SUMMARY OF PRODUCT CARACTERISTICS

1. Name of the medicinal product
TANTUM VERDE

2. Qualitative and quantitative composition

Clear, green liquid, with a typical mint flavour containing Benzydamine hydrochloride 0.15% w/v.

Active ingredient:
Each 1ml contains 0.0015g of benzydamine hydrochloride.

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

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.

Adults and children above the age of 12: 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.

Method of Administration: The solution should be expelled from the mouth after use.
Uninterrupted treatment should not exceed seven days, except under medical supervision.

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.
- women in the third trimester of pregnancy because it may harm the unborn baby or cause difficulties during labour (see section 4.6).

4.4 Special warnings and precautions for use
Benzydamine use is not advisable in patients with hypersensitivity to acetylsalicylic acid or other NSAID's.
Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma. Caution should be exercised in these patients.
Benzydamine Oral Rinse should generally be used undiluted, but if 'stinging' occurs, the rinse may be diluted with water.
Avoid contact with eyes.

Important information about some of the ingredients of this medicine

This medicine contains 1.2 g of alcohol (ethanol) in each 15 ml dose.
The amount of alcohol in 15 ml of this medicine is equivalent to 30.3 ml beer or 12.12 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains Methyl para-hydroxybenzoate that may cause allergic reactions (possibly delayed).

This medicine contains 2mg benzyl alcohol in each 15 ml dose which is equivalent to 0.14 mg/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, D-limonene and linalool. These substances may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per 15 ml dose, 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 Oral Rinse 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 Oral Rinse 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 Oral Rinse should not be given unless clearly necessary. If Benzydamine Oral Rinse 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 the duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Benzydamine Oral Rinse for several days from gestational week 20 onward. Benzydamine Oral Rinse 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 labor.
Consequently, Benzydamine Oral Rinse is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding
Benzydamine Oral Rinse 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 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 (≥ 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 reaction, Hypersensitivity reactions.
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
	Not known	Angioedema

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
Intoxication is only to be expected if large quantities of benzydamine 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 substances for local oral treatment.
ATC code: A01AD02

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 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

Ethanol 96%, Glycerol, Methyl parahydroxybenzoate, Mint flavour, Saccharin, Sodium hydrogen carbonate, Polysorbate 20, Quinoline yellow 70% (E104), Patent blue V 85% (E131), Purified water.

6.2 Incompatibilities

Not known.

6.3 Shelf life

After first opening, Tantum Verde can be used until the expiry date of the product that is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package to protect from light.

6.5 Nature and contents of container

Colorless glass bottles containing 120 and 240 ml solution, together with its dosing measure device with 15 and 30 ml lining.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

The solution should be expelled from the mouth after use.

7. Marketing Authorisation Holder and Importer

RAZ Pharmaceutics Ltd.,
31 Gesher haetz Street, Emek Hefer Industrial Park, Israel.

8. Marketing Authorization Number

140-35-31801-00

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