SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac STADA® 23.2 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of <Product name> contains 23.2 mg (2.32 %) of diclofenac diethylamine, which is equivalent to 20 mg of diclofenac sodium.

Excipient(s) with known effect
<Product name> contains 50 mg of propylene glycol per gram of gel.
<Product name> contains 0.2 mg of butylated hydroxytoluene per gram of gel.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Viscous white gel with characteristic odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For symptomatic treatment of local mild to moderate pain in muscle and joint injuries, e.g. sports injuries.

4.2 Posology and method of administration

Posology
For cutaneous use only. The patient should consult a doctor if the treatment has not had the intended effect after 7 days of if symptoms worsen.

Adults and adolescents aged 14 years and over
Apply <Product name> on the painful or inflamed area 2 times a day. The quantity of gel depends on the size of the affected site: 2-4 g of <Product name> (a gel strip of 5-10 cm) is sufficient to treat an area of 400-800 cm^2. The maximal daily dose is 8 g of gel.

Paediatric population
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 Contraindications).

Elderly
No special dose adjustment is required.

Method of administration
For cutaneous use only.

The gel is applied to the affected parts of the body 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 gel is accidentally applied, the excess gel 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.

Duration of treatment
Treatment duration depends on the indication and the clinical response. Treatment with the gel should not continue for more than 14 days in muscle or joint injuries except on the advice of a doctor.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have had symptoms of asthma, angioedema, urticaria or acute rhinitis following the use of acetylsalicylic acid of other non-steroidal anti-inflammatory drugs (NSAIDs).
- Third trimester of pregnancy.
- Must not be used by children and adolescents under the age of 14.

4.4 Special warnings and precautions for use

The risk of systemic undesirable effects (adverse effects that occur when using systemic forms of diclofenac) should be considered if <Product name> is used at high doses and for longer periods than recommended. The gel should therefore be used with caution by patients with reduced renal function, heart function or liver function as well as patients with active peptic ulcers in the stomach or duodenum (see also the SmPC for systemic diclofenac products).

<Product name> must not be used on pathologically changed skin, e.g. skin with eczema, acne, infection or open wounds. Eyes and mucous membranes must not come into contact with the medicinal product and it must never be taken orally.

Direct sunlight, including artificial sun, should be avoided during treatment and for two weeks after treatment as the risk of photosensitivity reactions cannot be excluded.

<Product name> must not be used with airtight occlusive bandage. Sprained joints may be supported with a bandage, but it must not be wrapped so tightly that it stops blood flow.

Do not exceed the recommended treatment duration, as the risk of developing contact dermatitis increases with time.

Discontinue treatment if a rash occurs after application.

Excipients
<Product name> contains propylene glycol which may cause skin irritation.
<Product name> also contains butylated hydroxytoluene which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interactions with other medicinal products and other forms of interactions

Since the systemic absorption of diclofenac is very low with cutaneous application, interactions of this type are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no clinical data from the use of <Product name> during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic diclofenac exposure reached after topical administration can be harmful to an embryo/foetus. 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 embryofoetal 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 embryofoetal 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, <Product name> should not be used 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 as possible, and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligohydramnios.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and foetus, 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, <Product name> is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses for the mother, effects on the child are thought to be unlikely. Because of a lack of controlled studies in breast-feeding women, the medicinal product should only be used during breast-feeding on the advice of a doctor.

<Product name> 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 <Product name> has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are listed in the table 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)

Adverse reactions observed after marketing authorisation are reported on a voluntary basis in an unknown population, the frequency of these adverse reactions is not known but is likely to be rare or very rare.

Infections and infestations	Very rare	Pustular rash.
Immune system disorders	Very rare	Angioedema, hypersensitivity (including urticaria).
Respiratory, thoracic and mediastinal disorders	Very rare	Asthma.
Skin and subcutaneous tissue disorders	Common	Dermatitis (including contact dermatitis), skin rash, erythema, eczema, pruritus.
	Rare	Bullous dermatitis.
	Very rare	Photosensitivity reactions.

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 national reporting system listed in Appendix V.

4.9 Overdose

Due to the low systemic absorption of topical diclofenac, an overdose is unlikely. However, undesirable effects similar to those observed following an overdose of diclofenac tablets can occur if the gel is swallowed (1 tube of 50 g contains the equivalent of 1 000 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. Treatment should continue if it is clinically indicated or in accordance with national guidelines, if any 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 and pharmacodynamic effect

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. It develops its therapeutic efficacy mainly via inhibition of prostaglandin synthesis by cyclo-oxygenase. Diclofenac gel is intended for topical application.

Diclofenac 23.2 mg/g gel has been shown to relieve pain and lead to a quicker return to function (as measured with the Karlsson scoring scale).

One ankle sprain study (VOPO-P-307) showed that treatment with diclofenac 23.2 mg/g gel relieved pain effectively. Two days after starting treatment, patients treated with diclofenac 23.2 mg/g gel experienced a 32 mm decrease of their Pain on Movement (POM), whilst POM had only decreased by 18 mm in the placebo group ($p < 0.0001$). POM after four days, which was a primary endpoint, reduced by 49 mm on a 100 mm visual analogue scale (VAS) in patients who used diclofenac 23.2 mg gel, compared with the reduction of 25.4 mm observed in the placebo group. Diclofenac 23.2 mg/g gel was shown to have a statistically significantly better efficacy than placebo ($p < 0.0001$).

Further evidence of the efficacy of diclofenac 23.2 mg/g is that the median time to a 50 % decrease of POM was 4 days after treatment initiation for the diclofenac 23.2 mg/g group, versus 8 days after treatment initiation for the placebo group ($p < 0.0001$). Treatment with diclofenac 23.2 mg/g gel is therefore considered to shorten recovery time by 4 days.

5.2 Pharmacokinetic properties

Absorption
The quantity of diclofenac that is systemically absorbed from diclofenac 23.2 mg/g gel 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 on 400 cm^2 skin, the systemic absorption (AUC and C_{max}) of diclofenac 23.2 mg/g gel twice daily was comparable to that of diclofenac 11.6 mg/g gel applied 4 times daily (the total daily dose of diclofenac being 80 mg in both cases). The relative bioavailability of diclofenac (AUC ratio) between diclofenac 23.3 mg/g gel and tablets at the equivalent dose was 4.5 % after 7 days. Absorption was not modified by a semi-occlusive bandage. A study with diclofenac 11.6 mg/g gel showed that ten hours use of an occlusive bandage led to a threefold increase of diclofenac absorption.

Distribution
Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after topical administration of diclofenac 11.6 mg/g gel to hands 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 concentrations are higher in synovial fluid than in plasma. This preferential distribution is due to diclofenac's degree of protein binding, distribution volume, the molecule's low pKa value and haemodynamic changes in inflamed tissue.

Biotransformation
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation. This results in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min. The terminal half-life in plasma 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. About 60 % of the administered dose is excreted in the urine in

the form of metabolites. Less than 1 % is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile and in the faeces.

Characteristics in patients
No accumulation of diclofenac and its metabolites is to be expected in patients with 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

Conventional studies on safety pharmacology, general toxicity, genotoxicity, carcinogenic potential, reproductive toxicity and teratogenicity have found no specific hazards for humans. Diclofenac gel 23.2 mg/g was well tolerated in a number of studies. No phototoxicity risk has been identified, and gel containing diclofenac does not cause skin sensitisation. No effects on fertility have been observed in male and female rats given diclofenac.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene
Carbomer
Cocoyl capryolcaprate
Diethylamine
Isopropyl alcohol
Liquid paraffin
Macrogol cetostearyl ether
Oleyl alcohol
Propylene glycol
Fragrance
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Aluminium tube with a polypropylene screw cap.

<Product name> comes in tubes of 30, 50, 60, 100, 120, 150 and 180 g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special precautions for storage.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

12-DEC-2024