

SUMMARY OF PRODUCT CHARACTERISTICS

1. THE NAME OF THE MEDICINAL PRODUCT

USYEX spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

30 ml spray solution contains 0.075 g flurbiprofen and 0.036 g chlorhexidine gluconate.

Excipients:

Sodium benzoate (E211) 0.06 g

See 6.1 for the list of excipients.

3. PHARMACEUTICAL FORM

Spray, solution for oral mucosa

Colorless, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

USYEX spray is used for the treatment of following conditions:

- Gingivitis, stomatitis, pharyngitis, tonsillitis, and aphthous ulcers of the oral and throat mucosa associated with inflammation and pain.
- Symptomatic relief of gingival conditions and swallowing functions and anti-sepsis of the oral and throat mucosa.
- Before or after periodontal interventions.
- Mucositis due to radiotherapy, chemotherapy or other causes
- Prevention of dental plaques.

4.2. Posology and method of administration

Posology/duration and frequency of administration:

USYSEX spray is directly sprayed onto the relevant oral area 3 times daily with two sprays in each administration. Each spray provides 0.2 ml of solution containing 0.50 mg of flurbiprofen and 0.24 mg of chlorhexidine gluconate.

Method of administration:

USYEX spray is sprayed onto the affected area in the mouth and throat and should not be swallowed.

Instructions for use:

- Before first use, the pump button should be pressed several times until a regular spraying is achieved. Care should be taken to avoid spraying onto the face.
- The applicator at the tip of the spray should be directed toward the desired location in the oral cavity and/or throat.
- After use, the product should be kept in its original packing in an upright position.

Additional information on special populations**Renal failure:**

Care should be taken in treating patients with renal failure.

Liver failure:

Care should be taken in treating patients with liver failure.

Pediatric populations:

Should not be used in children under 12 years of age

Geriatric populations:

No data on use in geriatric individuals.

4.3. Contraindications

- Hypersensitivity to flurbiprofen, chlorhexidine gluconate or to any of the excipients in the formulation.
- Hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- A history of bronchospasm, or rhinitis or urticaria due to use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs.
- Past or current history of peptic ulceration.
- Pregnancy and lactation.

4.4. Special warnings and precautions for use

- To be used externally.
- To be used only intra-orally. Care should be taken to avoid contact with eyes and ears.
- USYEX spray is sprayed onto the relevant part of the oral cavity and should not be swallowed.
- Care should be exercised in patients with renal, cardiac, or hepatic failure.
- Should not be used in children under 12 years of age. In children over 12 years of age, this product can be used in accordance with a doctor's recommendation.
- This medicinal product may cause temporary discoloration in the oral cavity, tongue, and teeth due to chlorhexidine gluconate in its formula. The discoloration in the teeth is harmless and can be minimized by tooth brushing.
- USYEX contains 0.06 g of sodium benzoate (E211) in each 30 ml. This agent may cause mild irritation in the skin, eyes, or mucous membranes.

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

Flurbiprofen may rarely reduce the diuretic activity of furosemide. Also, it may rarely interact with anticoagulant medications. No interaction between flurbiprofen and digoxin, tolbutamide, or antacids occur.

No data exists regarding the interaction between other medicinal products and chlorhexidine gluconate.

Additional information on special populations

No interaction studies have been performed in special populations.

Pediatric population:

No interaction studies have been performed in pediatric populations.

4.6 Pregnancy and lactation**General recommendation**

Pregnancy category: C (D in the third trimester).

Women of childbearing potential/Contraception

No data exists regarding the use of flurbiprofen and chlorhexidine gluconate in women of childbearing potential.

Pregnancy

USYEX spray is contraindicated during pregnancy.

Although animal studies did not show any teratogenic effects of flurbiprofen, human data is inadequate.

The effects of chlorhexidine gluconate on reproduction and fertility have been tested. In experimental studies no harmful effects on the fetus have been observed. No controlled studies examining the use of chlorhexidine gluconate in pregnant women exists.

Lactation period

USYEX Spray is contraindicated during lactation.

Due to potential effects of prostaglandin inhibitors on newborns, use of flurbiprofen during lactation is not recommended.

No data exists as to the use of chlorhexidine gluconate in breastfeeding women. Therefore its use in breastfeeding women is contraindicated.

Ability to reproduce/Fertility

No known effects on ability to reproduce.

4.5. Effects on the ability to drive and use machinery

No studies have been carried out to test the effect of flurbiprofen on the ability to drive or use machinery. However, based on its pharmacodynamic properties and overall safety profile, no effects are likely.

No studies have tested the effect of chlorhexidine gluconate on the ability to drive and use machinery.

4.8. Undesirable effects

The adverse effects were classified as follows based on their frequency of occurrence:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$), unknown (existing data does not allow frequency estimates).

Immune system disorders

Very rare: Allergic reactions, hypersensitivity and anaphylaxis

General disorders and disorders of the site of administration

Common: Change in the sense of taste, discoloration on teeth and other oral surfaces.

Unknown: Symptoms of sensitivity, local irritation, tingling and burning sensation in the mouth, dry mouth or thirst, increased dental calculus.

Reporting of suspected adverse reactions

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also 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 and its treatment

Symptoms

When the low concentration of the active ingredient as well as the intended local use are considered, overdose is unlikely.

Overdose symptoms may include nausea, vomiting, or gastrointestinal discomfort.

Treatment

In cases of accidental ingestion of USYEX symptomatic treatment should be given. There are no specific antidotes.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

Pharmacotherapeutic group: Throat preparations (flurbiprofen), Topical antiseptic (chlorhexidine gluconate).

ATC code: R02AX01 (flurbiprofen), A01AB03 (chlorhexidine gluconate).

USYEX contains a non-steroidal anti-inflammatory agent with anti-inflammatory, analgesic, and antipyretic properties, i.e. flurbiprofen, and a bactericidal cationic antiseptic agent, i.e. chlorhexidine gluconate.

Similar to other non-steroidal anti-inflammatory agents, the mechanism of action is not completely understood and is thought to be related with the inhibition of prostaglandin synthase.

Like other NSAIDs, flurbiprofen inhibits the cyclooxygenase (COX) enzyme including COX-1 and COX-2 isoenzymes in body tissues, leading to the inhibition of prostaglandin synthesis.

Flurbiprofen is one of the most potent prostaglandin inhibitors among NSAID class of drugs. Since chlorhexidine gluconate is a positively charged agent, it is adsorbed into the negatively charged cell walls of microorganisms as well as the surfaces of teeth, plaques, and oral mucosa, causing the breakdown of bacterial cell membrane. Chlorhexidine is gradually released for 24 hours at the sites of adsorption, leading to continued bacteriostatic activity.

5.2. Pharmacokinetic properties

General Properties

Absorption:

Flurbiprofen

Flurbiprofen is absorbed through the buccal mucosa via passive diffusion. Buccal membrane is essentially a lipid membrane, and flurbiprofen is readily transported into the buccal mucosa due to its high lipid solubility. Flurbiprofen is a weak acid, and therefore the rate of absorption is a function of pH.

Flurbiprofen is used for the treatment and prevention of periodontal diseases due to its anti-inflammatory effects. Since local administration into the oral cavity will have local effect, high systemic concentrations are not required. For this indication, weak buccal absorption is desired.

Chlorhexidine gluconate

Experimental studies suggest that gastrointestinal absorption of chlorhexidine gluconate is very low.

USYEX spray is a topical agent with local effects. Therefore it should not be swallowed. No significant systemic effects are expected with the use of USYEX spray. However, 50 to 100 mg of therapeutic doses of oral flurbiprofen display the following pharmacokinetic properties:

Distribution:

Plasma peak levels are reached within 1.5 to 2 hours. The apparent volume of distribution (V_z/F) of both R and S-flurbiprofen is approximately 0.12 L/kg. More than 99% of both enantiomers of flurbiprofen are bound to plasma proteins, mainly to albumin. Plasma protein binding is relatively stable with the typical average steady state concentrations achieved by the recommended doses ($\leq 10 \mu\text{g/ml}$).

Biotransformation:

A variety of flurbiprofen metabolites have been detected in human plasma and urine including the two major metabolites, ([2-(2-fluoro-4'-hydroxy-4-biphenyl) propionic acid] and [2-(2-fluoro-3'-hydroxy-4-methoxy-4-biphenyl)], as well as 4-hydroxy-flurbiprofen, 3,4-dihydroxyflurbiprofen, 3-hydroxy-4-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. In contrast with other arylpropionic acid derivatives (e.g. ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen occurs at a minimal rate. In vitro studies have shown that P450 2C9 plays an important role in the metabolism of the main metabolite 4-hydroxy-flurbiprofen. The 4-hydroxyflurbiprofen metabolite has demonstrated minimal anti-inflammatory activity in human models of inflammation. Flurbiprofen does not induce enzymes that alter its metabolism. The total plasma clearance of unbound flurbiprofen is not stereoselective, and clearance of flurbiprofen is independent of dose when used within the therapeutic range.

Elimination:

Elimination half life of flurbiprofen varies between 3 and 4 hours.

Following dosing with flurbiprofen tablets, less than 3% of flurbiprofen is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as the main drug and metabolites. Approximately 20% of the dose is excreted in the urine in free and conjugated form, while 50% is excreted as hydroxylated metabolites. Because renal elimination is a significant pathway of elimination of flurbiprofen metabolites, dosing adjustment in patients with moderate or severe renal dysfunction may be necessary to avoid accumulation of flurbiprofen metabolites. The mean terminal disposition half-lives (t) of R- and S-flurbiprofen are similar, about 4.7 and 5.7 hours,

respectively. There is little accumulation of flurbiprofen following multiple doses of flurbiprofen tablets.

Linearity/non-linearity:

Flurbiprofen pharmacokinetics is linear. Plasma levels increase in proportion to the dose administered.

5.3. Preclinical safety data

Preclinical safety data have not shown any specific risks for humans based on conventional safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential, reproduction, and toxicity studies. In reproduction studies in rats and rabbits, no developmental abnormalities have been observed. However, animal studies may not always reflect human drug toxicity. No adequate and well controlled studies have been conducted in pregnant women.

No relevant data exists for chlorhexidine gluconate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerin
Ethyl alcohol (96%)
Sorbitol (E420)
Cremophor RH40
Sodium saccharin
Sodium hydroxide
Sodium benzoate (E211)
Pepermint essence
Deionized water

6.2. Incompatibilities

None reported until now.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store in room temperature below 30°C in its original packing. Protect from light.

6.5. Nature and contents of container

USYEX spray is available in white opaque bottles of 30 ml in cartoon boxes together with the spray pump and instructions.

6.6 Special precautions for disposal and other handling

Unused medicinal products or waste should be disposed of in accordance with the “Directives for the Control of Medicinal Waste” and “Directives for the Control of Pack Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

2014/504

9. THE DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date of initial license: 27 June 2014

The date of license renewal: ---

10. THE DATE OF THE RENEWAL FOR SMPC

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