1 NAME OF THE MEDICINAL PRODUCT

Difflam 0.15% w/v Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each puff (175 microlitres) contains 262.5 micrograms Benzydamine hydrochloride (0.15% w/v).

Excipient(s) with known effects:
Methyl parahydroxybenzoate
Ethanol
Mint flavour with benzyl alcohol, cinnamyl alcohol, citral, citronellol, eugenol, geraniol, isoeugenol, limonene and linalool.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Benzydamine Spray is a metered dose pump throat spray.

4.1 Therapeutic indications

Benzydamine Spray is a locally acting analgesic and anti-inflammatory treatment for the throat and mouth. It is especially useful for the relief of pain in traumatic conditions such as following tonsillectomy or the use of a naso-gastric tube, dental surgery.

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 use

4.3 Contraindications

Difflam Spray is contra-indicated in patients with:

Hypersensitivity to the active ingredient, 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 medicine contains 14 mg of alcohol (ethanol) in each puff. The amount in 1 puff of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Methyl parahydroxybenzoate may cause allergic reactions (possibly delayed)

This medicine contains 0.025 mg benzyl alcohol in each 175 microlitre dose which is equivalent to 0.14mg/ml. Benzyl alcohol may cause allergic reactions and mild local irritation.

This medicinal product contains mint flavour with benzyl alcohol, cinnamyl alcohol, citral, citronellol, eugenol, geraniol, isoeugenol, limonene and linalool. These substances may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per dose of 8 puffs, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Fertility, pregnancy and lactation

Pregnancy

Benzydamine Spray should not be used in pregnancy unless considered essential by the physician. There is no evidence of a teratogenic effect in animal studies.

From the 20th week of pregnancy onward, Benzydamine Spray use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Benzydamine Spray should not be given unless clearly necessary. If Benzydamine Spray 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Benzydamine Spray for several days from gestational week 20 onward. Benzydamine Spray should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction (see above);

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, Benzydamine Spray is contraindicated during the third trimester of pregnancy (see sections 4.3)

Breast-feeding
Benzydamine Spray 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 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.

System organ class	Frequency	Adverse reaction
Immune system disorders	Not known	Anaphylactic reactions, Hypersensitivity reactions [20].
Respiratory, thoracic and mediastinal disorders	Very rare	Laryngospasm or bronchospasm
Gastrointestinal disorders	Uncommon	Oral numbness and a stinging feeling in the mouth. The stinging has been reported to disappear upon continuation of the of the treatment, however if it persists it is recommended that treatment be discontinued.
Skin and subcutaneous tissue disorders	Very rare	Pruritus, urticaria, photosensitivity reaction and rash
	Not known	Angioedema

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.

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 oesophageal 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 Spray 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

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 benzydamine 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.

6.1 List of excipients

Glycerol Ph. Eur.
Saccharin Ph. Eur
Sodium Bicarbonate Ph. Eur.
Ethanol Ph. Eur
Methyl hydroxybenzoate 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 30^0C, do not refrigerate or freeze. Keep out of the reach of children.

6.5 Nature and contents of container

Difflam Spray is presented in a 30 ml HDPE bottle fitted with metered 170 valve pump spray.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Mylan Products Ltd., Station Close, Potters Bar, Herts, EN6 1TL, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0160

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th November 1984 / 05th March 2004

10 DATE OF REVISION OF THE TEXT

08/05/2024