1 NAME OF THE MEDICINAL PRODUCT

Difflam 3% Cream
or
Difflam-P 3% Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tube of Difflam 3% Cream/ Difflam-P 3% Cream contains Benzydamine Hydrochloride 3% w/w.

Excipients with known effects

Contains methyl hydroxybenzoate, propyl hydroxybenzoate, cetyl alcohol propylene glycol, benzyl alcohol, benzyl benzoate, citral, citronellol, coumarin, eugenol, farnesol, geraniol, hydroxycitronellal, isoeugenol, limonene and linalool.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream for topical application to skin.

4.1 Therapeutic indications

Benzydamine 3% Cream/ Benzydamine-P 3% Cream is a topical analgesic and non-steroidal antiinflammatory agent.

It is recommended as a short-term treatment for the relief of symptoms associated with painful inflammatory conditions of the musculo-skeletal system, including:

Acute inflammatory disorders such as myalgia and bursitis.

Traumatic conditions such as sprains, strains, contusions and the after-effects of fractures.
Benzydamine 3% Cream/ Benzydamine-P 3% Cream is well absorbed through the skin and has been shown to have anti-inflammatory and local anaesthetic actions.

4.2 Posology and method of administration

Benzydamine 3% Cream/ Benzydamine-P 3% Cream should be massaged lightly into the affected area. Depending on the size of the site to be treated, 35 - 85 mm (1 - 2 g) should be applied three times daily and at the discretion of the doctor, up to six times daily in more severe conditions. It is recommended that treatment be limited to not more than ten days.

ELDERLY:
No special dosage recommendations are made for elderly patients.

4.3 Contraindications

Difflam 3% Cream/ Difflam-P 3% Cream is contraindicated in patients with known hypersensitivity to the active substance benzydamine hydrochloride or to any of the excipients listed in section 6.1.

- third trimester of pregnancy

4.4 Special warnings and precautions for use

Benzydamine use is not advisable in patients with hypersensitivity to acetylsalicylic acid or other NSAIDs.

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma. Caution should be exercised in these patients.

This product should not be applied to the eyes or mucosal surfaces

Cetyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Propylene glycol may cause skin irritation.

Methyl hydroxybenzoate and propyl hydroxybenzoate may cause allergic reactions (possibly delayed).

This medicine contains 0.04mg benzyl alcohol in each 2g dose which is equivalent to 0.02mg/g. Benzyl alcohol may cause allergic reactions and mild local irritation

This medicinal product contains fragrance with benzyl benzoate, citral, citronellol, coumarin, eugenol, farnesol, geraniol, hydroxycitronellal, isoeugenol, limonene and linalool. These substances may cause allergic reactions.

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

None.

4.6 Fertility, pregnancy and lactation

Pregnancy

Benzydamine 3% Cream/ Benzydamine-P 3% Cream should not be used in pregnancy unless considered essential by the physician.

There is no evidence of a teratogenic effect in animal studies.

There are no clinical data from the use of topical forms of Benzydamine 3% Cream during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Benzydamine 3% Cream exposure reached after topical administration can be harmful to an embryo/fetus. During the first and second trimester of pregnancy, Benzydamine 3% 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 Benzydamine 3% Cream may induce cardiopulmonary and renal toxicity in the foetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, Benzydamine 3% cream is contraindicated during the last trimester of pregnancy (see Section 4.3)

Breast-feeding

Benzydamine 3% Cream/ Benzydamine-P 3% Cream should not be used during lactation unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Very common ($\geq$ 1/10), Common ($\geq$ 1/100 to <1/10), Uncommon ($\geq$1/1,000 to <1/100), Rare ($\geq$1/10,000 to <1/1,000) and Very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	Not known	Photosensitivity reactions have been reported and local skin reactions which have varied from erythema to papular eruption. The skin returned to normal on

		stopping treatment.

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 App Store.

4.9 Overdose

Intoxication is only expected in case of accidental ingestion of large quantities of benzydamine (300 mg).
Symptoms associated with overdose of ingested benzydamine are mainly gastrointestinal symptoms and symptoms of the central nervous system. Most frequent gastrointestinal symptoms are nausea, vomiting, abdominal pain, and esophageal irritation. Symptoms of the central nervous system include dizziness, hallucinations, agitation, anxiety, and irritability.
In acute overdose only symptomatic treatment is possible. Patients should be kept under close observation and supportive treatment should be given. Adequate hydration must be maintained

Benzydamine 3% Cream/ Benzydamine-P 3% Cream is unlikely to cause adverse systemic effects, even if accidental ingestion should occur. No special measures are required.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory and antirheumatic agents, non-steroids/Anti-inflammatory preparations, non-steroids for topical use, ATC code: M01AX07/M02AA05

Mechanism of action
The indazole analogue benzydamine has physicochemical properties and pharmacological activities which differ from those of the aspirin-like NSAIDs. Unlike aspirin-like NSAIDs which are acids or metabolised to acids, benzydamine is a weak base. In further contrast, benzydamine is a weak inhibitor of the prostaglandin synthesis. Only at concentration of 1 mM and above benzydamine effectively inhibits cyclooxygenase and lipooxygenase enzyme activity. It mostly exerts its effects through inhibition of the synthesis of proinflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and Interleukin-1β (IL-1β) without significantly affecting other pro-inflammatory (IL-6 and 8) or anti-inflammatory cytokines (IL-10, IL-1 receptor antagonist). Further mechanisms of action are hypothesised including the inhibition of the oxidative burst of neutrophils as well as membrane stabilisation as demonstrated by the inhibition of granule release from neutrophils and the stabilization of lysosomes. The local anaesthetic activity of the compound has been related to an interaction with cationic channels

Pharmacodynamic effects

Benzydamine specifically acts on the local mechanisms of inflammation such as pain, oedema or granuloma. Benzydamine topically applied demonstrates anti-inflammatory activity reducing oedema as well as exudate and granuloma formation. Further, it exhibits analgesic properties if pain is caused by an inflammatory condition and local anaesthetic activity. Hyperthermia, which is indicative of systemic functional involvement, is poorly affected by benzydamine

Clinical efficacy and safety

In a clinical study in 24 patients with pharyngitis following tonsillectomy rinsing with Benzydamine0.15% 5 times a day for 6 days significantly better and more rapidly relieved throat pain, difficulty in swallowing and improved clinical signs including hyperaemia and oedema versus placebo on day 7. Similar results were found in other studies in patients with tonsillitis or pharyngitis or following dental surgery. The gargling with 30 ml 0.075% benzydamine prior to the induction of anaesthesia in 58 adults undergoing general anaesthesia with endotracheal tube intubation significantly reduced postoperative sore throat versus water control for the first 24 hours whereas aspirin gargles reduced it for 4 hours.

In a clinical study with 48 patients rinsing four times daily with 0.15% benzydamine during a 3 to 5-week radiotherapy of oral cancer provided significant pain relief and reduction of size and severity of mucositis in the oropharynx. Similar effects were seen in a study in patients undergoing chemotherapy for oral cancer. In a study in 67 patients with severe oropharyngeal mucositis following radiotherapy who rinsed with benzydamine solution pain with swallowing, hyperaemia and severity of mucositis were significantly reduced compared to placebo treatment within the first three treatment days.

A higher incidence of transient numbness and stinging was noted among the patients using benzydamine that was attributed to the medication’s local anaesthetic effect.

The topical application of Difflam cream 3% 3 times daily for 6 days in 50 patients with soft tissue injuries significantly better relieved pain, tenderness, erythema, functional impairment and swelling compared to placebo on day 6.

Overall, benzydamine was well tolerated in clinical trials.

Difflam cream has been clinically tested as a short-term treatment for the relief of symptoms associated with painful inflammatory conditions of the musculo-skeletal system including myalgia and bursitis. Further, it showed clinical benefit in traumatic conditions such as sprains, strains, contusions and post fractures (Diebschlag 1985; Haig 1986; Chatterjee 1977). Difflam Cream is well absorbed through the skin and has been shown to have anti-inflammatory and local anaesthetic actions.

5.2 Pharmacokinetic properties

Following topical administration, benzydamine is absorbed through intact skin and reaches peak levels between 24 - 32 hours, amounting to about 20 - 25% of the plasma levels obtained after the oral administration of the same dose.

About half of the benzydamine is excreted unchanged via the kidney at a rate of 10% of the dose within the first 24 hours. The remainder is metabolised, mostly to N-oxide.

5.3 Preclinical safety data

Non-Clinical Data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated toxicity, genotoxicity, cardiogenic potential, and toxicity to reproduction.

6.1 List of excipients

Glycerol stearate 'Cutina'
Cetyl Alcohol USNF
Decyl oleate 'Cetiol V'
Macrogol cetostearyl ether 'Eumulgin B1'
Propylene Glycol Ph Eur
Perfume, 'Crematest' 0/064060'
Methyl Hydroxybenzoate Ph Eur
Propyl Hydroxybenzoate Ph Eur
Purified Water Ph Eur

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store between 5 - 30°C. Do not freeze.

6.5 Nature and contents of container

Collapsible Aluminium tube closed with plastic screwcap

or

Laminate tube closed with plastic screwcap.

Contents: 35 g, 50 g or 100 g

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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06/03/1980 / 06/09/2002

10 DATE OF REVISION OF THE TEXT

08/05/2024