1 NAME OF THE MEDICINAL PRODUCT

Difflam 0.15% w/v Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose pump spray delivers Benzydamine hydrochloride 0.15% w/v, approximately 175 microlitres per puff.

Contains methyl parahydroxybenzoate and Ethanol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Difflam 0.15% Spray is a metered dose pump throat spray.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Difflam 0.15% Spray is a locally acting analgesic and anti-inflammatory treatment for the throat and mouth.
It is used to treat various painful oropharyngeal conditions such as mouth ulcers, sore throat, sore mouth or gums, dental pain.

4.2 Posology and method of administration

Posology

Adults, adolescents and elderly: 4 to 8 puffs every 1½-3 hourly.

Children(6-12): 4 puffs every 1½-3 hourly.

Children under 6: One puff to be administered per 4 kg body weight, up to a maximum of 4 puffs, 1½-3 hourly.

Elderly: Because of the small amount of drug applied, elderly patients can receive the
same dose as adults.

Method of administration
For oral administration

4.3 Contraindications

Difflam 0.15% w/v Spray is contra-indicated in patients with known hypersensitivity to the active substance benzydamine hydrochloride or to any of the excipients listed in section 6.1.

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.

Avoid contact with the eyes.

If the condition is aggravated or not improved use should cease.

This medicinal product contains 10 vol % ethanol.

Methyl hydroxybenzoate may cause allergic reactions (possibly delayed)

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Fertility, pregnancy and lactation

Pregnancy
Difflam 0.15% w/v Spray should not be used in pregnancy unless considered essential by the physician. There is no evidence of a teratogenic effect in animal studies.

Breast-feeding
Difflam 0.15% w/v Spray should not be used in lactation unless considered essential
by the physician.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness
The following rate values have been used: 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) and Very rare (<1/10,000), not known (cannot be estimated from the available data).

The most common side effects are numbness and a stinging feeling in the mouth.

Respiratory, thoracic and mediastinal disorders
Very rare: Laryngospasm or bronchospasm.

Gastrointestinal disorders
Uncommon: Oral numbness (hypoesthesia) and a stinging feeling in the mouth (oral pain).

Skin and subcutaneous tissue disorders
Very rare: pruritus, urticaria, photosensitivity reaction and rash
Frequency not known: Angioedema

Immune system disorders
Frequency not known: Anaphylactic reaction which can be potentially life-threatening. Hypersensitivity reactions.

Methyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

4.9 Overdose

Difflam is unlikely to cause adverse systemic effects, even if accidental ingestion should occur. Intoxication is only to be expected if large quantities of Difflam Oral Rinse are swallowed (> 300mg).

Symptoms associated with ingested overdose of 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 1mM 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 Difflam 0.15% 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.

5.2 Pharmacokinetic properties

Following oral administration, Benzydamine is rapidly absorbed from the gastrointestinal tract and maximum plasma levels reached after 2-4 hours. The most important aspect of the tissue distribution of Benzydamine is its tendency to concentrate at the site of inflammation. 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 PHARMACEUTICAL PARTICULARS
6.1 **List of excipients**

- Glycerol Ph. Eur.
- Saccharin FU
- Sodium Bicarbonate Ph. Eur.
- Ethanol FU
- Methylhydroxybenzoate Ph. Eur.
- Mouthwash Flavour
- Polysorbate 20 Ph. Eur.
- Purified Water Ph. Eur.

6.2 **Incompatibilities**

None.

6.3 **Shelf life**

The shelf life expiry date for this product shall not exceed 3 years from the date of its manufacture.

6.4 **Special precautions for storage**

Do not store above 30°C, do not refrigerate or freeze. Keep out of the reach of children.

6.5 **Nature and contents of container**

Difflam 0.15% Spray is presented in a 30 ml HDPE bottle with 170 μl valve pump spray.

6.6 **Special precautions for disposal**
No special requirements

7. MARKETING AUTHORISATION HOLDER

Meda Pharmaceuticals Ltd
Skyway House
Parsonage Road
Takeley
Bishop’s Stortford
CM22 6PU

8. MARKETING AUTHORISATION NUMBER(S)

PL 15142/0046

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th November 1984 / 05th March 2004

10. DATE OF REVISION OF THE TEXT

12/12/2016