to painkillers and anti-rheumatic medicinal products of all kinds are rather at risk to asthma attacks (so called analgesic intolerance / analgesic asthma), to local skin or mucous membrane swelling (so-called quincke edema) or to urticaria than other patients when treated with Diclofenac 1.16% cream .

In these patients, Zortafen cream may only be used under certain precautions (emergency preparedness) and direct medical supervision. The same applies for patients who are also allergic to other substances e.g. with skin reactions, itching or urticaria.

If a skin rash occurs during the treatment with Diclofenac 1.16% cream , the treatment should be stopped.

Direct sunlight or artificial sun should be avoided during treatment and two weeks after treatment to avoid the risk of photosensitivity.

Preventive measures should be taken so that children do not contact the skin areas to which the cream has been applied.

Zortafen cream contains butylhydroxytoluene which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

This medicinal product contains fragrance with benzyl alcohol (0.15 mg/g, E1519), citral, citronellol, coumarin, eugenol, farnesol, geraniol, d-limonene and linalool which may cause allergic reactions.

In addition, benzyl alcohol may cause mild local irritation.

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 the systemic absorption of diclofenac is very low with topical application, interactions are very unlikely in use as intended.

4.6 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:

**Pregnancy**

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.

There are no clinical data from the use of Zortafen cream during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Zortafen cream exposure reached after topical administration can be harmful to an embryo/fetus.

During the first and second trimester of pregnancy, Zortafen cream should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including diclofenac may induce cardiopulmonary and renal toxicity in the fetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, Zortafen cream is contraindicated during the last trimester of pregnancy (see Section 4.3).

**Breast-feeding**

Diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Zortafen cream no effects on the breast-fed child are anticipated. Because of a lack of controlled studies in breast-feeding women, the medicinal product should only be used during breast-feeding under advice from a healthcare professional. Under this circumstance, Zortafen cream should not be applied on the breasts of breast-feeding 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

The topical use of diclofenac has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
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), *Not known* (cannot be estimated from the available data).

| System organ class database | Adverse reactions and frequency |
|---|---|
| **Infections and infestations** | *Very rare*: Rash pustular |
| **Immune system disorders** | *Very rare*: Hypersensitivity (including urticaria), angioedema |
| **Respiratory, thoracic and mediastinal disorders** | *Very rare*: Asthma |
| **Gastrointestinal disorders** | *Very rare*: Gastrointestinal complaints |
| **Skin and subcutaneous tissue disorders** | *Common*: Dermatitis (including contact dermatitis), skin rash, erythema, eczema, pruritus<br>*Uncommon*: Scaling, dehydration of the skin, oedema<br>*Rare*: Dermatitis bullous<br>*Very rare*: Photosensitivity reaction<br>*Not known*: Burning sensation at the application site, dry skin |

When the cream is applied on large areas of skin and over a prolonged period, the possibility of systemic undesirable-effects (e.g. renal, hepatic or gastrointestinal undesirable effects, systemic hypersensitivity reactions), as they occur possibly after systemic administration of diclofenac-containing medicinal products, cannot be excluded.

**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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple Ap Store.

4.9 Overdose
Due to the low systemic absorption of diclofenac in limited topical use an overdose is unlikely.

If the recommended dose is significantly exceeded, the cream should be removed from the skin and washed off with water.

Undesirable effects similar to those observed following an overdose of systemic diclofenac can occur if topical diclofenac is inadvertently ingested (1 tube of 100 g contains the equivalent of 2,320 mg diclofenac diethylamine corresponding to 2,000 mg 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 medicinal products should

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

A specific antidote does not exist.

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: M02AA15

**Mechanism of action**

Diclofenac is a potent non-steroidal anti-inflammatory drug. It develops its therapeutic efficacy mainly via inhibition of prostaglandin synthesis by cyclooxygenase 2 (COX-2). Diclofenac has proven to be effective via the prostaglandin synthesis inhibition in the conventional animal-experiment inflammation models. In humans, diclofenac reduces inflammatory-related pain, swellings and fever. Furthermore, diclofenac inhibits reversibly the ADP and the collagen-induced thrombocyte aggregation.

In a clinical study on patients 23.2 mg of diclofenac diethylamine salt/g cream reduced clinically relevant and statistically significantly the pain (on movement) three days after start of treatment compared with the placebo group. In addition, the cream significantly improved functioning of the foot joint within the first three days of treatment.

5.2 Pharmacokinetic properties
**Absorption**

The quantity of diclofenac absorbed through the skin is proportional to the duration of skin contact and the size of the treated area , and depends on both the total dose applied and the degree of skin hydration. After local application of Zortafen cream to hand and knee joints, the active substance is absorbed through the skin and detectable in the plasma as well as the tissue in varying quantities – depending on the diffusion range – beneath the application site. Absorption amounts to about 6 % of the applied dose of diclofenac after topical application of 2.5 g diclofenac cream on 500 $cm^2$ skin, determined by measuring total renal elimination of diclofenac and its hydroxylated metabolites, compared with oral administration of diclofenac sodium. Due to a depot-effect in the skin, there is a delayed and prolonged release of active substance into the underlying tissue and the plasma. Under occlusive conditions (10 hours), percutaneous absorption of diclofenac in adults can be increased three-fold (serum concentration).

**Distribution**

99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %). Plasma levels after application of diclofenac cream are not sufficient to explain the observed therapeutic efficacy; this is more likely due to the

presence of significantly higher active substance concentrations beneath the application site. Due to its properties (such as short plasma half-life, low pKa value, small distribution volume, high protein binding), diclofenac has an affinity to inflamed tissue. Diclofenac preferentially distributes and persists in inflamed tissue. 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.

**Special population**

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
Based on conventional studies on safety pharmacology, genotoxicty and carcinogenic potential, the pre-clinical data do not reveal any specific hazards for humans apart from those already described in other sections of the SPC. In animal studies the chronic toxicity of diclofenac following systemic application mainly manifested as gastrointestinal lesions and ulcers. In a 2-year toxicity study, a dose-dependent increase in the incidence of thrombosis of the heart was observed in diclofenac-treated rats.

In animal studies on reproductive toxicity, systemically administered diclofenac caused inhibition of ovulation in rabbits and impairment of implantation and early embryonic development in rats. Gestation and duration of parturition were prolonged by diclofenac. The embryotoxic potential of diclofenac was investigated in three animal species (rat, mouse, rabbit). Fetal death and growth retardation occurred at materno-toxic dose levels. Based on the available non-clinical data, diclofenac is regarded as being non-teratogenic. Doses below the maternotoxic threshold had no impact on the postnatal development of the offspring

Diclofenac poses a risk to the aquatic environment (see section 6.6).

6. Pharmaceutical particulars
6.1 List of excipients
Isopropyl alcohol

Propylene glycol (E1520)

Cocoyl Caprylocaprate

Paraffin, Liquid

Carbomer

Macrogol cetostearyl ether

Diethylamine

Oleic acid (E570)

Butylhydroxytoluene (E321)

Fragrance (contains citronellol, geraniol, benzyl alcohol (E1519), linalool, limonene, citral, farnesol, coumarin, eugenol)

Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months

6.4 Special precautions for storage
Store in the original tube in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
The cream is packed in aluminium laminated tubes, closed with PE seal and PP screw caps.

Pack sizes: 60g and 100g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
This medicinal product poses a risk to the environment (see section 5.3).

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

7. Marketing authorisation holder
FLOWERGATE MIXED DEVELOPMENT SCHEME,KM 1 SAGAMU/BENIN EXPRESSWAY,SAGAMU,OGUN STATE., NIGERIA
8. Marketing authorisation number(s)
A11-100149

9. Date of first authorisation/renewal of the authorisation

June 2021

10. Date of revision of the text

NA