SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KLOROBEN Oral Rinse

2. QUANTITATIVE COMPOSITION

In 100 mL,

Active Substance

Chlorhexidine Gluconate	120 mg (%0.12)
Benzydamine Hydrochloride	150 mg (%0.15)

Excipients

Sorbitol (%70)	10 g
Propylene glycol	10 g

See 6.1 for all excipients.

3. PHARMACEUTICAL FORM

Rinse Solution

Green in color, with a sweetish sour taste, refreshing mint smelling, clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- In mouth and throat mucosa inflammation and pain associated gingivitis, stomatitis, pharyngitis, tonsillitis and aphthous lesions,
- Mouth and throat antisepsis relaxation of the patient’s swallowing function and in gingival disturbances in the form of symptom eliminating agent,
- Before and after periodontal interferences,
- Pose radiotherapy and chemotherapy or due to alternatives causes in mucositis,
- Applied in the intention of preventing dental plates.

4.2 Posology and method of administration

Posology / Term and frequency of administration:

Adult dose: Usual dose is 15 ml. It is administered at intervals of 1.5-3 hours during the day.

Application Form:

KLOROBEN is used for mouthwashing and gargling

KLOROBEN KLOROBEN is usually used without diluting.

It should rinsed for 30 seconds.

It should discarded orally after use.

Chlorhexidine gluconate in the KLOROBEN content induces plaque and gingivitis during treatment.If KLOROBEN is as an alternative to oral hygiene procedures, mouth rinses at least 1 minute. Before using teeth must be brushed to minimize colouring effect of chlorhexidine gluconate.

Additional information considering special populations:

Kidney/Liver failure:

Since absorbed benzidamine is largely metabolized in the liver, the possibility of systemic effects should be considered in patients with severe hepatic impairment.

The possibility of systemic effects should be considered in patients with severe liver and renal impairment as absorbed benzydamine and its metabolites are excreted in the urine.

Pediatric population: (12 years and above)

KLOROBEN can be used over above 12 years old children.

Usual dose is 5-15 ml. It should rinsed for 30 seconds. It can be repeated in 1.5 – 3 hours.

KLOROBEN shouldn’t be used continuously over 7 days.

KLOROBEN can be diluted with water in patients if burning or stringing occurs

Due to lack adequate clinical studies KLOROBEN is not recommended for children younger than 12 years of age.

Geriatric population:

Elderly patients do not need any dose changes.

4.3 Contraindications

- KLOROBEN is contraindicated in patients with hypersensitivity to benzydamine and chlorhexidine.

KLOROBEN should not be used;

- Hypersensitivity to any of the substances in the formulation
- during pregnancy and lactation

4.4 Special warnings and special precautions for use

Applied externally.

Owing to lack of satisfactory number clinical studies KLOROBEN is not recommended for children under 12 years of age.

Only used in mouth region, contact with eyes, ears must be avoided.

In the mouth over tongue and teeth reversible color change may be caused.

KLOROBEN must not be swallowed and by the way of swallowing must be eliminated from the mouth.

It is used without dilatation.

Throat pain if associated with bacterial infection or if found in correlation with infection in addition to KLOROBEN administration antibacterial therapy may be anticipated.

Impaired renal function: Absorbed Benzydamine and its metabolites since discharged via urinary duct over patients with elevated renal failure systematic effect possibility must be kept into consideration.

Impaired liver function: Absorbed Benzydamine since considerably metabolized with liver over the patients with intensified liver failure systematic possibility effect must be evaluated.

Because this medicinal product contains sorbitol, patients with rare hereditary fructose intolerance problems should not use this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Chlorhexidine;

Chlorhexidine salts are incompatible with soap and other anionic components.

Chlorhexidine salts are tolerated with cationic and nonionic surface active substances; whereas in elevated concentrations when applied in association as the result of micelle binding Chlorhexidine may attenuate its activity.

Chlorhexidine salts may elevated their solubility in surfactants such as cetrimide and lissapol NX.

Chlorhexidine is incompatible with gum Arabic, sodium alginate, sodium carboxyl methyl cellulose likewise anionic polyelectrolyte materials, starch and gummi tragacanthae, at the same time effects with these substances remain infinitesimal.

Chlorhexidine is incompatible with brillant green, chloramphenicol, copper sulphate, floressein sodium, formaldehyde, silver nitrate, zinc sulphate.

When diluted with hard water, it can precipitate into insoluble salts as it interacts with Ca + 2 and Mg + 2 cations.

In association with benzoates, bicarbonats, carbons, borats, nitrates, phosphates, sulphate combined Chlorhexidine salt solvents if remains in concentrated form over 0.05% they are precipitated due to the emergence of higher soluble salts. Cetrimide since elevating the solubility of these salts upon combination with cetrimide these sedimentations are eliminated.

Chlorhexidine is compatible with gluconate, cetrimide and benzalconium chloride. They synergically rise up the bactericide impact. Cetrimide prevents Chlorhexidine sedimentation in combination with hard waters.

Chlorhexidine gluconate excluded Chlorhexidine and its salts are better dissolved in alcohol compare to water. Chlorhexidine gluconate solvent may be precipitated when added to alcohol.

In combination with benzydamine no medication compatibility has been reported.

Additional information pertaining to special population

Over the special population no compatibility study has been ever performed.

Pediatric population

Over the pediatric population none of any compatibility analysis has been incorporated.

4.6 Pregnancy and lactation

Overall recommendation

Pregnancy category: C

Women with childbearing potential /(Contraception)

KLOROBEN is affectless for contraception.

Pregnancy period:

The use of KLOROBEN during pregnancy is contraindicated.
Animal studies are useless in terms of pregnancy/and-or/embryonic/fetal progression/and-or/delivery-and-or/post-delivery progression related outcomes.
The potential risk for human is unkown.

Lactation period:

No data are available on whether benzydamine and chlorhexidine gluconate are excreted in human or animal milk. Therefore, it cannot be excluded that there is a risk for the breast child. The use of KLOROBEN in breastfeeding mothers is contraindicated.

Reproduction power/ Fertility:

Studies on reproduction and fertility with chlorhexidine gluconate are available. On fertility in rats; no harmful effects were observed on the fetus again in rats and rabbits. There is not enough research on benzidamine in animals.

4.7 Effects on ability to drive and use machines

On vehicle or mechanical use no effect is observed.

4.8 Undesirable effects

The reported undesirable effects are listed according to the following frequency rating.
Very common (≥1/10); common (≥1/100 and <1/10); not common (≥1/1000 and <1/100); rare (≥1/10.000, and <1/1000); very rare (<1/10.000), unknown (can not be predicted on the basis of available data)

Immune system diseases:

Very rare: Allergic reaction, hypersensitivity and anaphylaxis

Endocrine system diseases:

Very rare: temporary swelling in the parotid gland

Nerve system diseases:

Very common: In the mouth temporary sense loss

Common: In mouth stick and burning sense

Unknown: Dizziness, headache, narcotics feel

Respiration, chest malformations and mediastinal diseases

Very rare: Laryngospasm, broncospasm

Unknown: Pharyngeal irritation, coughing

Gastrointestinal illnesses :

Common: oral numbness, nausea, vomiting, gagging

Unknown: Mouth dryness

Skin and subcutaneous tissue diseases:

Very rare: Irritation related skin reactions, spillage associated itching, urticar, photodermatitis, oral desquamation.

General disorders and application region related diseases:

Common : Variations in taste feeling, staining on teeth and other oral surfaces and increasing in calculus formations.

Tooth staining is harmless and can be minimized by brushing prior to application.

Very rare: Local dryness, thirst, pain, freshness feeling in mouth

4.9. Overdose and Treatment

But if KLOROBEN is drunk accidentally symptomatic and supportive therapy is required. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic cohort: Oropharynx drugs, Antiseptic drugs (Topical oral), oral anti- inflammatory drugs (topical oral)

ATC Code : A01AD11

Structurally benzydamine is an anti-inflammatory analgesic agent irrelevant with steroid group.

Benzidamine is different from other non-steroidal anti-inflammatory agents in terms of base formation.

In topical treatment used concentrations benzydamine may reveal local anesthetic effect. Benzydamine analgesic activity in experimental inflammation possessing models was reported much more than non-inflammatory pain.

Chlorhexidine is a biguanide antiseptic and when general oral hygiene is interrupted, it helps reduce plaque and gingivitis development. It has affinity for oral structures including tooth enamel hydroxyapatite, tooth surface, bacteria and saliva proteins. Chlorhexidine reduces dental plaque deposition and associated gingivitis characterized by redness, swelling or bleeding in the gingiva. It reduces the incidence of aphthous ulcers and increases the recovery rate after periodontal surgery.

The antiinflammatory mechanism of action of benzindamine is not associated with adrenal axis secretion. Such as the other non-steroidal anti-inflammatory agents benzydamine under certain conditions inhibits prostaglandin biosynthesis. But that feature is not reported completely.

It may be attributed to stabilizing effect mechanism over cellular membranes After normal topical administration of the drug, chlorhexidine exhibits a bacteriocidal effect following the prolonged bacteriostatic effect. Chlorhexidine is effective for most microorganisms such as gram (+), gram (-) bacteria, yeast and some fungi and viruses. Chlorhexidine delays bacterial growth due to delayed surface effect. It absorbs through microbial cell walls and causes membrane leakage.

5.2 Pharmacokinetic properties

Absorption:

Following administration of topical oral solution of chlorhexidine gluconate as oral gargle, systemic absorption does not appear. When used as described, 4% of the oral mouthwash dose is swallowed and some are absorbed. 90% of the ingested chlorhexidine dose is not absorbed and is excreted directly in faeces.

When a topical oral solution of 0.12% chlorhexidine gluconate is administered as mouthwash, approximately 30% of the drug remains in the oral cavity. Chlorhexidine gluconate is gradually released for 24 hours.

Following topical administration of benzidamine hydrochloride, benzidamine is absorbed by the inflamed oral mucosa and exhibits anti-inflammatory and local anesthetic effect at the site of administration. Following oral administration of Benzydamine provided plasma benzydamine level seems low and actively remains proportionately with delivery volume.

Dispersion:

KLOROBEN is a locally effected medication. So it must not be swollen in tariff convenient use.Thus systematic absorption and dispersion are not expected. In addition, the absorption of both components from the gastrointestinal mucosa is low.

Biotransformation:

Since the absorption of chlorhexidine is minimal, it cannot be measured in plasma. Benzidamine is generally metabolized by oxidation and conjugation.

Elimination:

Chlorhexidine does not accumulate in the body and only a very small amount is metabolized. Approximately 10% of the ingested chlorhexidine is excreted by the kidney following absorption; 90% nonabsorbable drug is excreted with faeces.

Benzidamine and its metabolites that are introduced into the systemic circulation are largely excreted in the urine.

5.3. Preclinical safety data

Oral LD50 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; IV LD50 was 21 mg / kg in male rats, 23 mg / kg in female rats, 25 mg / kg in male rats and 24 mg / kg in female rats; subcutaneous LD50 is greater than 1 g / kg in male and female rats, 637 mg / kg in male rats and 632 mg / kg in female rats. The oral LD50 of chlorhexidine gluconate in humans is approximately 2 g / kg. In acute studies, the lethal dose of benzidamine is well above the treatment dose. The therapeutic dose in humans is 0.7-1.0 mg / kg. LD50 values in mice (mg / kg) 33 i.v .; 218 s.c .; and 515 p.o; 100 i.p. and 1050 p.o. as determined.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol %70
Polysorbate 20
Propylene glycol
Ecocool MP (aroma)
Sucralose
Citric acid monohydrate
Sodium Citrate dehydrate
Peppermint essence
Quinoline yellow
Patent V blue
Purified water

6.2 Incompatibilities

Chlorhexidine gluconate solution may precipitate when added onto alcohol. Arab gum is incompatible with anionic polyelectrolytes such as sodium alginate, sodium carboxy methyl cellulose, starch and gum tragacanth. Chlorhexidine salts are incompatible with soap and other anionic compounds. It is also incompatible with substances such as brillant green, chloramphenicol, copper sulphate, sodium fluoracein, formaldehyde, silver nitrate, zinc sulfate.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Keep in room temperature under 25^{o}C and away from light.

6.5 Nature and contents of container

With 200 ml solution in amber colored PET bottles and together with 2.5, 3, 5, 7.5, 10 and 15 ml scaled, cardboard box.

Each box includes one bottle.

6.6 Instructions for use and handling

Unused products or waste materials must be destructed in accordance with "Medical Products Control Directive" and "Package and Package Waste Control Directive".

7. MARKETING AUTHORISATION HOLDER

DROGSAN İlaçları Sanayi ve Ticaret A.Ş.
Oğuzlar mahallesi 1370. Sokak 7/3
06520 Balgat- ANKARA
Tel: 0312 2877410
Fax: 0312 2876115

8. MARKETING AUTHORIZATION NUMBER

202/13

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of First Authorization: 05.03.2003
Renewal of the Authorization: 11.01.2013

10. DATE OF REVISION OF THE TEXT

10.01.2022