SUMMARY OF PRODUCT CARACTERISTICS

1. Name of the medicinal product
TANTUM VERDE

2. Qualitative and quantitative composition

Benzydamine hydrochloride 0.15% w/v.

100 ml contain:
Active ingredient: benzydamine hydrochloride 0.15 (equivalent to benzydamine 0.134 g);
(contains methyl parahydroxybenzoate and ethanol).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Liquid for use as mouthwash/gargle.

4. Clinical particulars

4.1 Therapeutic indications

Tantum Verde is a locally acting analgesic and anti-inflammatory treatment for the relief of painful inflammatory conditions of the mouth and throat including:
Traumatic conditions: Pharyngitis following tonsillectomy or the use of a naso-gastric tube.
Inflammatory conditions: Pharyngitis, aphthous ulcers and oral ulceration due to radiation therapy.
Dentistry: For use after dental operations.

4.2 Posology and method of administration

For oromucosal administration.

CHILDREN: Not suitable for children aged 12 years or under.

Rinse or gargle with 15 ml of Tantum Verde mouthwash for 2-3 times daily, to be used pure or diluted (in this case adding in the dosage measure 15 ml of water). Do not exceed the prescribed dose.

4.3 Contraindications

Tantum Verde is contra-indicated in patients with known hypersensitivity to the active substance benzydamine hydrocholoride 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 NSAID's.
Tantum Verde should generally be used undiluted, but if 'stinging' occurs, the rinse may be diluted with water.
Avoid contact with eyes.
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
Tantum Verde 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
Tantum Verde should not be used during lactation unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Not applicable.

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).

Reporting side effects:
Side effects can be reported to the Ministry of Health (MoH) by clicking on the "Report on side effects due to medication therapy" link on the MoH home page (www.health.gov.il) which refers to the online form for side effects reporting, or by entering the link: https://sideeffects.health.gov.il

4.9 Overdose
Tantum Verde is unlikely to cause adverse systemic effects, even if accidental ingestion should occur. Intoxication is only to be expected if large quantities of Tantum Verde 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 substances for local oral treatment.
ATC code: A01A D02

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 HCl 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 Benzydamine Hcl 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
Oral doses of benzydamine are well absorbed and plasma drug concentrations reach a peak fairly rapidly and then decline with a half-life of about 13 hours. Less than 20% of the drug is bound to plasma proteins.

Although local drug concentrations are relatively large, the systemic absorption of mouthwash-gargle doses of benzydamine is relatively low compared to oral doses. This low absorption should greatly diminish the potential for any systemic drug side-effects when benzydamine is administered by this route. Benzydamine is metabolized primarily by oxidation, conjugation and dealkylation.

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, Ethanol (96%), Methyl p-hydroxybenzoate, saccharin, sodium hydrogen carbonate, Mint flavor, Polysorbate 20, Quinoline yellow (E104), Patent blue V (E131), Purified water.

6.2 Incompatibilities
None known.

6.3 Shelf life
After first opening, Tantum Verde can be used until the expiry date.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Colorless glass bottles containing 120 and 240 ml solution, together with its dosing measure of 15 and 30 ml.

6.6 Special precautions for disposal and other handling
The solution should be expelled from the mouth after use.

7. Marketing Authorisation Holder

RAZ Pharmaceutics Ltd., 6 Hamatechet St., Kadima, Israel.

8. Marketing Authorization Number

140-35-31801-00

9. Manufacturer

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