SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FARDOBEN 0.15% + 0.12% Oral Spray, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
In 30 ml (1 bottle);
Active substance(s):
Chlorhexidine gluconate_____36 mg (0.12%)
Benzydamine HCl_____45 mg (0.15%)
Excipient(s) with known effect:
Sorbitol liquid (non-crystallising) 70%_____3000 mg
Ethanol 96%_____2340 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Spray.
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
The usual dose of FARDOBEN is 5-10 sprays as direct application onto throat/inflamed area.
To be repeated every 1.5-3 hours as necessary.
It should not be used for more than 7 days continuously.

Method of administration
FARDOBEN is used without dilution. FARDOBEN should not be swallowed and should be expectorated after each use.
Before the initial use, it should be directed into an area away from the face and pumping button should be pressed couple of times until a fine spray is obtained.
Mouth should be opened wide; spray nozzle should be put inside the mouth and sprayed into the oral cavity. This procedure should be repeated at different areas at least for 4 times.
After application, bottle should be placed inside its box and kept in upright position.
Chlorhexidine in FARDOBEN reduces plaque and gingivitis during treatment. If FARDOBEN is used as an alternative to oral hygiene procedures, FARDOBEN should be held in the mouth 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
Possibility of systemic effect should be taken into consideration and therefore caution is advised in patients with severe renal and hepatic impairment (see section 4.4.).

Pediatric population
In children 12 years of age and above, spray is directly applied to throat/inflamed area.
The usual dose is 5 sprays. To be repeated every 1.5-3 hours as necessary.
It should not be used in 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.

Geriatric population
The same dose as adults can be applied to geriatric patients.

4.3. Contraindications
It is contraindicated in patients with hypersensitivity to benzydamine and chlorhexidine and any of the ingredients in FARDOBEN.
It should not be used during pregnancy and lactation (see section 4.6.).
It should not be used in children 6 years of age and under.

4.4. Special warnings and precautions for use
- For external use.
- It is used only in the mouth; contact with eyes and ears should be avoided. In contacts with eyes, eyes should be well rinsed with plenty of water.
- It may cause reversible color change in mouth, on tongue and teeth. Teeth should be brushed before use in order to minimize the discoloration.
- 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 should be considered in addition to FARDOBEN use.
- 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.
- As absorbed benzydamine is metabolized highly in the liver, possibility of systemic effect should be taken into consideration in patients with severe hepatic impairment.
- This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- This medicinal product contains ethanol (alcohol) in small amounts – less than 100 mg per dose.
- It should not be used for more than 7 days continuously.

4.5. Interaction with other medicinal products and other forms of interaction
- FARDOBEN does not have any known significant drug interactions. Chlorhexidine, one of the drug substances it contains, is incompatible with some agents.
- 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.
- Solubility of chlorhexidine salts can be increased 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 gum tragacanth; their effects are also reduced with these agents.
- Chlorhexidine is also incompatible with substances such as brilliant green, chloramphenicol, copper sulfate, 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 are combined with benzoates, bicarbonates, carbonates, borates, nitrates, phosphates and sulfates 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 with childbearing potential/Contraception
FARDOBEN does not have any effect on contraception; however, as FARDOBEN contains alcohol, women of childbearing potential should use it cautiously.

Pregnancy
Animal studies are insufficient with respect to effects on pregnancy/and-or/embryonal/fetal development/and-or/parturition/and-or/postnatal development (see section 5.3). The potential risk to humans is unknown.
Controlled studies with chlorhexidine gluconate in pregnant women have not been conducted.
For benzydamine, there is not any sufficient study conducted in animals and pregnant women.
Safety use of the combination of drug substances in the combination was not determined in animals and in pregnant women. Therefore, use of this drug is contraindicated during pregnancy.

Breast-feeding
No data are available for lactating women. Therefore, it is contraindicated in nursing women.

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.

4.7. Effects on ability to drive and use machinery

It does not have any effect on the ability to drive and use machinery.

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 (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000) and unknown (cannot be estimated based on available data).
FARDOBEN is generally well tolerated and its side effects are minor.
There is not any serious side effect and adverse effect reported at the end of clinical studies.
Mostly, local side effects are observed. Systemic side effects, generally, are not observed and not serious.

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

Endocrine disorders
Very rare: Temporary swelling of parotid gland

Central nervous system disorders
Very common: Transient numbness in the mouth
Common: Stinging and burning sensation in the mouth
Unknown: Dizziness, headache and drowsiness

Respiratory, thoracic and mediastinal disorders
Very rare: Laryngospasm, bronchospasm
Unknown: Pharyngeal irritation, coughing

Gastrointestinal disorders
Common: Nausea, vomiting, retching
Unknown: Dry mouth

Skin and subcutaneous tissue disorders
Very rare: Irritation-associated skin reactions, itching accompanied by rash, urticaria, photodermatitis and oral desquamation

General disorders and administration site disorders
Common: Other side effects like altered taste and staining of teeth and other oral surfaces and increased calculus formation generally occur less. Tooth staining is harmless and can be minimized through tooth brushing before application.
Very rare: Local dryness or thirst, tingling, 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 in accordance with local requirements.

4.9. Overdose
Intoxication is not possible considering method of administration of the drug substance.
However, if FARDOBEN is accidentally swallowed, symptomatic 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.

Like other non-steroidal anti-inflammatory agents, benzydamine inhibits the biosynthesis of prostaglandins under certain conditions, but its properties in this respect have not been fully explained. The stabilizing effect on cellular membranes may be involved in the mechanism of action.

Following normal topical application of the drug, chlorhexidine produces bactericidal effect, followed by a prolonged bacteriostatic action.

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.

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 properties
Absorption:
No systemic absorption is observed after application of chlorhexidine gluconate topical oral solution as a mouthwash. When used as described, 4% of the oral gargle dose is swallowed and a portion is absorbed. Ninety-percent (90%) of the swallowed chlorhexidine dose is not absorbed and is excreted directly with feces. Approximately 30% of the drug remains in the oral cavity when applied as a 0.12% chlorhexidine gluconate solution topical oral mouthwash.

Chlorhexidine gluconate is released gradually over 24 hours. Following topical administration of benzydamine hydrochloride, benzydamine is absorbed by the inflamed oral mucosa and shows anti-inflammatory and local anesthetic effect at the site of administration. The level of plasma benzydamine obtained after oral administration of benzydamine is low and is directly proportional to the amount taken.

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 its metabolites entering in 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-crystallising) 70%
Glycerol
Polysorbate 20 (Tween 20)
Peppermint flavor
Ethanol 96%
Sodium hydrogen carbonate
Concentrate hydrochloric acid solution
Purified water

6.2. Incompatibilities

Chlorhexidine salts are incompatible with soap and other anionic compounds; with anionic poly-electrodes such as gum arabic, sodium alginate, sodium carboxy methyl cellulose; and with substances such as brilliant green, chloramphenicol, copper sulfate, fluorescein sodium, formaldehyde, silver nitrate and zinc sulfate (see section 4.5.).

6.3. Shelf life
36 months.

6.4 Special precautions for storage
It should be kept at room temperature below 25°C and protected from light.
Bottle should be placed inside its box and kept in upright position.

6.5 Nature and contents of container
A 30 mL, white HDPE plastic bottle with spray pump is used as the primary packaging material.
Each cardboard box includes 1 bottle.

6.6 Special precautions for disposal
Any unused material should be disposed according to local disposal regulations.

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

8. MARKETING AUTHORIZATION NUMBER
245/49

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 12.10.2012
Date of last renewal :

10. REVISION DATE OF TEXT
25.01.2024