SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KLOROBEN Oral Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMPOSITION: Active ingredient:

30 ml (1 bottle) contains:

Chlorhexidine gluconate	36 mg
Benzydamine hydrochloride	45 mg

Excipients:

30 ml (1 bottle) contains:

Sorbitol (%70)	3 g
Propylene glycol	3 g

See 6.1 for a list of excipients.

3. PHARMACEUTICAL FORM

Spray

Green coloured, sweetish sour, refreshing mint odour, clear solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Inflammation in mouth and throat mucosa and painful gingivitis, stomatitis, pharyngitis, tonsillitis and aphthous lesions
- Mouth and throat antisepsis, relieving the deglutition, and alleviating the symptoms of gingivitis,
- Before and after periodontal interventions,
- In mucositis after radiotherapy and chemotherapy or due to other causes
- Prevention of dental plaques.

4.2. Posology and method of administration

Posology/ frequency and duration of administration:

The usual dose for the administration of KLOROBEN directly to the throat/ inflamed area is 5-10 sprays. If necessary, it is repeated every 1,5-3 hours.

Method of administration:

KLOROBEN is used without diluting. KLOROBEN should not be swallowed and must be expectorated.

Prior to the first usage, it is necessary to press the pump a few times, holding it away from the face, until regular spraying is achieved.

The mouth must be opened widely, and the spray must be administered into the oral cavity, by inserting the nozzle of the spray in the mouth. This must be repeated at least 4 times in various areas.

Following the administration the bottle should be stored in its box vertically.

Chlorhexidine, which KLOROBEN contains alleviates the formation of plaque and gingivitis during the treatment. If used as an alternative to oral hygene procedures, KLOROBEN should be kept in mouth for at least 1 minute.

In order to minimise the staining caused by chlorhexidine in KLOROBEN, it is necessary to brush the teeth before using it.

Additional information about special populations:

Renal/Liver failure:

Patients with severe renal failure and severe liver failure must use it with caution, considering the possibility of systemic effect (See Section 4.4).

Pediatric population:

In children above the age of 6, the spray is administered directly on the throat or the inflamed area.

The usual dose is 5 sprays. If necessary it can be repeated every 1,5- 3 hours. KLOROBEN is not recommended for children under the age of 6 due to the insufficiency of clinical trials. (See Section 4.4).

Geriatric population:

Geriatric patients can be administered the same dosage with adults.

4.3. Contraindications

KLOROBEN is contraindicated in patients with hypersensitivity to benzydamine and chlorhexidine and any one of the ingredients in the formula.

It should not be used during pregnancy and lactation (See Section 4.6)

4.4. Special warnings and precautions for use .

It is used externally.

It is not recommended for children under the age of 6 due to the insufficiency of clinical trials.

It is used exclusively inside the mouth; contact with eyes and ears should be avoided.

In the case of contact with eyes, they should be washed with plenty of water.

It can cause reversible staining in the mouth, on the tongue and the teeth. It is appropriate to brush teeth before administration to minimise staining.

KLOROBEN should not be swallowed and must be orally removed by spitting.

It is used without diluting.

If throat pain is caused by a bacterial infection or is seen with infection, antibacterial treatment may be considered in addition to the use of KLOROBEN.

As the absorbed benzydamine and its metabolites are disposed with urine, systemic effect should be considered in patients with severe liver failure.

As absorbed benzydamine is metabolized in the liver at high doses, the possibility of systemic effects should be considered in patients with severe hepatic impairment.

This medicinal product should not be used in patients with rare genetic fructose intolerance as it contains sorbitol.

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

- There is no known major interaction of KLOROBEN. Chlorhexidine, an active ingredient in the formula is incompatible with some substances.
- The salts of chlorhexdine are incompatible with soap and other anionic compounds,

- Chlorhexidine salts are compatible with cationic and non-ionic surface active agents; however, when used together in high concentrations chlorhexidine activity can decrease due to micellar bounding.
- The solubility of chlorhexidine salts can be increased via such surfactants as cetrimide and lissapol NX.
- Chlorhexidine is incompatible with anionic polyelectrolytes such as arabic gum, sodium alginate, sodium carboxymethyl cellulose, starch and gummi tragachantae; with these substances its effect is also decreased.
- Chlorhexidine is also incompatible with brillant green, chloramphenicol, copper sulphate, fluorescein sodium, formaldehyde, silver nitrate, zinc sulphate.
- When chlorhexidine is diluted with hard water, it can precipitate as insoluble salts since it interacts with Ca and Mg cations.
- If the solutions of chlorhexidine salts are more concentrated than 0.05% which are combined with benzoates, bicarbonates, carbonates, borates, nitrates, phosphates, sulphates, they precipitate since they will form less soluble salts. As cetrimide increases the solubility of these salts, they won't precipitate when combined with cetrimide.
- Chlorhexidine gluconate is compatible with cetrimide and benzalconium chloride. They increase the bactericide effect sinergically. Cetrimide prevents chlorhexidine precipitation with hard water.
- Chlorhexidine and its salts except chlorhexidine gluconate dissolve better in alcohol than in water. Chlorhexidine gluconate solution can precipitate when alcohol is added.
- No drug interaction is established with benzydamine.

Additional information about special population

Interaction studies have not been performed on special population yet.

Pediatric population

Interaction studies have not been performed on pediatric population yet.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women with the potential to give birth/ Birth control (Contraception)

KLOROBEN has no effect on contraception.

Pregnancy period:

Studies on animals are inadequate in terms of the effect on pregnancy/and-or/embriyonal/fetal development/and-or/birth/and-or/postnatal development (See Section 5.3.). Potential risk on humans is not known.

No controlled studies have been conducted with chlorhexidine gluconate on pregnant women.

Benzydamine has not been studied adequately on animals and pregnant women.

Safe usage of the active ingredients that form the combination has not been established in animals and pregnant women. Therefore, using it during pregnancy is contraindicated.

Lactation period:

There is no data on lactating women. It is therefore contraindicated in lactating women.

Fertility:

Studies have been conducted on chlorhexidine gluconate and fertility. No harmful effect on fertility has been observed in rats, and no harmful effect on fetus has been observed in rats and rabbits.

Regarding benzydamine, there is not enough research in animals.

4.7. Effects on ability to drive and use machines

No adverse effect on the ability to drive and use machines has been reported.

4.8. Undesirable effects

Undesirable effects listed below are classified according to frequency groupings through the following convention.

Very common (≥1/10); common (between ≥1/100 and <1/10); uncommon (between ≥1/1000 and <1/100); rare (between ≥1/10.000, and <1/1000); very rare (<1/10.000), not known (cannot be estimated with the available data)

KLOROBEN is usually well tolerated and its side effects are few.

No serious side effects and advers effects have been reported as a result of clinical studies. It is usually local side effects that are observed. Systemic side effects are usually not observed and not serious.

Immune system diseases:

Very rare: Allergic reaction, hypersensitivity and anaphylaxis

Endocrine system diseases:

Very rare: Transient swelling of the parotid gland.

Neurologic diseases:

Very common: Temporary sensation decrease in mouth

Common: Stinging and burning sensation in the mouth

Not known: Dizziness, headache, drowsiness

Respiratory, Thoracic diseases and mediastinal diseases:

Very rare: Laryngospazm, bronchospazm

Not known: Pharyngeal irritation, coughing

Gastrointestinal diseases:

Common: Nausea, vomiting, retching

Not known: Mouth dryness

Dermatological and subcutaneous tissue diseases:

Very rare: Irritation-related skin reactions, rash associated with itching, urticaria, photodermatitis, oral desquamation.

General disorders and diseases related to administration area:

Common: Other side effects such as alteration in taste sensation, staining on the teeth and other oral surfaces, increase in calculus formation are usually fewer. Teeth staining is harmless and can be minimised by brushing the teeth before administration.

Very rare: Local dryness and thirst, tingling, a feeling of coolness in the mouth.

4.9. Overdose and its treatment

Considering the method of administration of the active ingredient, intoxication is not possible. However, if KLOROBEN is ingested by accident, symptomatic treatment is necessary. It has no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiseptic (Topical Pharengeal), Topical oral anti-inflammatory

ATC Code: A01AD11

Benzydamine is an anti-inflammatory analgesic agent structurally unrelated to steroid group.

Benzydamine is different from other non-steroid anti-inflammatory agents due to its base nature.

In concentrations used in topical treatment, benzydamine has local anaesthetic effect.

Benzydamine analgesic activity is reported more in models involving experimental inflammation than noninflammatory pains.

Benzydamine's anti-inflammatory mechanism of action is not related to adrenal axis secretion.

Like other non-steroid anti-inflammatory agents, benzydamine inhibits prostaglandin biosynthesis under certain conditions. However, this property could not be explained precisely. Their stabilising effect on cellular membranes can be attributed to its mechanism of action.

Following the normal topical administration of the medication, chlorhexidine shows bacteriocidal action after prolonged bacteriostatic action.

Chlorhexidine is a biguanide antiseptic and aids alleviate plaque and gingivitis formation when oral hygiene maintenance is discontinued. It has a strong affinity with tooth enamel hydroxyapatite, tooth surface, oral forms containing saliva proteins and bacteria. Chlorhexidine alleviates dental plaque deposition and gingivitis characterised as accompanying redness, swelling or bleeding in gingival. It reduces the formation of aphthous ulcers and promotes recovery of post periodontal surgery.

Chlorhexidine is effective on gram(+) and gram(-) bacteria, yeast and some fungi and most viruses. Chlorhexidine delays bacterial reproduction with its delayed surface action. It is absorbed through microbial cell walls and leads to membrane leakage.

5.2. Pharmacokinetic properties

General properties

Absorption:

Chlorhexidin gluconate topical oral solution has no systemic absorption following its administration as oral rinse. When used as instructed, 4% of the oral rinse dose is ingested and some of its absorbed. 90% of the chlorhexidine dose ingested is not absorbed and disposed with faeces.

When the administration of chlorhexidine gluconate 0.12% topical oral solution as oral rinse, 30% of the medication remains in the oral cavity. Chlorhexidine gluconate is gradually released over 24 hours.

Following the topical administration of benzydamine hydrochloride, benzydamine is absorbed by inflammatory oral mucosa and shows anti-inflammatory and local anaesthetic action on the area of administration. Plasma benzydamine level obtained after benzydamine oral administration is low and directly proportional to the dose actively taken.

Distribution:

KLOROBEN is a medication with local effect. Therefore, it must not be swallowed, as instructed. Thus systemic absorption and distribution are not expected. Besides, the gastrointestinal mucosal absorption of both ingredients is low.

Biotransformation:

Chlorhexidine cannot be measured in plasma as its absorption is at minimal level. Benzydamine is usually metabolised through oxidation and conjugation.

Elimination:

Chlorhexidine does not accumulate in the body and a very little amount is metabolised. Approximately 10% of the ingested chlorhexidine is disposed through kidneys following the absorption; the remaining 90% unabsorbed medication is disposed through faeces.

Benzydamine and its metabolites getting into the systemic circulation are disposed with urine.

5.3. Preclinical safety data

Oral LD 50 of Chlorhexidine gluconate exceeds 3 mg/kg in male and female rats, 2,5 mg/kg in male mice, 2,6 mg/kg in female mice; IV LD50 of it is 21 mg/kg in male rats, 23 mg/kg in female rats, 25 mg/kg in male mice, 24 mg/kg in female mice; subcutaneous LD50 of it is over 1 g/ kg in male and female rats, 637 mg/kg in male mice, 632 mg/kg in female mice.

Oral LD50 of chlorhexidine gluconate in humans is approximately 2 g/kg. The lethal dose of benzydamine in acute trials is well above the treatment dose. The therapeutic dose in humans is 0.7-1.0 mg/kg. LD50 values (mg/kg) is specified as 33 i.v.; 110 i.p.; 218 s.c.; and 515 p.o in mice; and 100 i.p. and 1050 p.o in rats.

Studies have been conducted on chlorhexidine gluconate and fertility. No harmful effect on fertility has been observed in rats, and no harmful effect on fetus has been observed in rats and rabbits.

6. Pharmaceutical particulars

6.1. List of excipients

Sorbitol %70

Polysorbate 20

Propylene glycol

Patent V blue

Quinoline yellow

Ecocool MP (flavour)

Sucralose

Peppermint extract

Citric acid monohydrate

Sodium citrate dihydrate

Purified water

6.2. Incompatibilities

Chlorhexidine salts are is incompatible with soap and other anionic compounds, anionic polyelectrolytes such as arabic gum, sodium alginate, sodium carboxymethyl cellulose, starch and gummi tragachantae and brilliant green, chloramphenicol, copper suphate, fluorescein sodium, formaldehyde, silver nitrate, zinc sulphate (See Section 4.5).

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at room temperature below 25 ºC and protect from light.
It should be placed in the bottle box and stored vertically.

6.5. Property and contents of container

White HDPE bottle with spray pump apparatus is used as primary packaging material.
Each box contains 1 bottle.

6.6. Special precautions for disposal and other handling

Unused products or waste materials must be disposed in compliance with “Regulation for Control of Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

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