SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FARDOBEN 0.15% + 0.12% Gargle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of solution contains:

Active substance(s):

Chlorhexidine gluconate ..... 6 mg (0.12%)
Benzydamine hydrochloride ..... 7.5 mg (0.15%)

Excipient(s) with known effect:

Ethanol 96% ..... 390 mg
Sorbitol, liquid (non-crystallizing) 70% ..... 500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gargle solution.
Colorless or yellowish clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- For inflammatory and painful conditions of oropharyngeal mucosa such as gingivitis, stomatitis, pharyngitis, tonsillitis and aphthous lesions
- For antisepsis of oropharyngeal region, facilitating the swallowing function of the patient, and for symptomatic relief of gingival disorders
- Before and after periodontal interventions
- For mucositis due to radiotherapy, chemotherapy and other reasons
- For prophylactic treatment of dental plaques

4.2. Posology and method of administration

Posology / Frequency and duration of administration

Adult dose of FARDOBEN is 15 ml.
It is administered at 1.5-3-hour intervals during a day.
It should not be used for more than 7 days continuously.

Method of administration:

FARDOBEN is for mouth rinse or gargle.
FARDOBEN is used without dilution.
It is kept in mouth for minimum 30 seconds.
It is expectorated after each use.

Chlorhexidine in FARDOBEN reduces plaque and gingivitis during treatment. If FARDOBEN is used as an alternative to oral hygiene procedures, the mouth should be rinsed with FARDOBEN for at least 1 minute. Teeth should be brushed before use in order to minimize the discoloration induced by chlorhexidine in FARDOBEN.

Additional information on special population
Renal/Hepatic impairment:
As absorbed benzydamine is mainly metabolized in the liver, the possibility of systemic effect should be taken into consideration in patients with severe hepatic impairment.

As absorbed benzydamine and its metabolites are excreted in the urine, the possibility of systemic effect should be taken into consideration in patients with severe renal impairment.

Pediatric population:
Children 12 years of age and above should gargle with 5-15 ml FARDOBEN for 30 seconds every 1.5-3 hours.

It should not be used by children 6 years of age and under.

Unless recommended by a doctor, it should not be used in children over 6 years of age and under 12 years of age.

It should not be used for more than 7 days continuously.

In case of burning and stinging sensation, the gargle should be diluted with some water.

Geriatric population:
No dose changes are required in the elderly.

4.3. Contraindications
- It is contraindicated in patients with hypersensitivity to benzydamine and chlorhexidine and any of the other ingredients in FARDOBEN.
- It should not be used during pregnancy and lactation.
- It should not be used in children aged 6 years and below.

4.4. Special warnings and precautions for use
For external use.

It is used only in the mouth; its contact with eyes and ears should be avoided. If it contacts with eyes, eyes should be well-rinsed with plenty of water.

It may cause reversible color change in mouth, on tongue and teeth.

FARDOBEN should not be swallowed and should be expectorated after each use.
It is used without dilution.

If sore throat is caused by bacterial infection or accompanied by infection, antibacterial treatment can be considered in addition to FARDOBEN use.

Impaired renal function: As absorbed benzydamine and its metabolites are excreted in urine, possibility of systemic effect should be taken into consideration in patients with severe renal impairment.

Impaired hepatic function: As absorbed benzydamine is metabolized highly in liver, possibility of systemic effect should be taken into consideration in patients with severe hepatic impairment.

This medicinal product contains ethanol (alcohol) up to 9.5% by volume; for example, up to 1123.2 mg per dose (15 ml), equivalent to 28.5 ml beer per dose, equivalent to 11.9 ml wine per dose.

It can be harmful for those with alcohol addiction.

It should be taken into consideration in pregnant or lactating women, children, and patients at high risk, such with liver disease or epilepsy.

Because this product contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

It should not be used for more than 7 days continuously.

4.5. Interaction with other medicinal products and other forms of interaction

Chlorhexidine:

Chlorhexidine salts are incompatible with soap and other anionic compounds.

Chlorhexidine salts are compatible with cationic and nonionic surface active agents; however, when they are co-administered at high concentrations, chlorhexidine activity may be reduced due to micellar binding.

Chlorhexidine salts solubility can be raised with surfactants such as cetrimide and lissapol NX.

It is incompatible with anionic poly-electrodes such as gum arabic, sodium alginate, sodium carboxy methyl cellulose and it is incompatible with starch and gummi tragacanthae; their effects are also reduced with these agents.

Chlorhexidine is also incompatible with substances such as brilliant green, chloramphenicol, copper sulphate, fluorescein sodium, formaldehyde, silver nitrate and zinc sulphate.

As chlorhexidine interacts with Ca^{+2} and Mg^{+2} cations when diluted with hard water, it may precipitate as insoluble salts.

If solutions of chlorhexidine salts combined with benzoates, bicarbonates, carbonates, borates, nitrates, phosphates and sulphates are more concentrated than 0.05%, its solubility precipitates as it will form salts with less solubility. As cetrimide enhances solubility of these salts, these precipitations do not occur when they are combined with cetrimide.

Chlorhexidine gluconate is compatible with cetrimide and benzalkonium chloride. These synergistically enhance bactericide effect. Cetrimide prevents precipitation of chlorhexidine with hard waters.

Except for chlorhexidine gluconate, chlorhexidine and its salts dissolve better in alcohol than

water.

Chlorhexidine gluconate solution may precipitate when it is added over alcohol. Ethanol in formulation renders the solution more effective against Gram negative microorganisms. They can be adsorbed during filtration through cellulosic filters.

Drug interactions with benzydamine have not been reported.

Additional information on special populations
No interaction study was conducted in special populations.

Pediatric population
No interaction study was conducted in pediatric population.

4.6. Fertility, pregnancy and lactation
General advice
Pregnancy category is C.

Women of child-bearing potential/Contraception
FARDOBEN does not have any effect on contraception; however, as FARDOBEN contains alcohol, women of child-bearing potential should use it cautiously.

Pregnancy
FARDOBEN is contraindicated during pregnancy.
Animal studies are insufficient with respect to effects on pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development (see section 5.3). The potential risk for humans is unknown.

Breast-feeding
There is no available data regarding for excretion in human or animal milk of benzydamine and chlorhexidine gluconate. Therefore, it cannot be ignored that there is a risk for the child in the breast. FARDOBEN is contraindicated in breast-feeding women.

Reproduction ability /Fertility
Reproduction and fertility studies with chlorhexidine gluconate have been conducted. No evidence of impaired fertility was observed in rats, and no evidence of harm to the fetus was observed in rats and rabbits. There is no sufficient study conducted on animals for benzydamine.

4.7. Effects on ability to drive and use machines
No effects on the ability to drive or operate machinery have been observed.

4.8. Undesirable effects
Reported undesirable effects are listed according to the following frequency. 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), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Immune system disorders
Very rare: Allergic reactions, hypersensitivity and anaphylaxis

Endocrine disorders
Very rare: Transient swelling of the parotid gland

Nervous system disorders
Very common: Temporary decreased sensation in the mouth
Common: Stinging and burning sensation in the mouth
Not known: Dizziness, headache, drowsiness

Respiratory, thoracic and mediastinal disorders
Very rare: Laryngospasm, bronchospasm
Not known: Pharyngeal irritation, cough

Gastrointestinal disorders
Common: Oral numbness, nausea, vomiting, retching
Not known: Dry mouth

General disorders and administration site disorders
Common: Altered taste and staining of teeth and other oral surfaces and increased calculus formation Tooth staining is harmless and can be minimized through tooth-brushing before application.
Very rare: Local dryness, thirst, tingling, and feeling of coolness in the mouth

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9. Overdose
If FARDOBEN is accidentally swallowed, symptomatic and supportive treatment should be instituted. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic Group: Antiseptic (topical pharyngeal), topical oral anti-inflammatory
ATC code: A01AD11

Benzydamine is an anti-inflammatory analgesic agent structurally unrelated to the steroid group. Benzydamine differs from other non-steroid anti-inflammatory agents in that it is a base.
At concentrations used for topical treatment, benzydamine exerts local anesthetic effect. The analgesic activity of benzydamine was more reported in models involving experimental inflammation rather than non-inflammatory pain.

Chlorhexidine is a biguanide antiseptic that helps to reduce the development of plaque and gingivitis when usual oral hygiene measures are interrupted. It is a strong base with affinity for oral structures including hydroxyapatite of tooth enamel, pellicle of tooth surface, bacteria and salivary proteins. Chlorhexidine reduces dental plaque deposition and associated gingivitis as characterized by redness, swelling or bleeding of the gingiva. It reduces frequency of aphthous ulcer formation and increases the rate of healing following periodontal surgery.

The antiinflammatory action mechanism of benzydamine is not associated with adrenal axis secretion. Like other non-steroidal anti-inflammatory agents, benzydamine inhibits prostaglandin biosynthesis in certain conditions. But this function has not been explained completely. The stabilizing effects on cellular membranes can be attributed to the mechanism of action.

After topical administration, chlorhexidine has a bacteriocidal effect following the prolonged bacteriostatic effect. Chlorhexidine is active against a wide range of microorganisms including gram-positive, gram-negative bacteria, yeast and some fungi and viruses. Chlorhexidine appears to delay bacterial growth by a delayed surface action. It is absorbed onto microbial cell walls and causes membrane leakage.

5.2. Pharmacokinetic properties

General characteristics

Absorption:

Systemic absorption does not appear to occur following administration of chlorhexidine gluconate topical oral solution as mouth gargle. When it is administered as described, 4% of mouth gargle dose is ingested and some part is absorbed. 90% of the ingested chlorhexidine dose is not absorbed and excreted directly in feces.

Following administration of chlorhexidine gluconate 0.12% topical oral solution as a mouth gargle, approximately 30% of the medicine is retained in the oral cavity. Chlorhexidine is gradually released for up to 24 hours.

Following topical administration of benzydamine hydrochloride, benzydamine is well absorbed into the inflamed oral mucosa where it exerts anti-inflammatory and local anesthetic effect on administration site. Plasma benzydamine level following use of benzydamine is low and parallel the amount actually ingested.

Distribution:

FARDOBEN is a locally acting drug. Therefore, it should not be swallowed according to the described administration. Thus, systemic absorption and distribution is not expected. Moreover, absorption of both components through gastrointestinal mucosa is low.

Biotransformation:

As chlorhexidine gluconate is poorly absorbed, no detectable blood levels have been found. Benzydamine is metabolized generally by oxidation and conjugation.

Elimination:

Chlorhexidine is not accumulated in body and only small amount of it is metabolized. Approximately 10% of the ingested chlorhexidine is excreted via kidneys following absorption;

90% unabsorbed is excreted in feces.

Benzydamine and metabolites entering the systemic circulation are excreted largely in the urine.

5.3. Preclinical safety data
The oral LD_{50} of chlorhexidine gluconate exceeds 3 mg/kg in male and female rats, 2.5 mg/kg in male mice, and 2.6 mg/kg in female mice; its IV LD_{50} is 21 mg/kg in male rats, 23 mg/kg in female rats, 25 mg/kg in male mice, and 24 mg/kg in female mice; its subcutaneous LD_{50} is more than 1 g/kg in male and female rats, more than 637 mg/kg in male mice, and more than 632 mg/kg in female mice. The oral LD_{50} of chlorhexidine gluconate in humans is about 2 g/kg.

In acute studies, lethal dose of benzydamine is far above the therapeutic dose. Human therapeutic doses are 0.7-1.0 mg/kg. The LD_{50} values (mg/kg) in mice were 33 IV; 110 IP; 218 SC and 515 PO and in rats 100 IP and 1050 PO.

Studies on reproduction and fertility with chlorhexidine gluconate were performed. No harmful effects were seen on fertility in rats, or on the fetus of rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sorbitol, liquid (non-crystallizing) 70%
Glycerol
Polysorbate 20
Peppermint flavor
Ethanol 96%
Vaporboost flexarome
Sodium bicarbonate
Hydrochloric acid
Purified water

6.2. Incompatibilities
Chlorhexidine gluconate solution may precipitate when it is added over alcohol. It is incompatible with anionic poly-electrodes such as gum arabic, sodium alginate, sodium carboxy methyl cellulose and it is incompatible with starch and gummi tragacanthae. Chlorhexidine salts are incompatible with soap and other anionic compounds. Chlorhexidine is also incompatible with substances such as brilliant green, chloramphenicol, copper sulphate, fluorescein sodium, formaldehyde, silver nitrate and zinc sulphate.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 25°C and protect from light.

6.5. Nature and contents of container
The product is available in a 200 ml, PP, amber-colored glass bottle with a plastic cap. Each

cardboard box includes 1 bottle and 1 measuring cup marked at 5 ml, 10 ml, 15 ml and 20 ml.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

245/58

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 12.10.2012
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT

25.01.2024