SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BRONQUIDIACINA CR oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Every 7.5 ml of suspension contains:

Trimethoprim	80 mg
Sulfamethoxazole	400 mg
Bromhexine hydrochloride	4 mg
Sodium benzoate	250 mg
Balsamic syrup of Tolu	325 mg

Excipients:
Every 7.5 ml of suspension contains:

Glycerol (E-422)	943.125 mg
Sucrose	415 mg
Methyl parahydroxybenzoate (E-218)	15 mg
Propylparahydroxybenzoate (E-216)	3.75 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White homogeneous suspension with an anisette odor.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral treatment of infections of the upper or lower airway, produced by gram-positive and gram-negative germs sensitive to the combination sulfamethoxazole / trimethoprim (See Section 5), as in: acute bronchitis, exacerbation of chronic bronchitis, pneumonia, middle ear infections and sinusitis. Treatment and prevention of *Pneumocystis carinii* pneumonia.

The combination sulfamethoxazole / trimethoprim should not be used for the treatment of pharyngo-tonsillitis caused by group A betahemolytic streptococcus, since clinical studies have evidenced an increased bacteriological failure rate in patients treated with the combination sulfamethoxazole / trimethoprim compared to those treated with penicillin.

4.2. Posology and method of administration

For oral use.

It is advisable to take the medication after the main meals, in order to reduce the risk of gastrointestinal intolerance.

SHAKE BEFORE USE

Adults and children over 12 years of age: 7.5 ml three times a day

Children between 2 and 12 years of age: 2.5 ml three times a day

Renal failure:

* **Adults with creatinine clearance**

Over 30 ml/min: normal adult dose.
Between 15-30 ml/min: half the normal adult dose.
Under 15 ml/min: administration is not advised.

* **Children with creatinine clearance**

Over 30 ml/min: usual pediatric dose.
Between 20-30 ml/min: half the usual pediatric dose.
Under 20 ml/min: contraindicated.

Treatment duration
Treatment should be continued for at least 7-10 days.

4.3. Contraindications

BRONQUIDIAZINA CR is contraindicated in:

- Individuals with a history of hypersensitivity to any of the ingredients of the medicinal product, or to sulfamides in general (sulfonylurea oral antidiabetic drugs, thiazide diuretics, furosemide or carbonic anhydrase inhibitors).
- Advanced kidney or liver failure.
- Blood disorders, particularly megaloblastic anemia.
- Pregnancy.
- Infants under 2 years of age.
- Active peptic ulcer, since mucosal damage may be worsened.

4.4. Special warnings and precautions for use

This medication must be used with caution in patients with renal or liver failure, with folic acid deficiency (denutrition or alcoholism), with congenital glucose-6-phosphate dehydrogenase deficiency, or a history of severe allergies or bronchial asthma.

In order to ensure adequate renal elimination and lessen the risk of crystalluria, the patient should receive adequate fluid support, and the urine pH value should be kept within normal limits, avoiding urine acidification.

Dose reduction is required in patients with renal failure (see section 4.2).

Cotrimoxazole treatment is to be avoided in patients with a known risk of acute porphyria, since both trimethoprim and sulfamides have been associated with clinical exacerbation of porphyria.

The medication must be used with caution in patients with a history of gastrointestinal ulcer.

Special care is required when using this medication to treat elderly patients, since they are more susceptible to serious adverse reactions.

During treatment, prolonged exposure to sunlight is to be avoided, since photosensitivity reactions may occur.

Regular blood counts must be taken when administering sulfamethoxazole / trimethoprim in prolonged treatments, since changes may occur in the hematological parameters as a result of a lack of available folate. These changes can be reverted by administering folinic acid (5-10 mg day), without interfering with the antibiotic activity.

Respiratory toxicity
Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Warnings on excipients
This medication contains glycerol, which may cause headache, stomach problems and diarrhea.

This medication contains sucrose. Patients with hereditary intolerance to fructose, poor glucose or galactose absorption, or sucrose-isomaltase deficiency should not take this medication.

This medicinal product contains methyl parahydroxybenzoate (E-218) and propyl parahydroxybenzoate (E-216), which may induce allergic reactions (possibly of a delayed nature).

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

Sulfamides can enhance the action of other drugs by displacing them from binding to plasma proteins. In particular, patients receiving anticoagulants or oral antidiabetic treatment should be monitored during combined therapy. If variation is observed in patient response to the usual anticoagulant or antidiabetic drug dosage, the latter should be readjusted during the period of concomitant therapy with sulfamide.

The prior or simultaneous administration of diuretics, fundamentally thiazides, with sulfamethoxazole / trimethoprim can imply an increased risk of thrombocytopenia, particularly in elderly patients with heart failure.

The medicinal product prolongs the elimination half-life of phenytoin; therefore, when both drugs are administered simultaneously, the excessive effect of phenytoin must be taken into account. The patient condition must be monitored, along with the amount of phenytoin in serum.

The toxic effects of digoxin, procainamide and warfarin can also be enhanced.

Do not administer in combination with excessively acid or alkaline products or with heavy metals.

In addition, enhancement of the antifolic action can occur in patients concomitantly treated with other folate-depleting medications such as phenytoin or methotrexate. The plasma methotrexate concentration can be increased because the sulfamidic component of cotrimoxazole increases its free fraction as a result of competition for the plasma protein binding site.

Reversible alterations in renal function can occur in patients treated with sulfamethoxazole/trimethoprim and cyclosporine following kidney transplantation.
Combined treatment with other bone marrow depressors can increase the risk of myelosuppression. The concurrent use of trimethoprim and dapsone generally results in increased plasma levels of both drugs.

The simultaneous use of other hemolytic agents and sulfamides can enhance the toxic side effects, while joint administration with other hepatotoxic medications can increase the incidence of liver toxicity.

Trimethoprim can reduce renal excretion and increase blood concentrations of zidovudine and lamivudine.

Interference with laboratory tests: trimethoprim can interfere with serum methotrexate determination using the competitive protein binding method commented above, if a bacterial dihydrofolate reductase is used as the binding protein. In contrast, no interactions occur on using a radioimmunoassay test for the determination of methotrexate.
The results of the Jaffe test (determination of creatinine, alkalinized with picric acid) can also be altered, with value elevations of approximately 10%.
Benedict test: sulfamides can yield false positive results in urine glucose tests.

4.6. Pregnancy and lactation

The safety of sulfamethoxazole / trimethoprim in pregnant women has not been established. However, BRONQUIDIAZINA is contraindicated during pregnancy, since these drugs can interfere with folic acid metabolism.

Sulfamethoxazole / trimethoprim is excreted in breast milk. Therefore, its administration to nursing women may pose a small risk of kernicterus in infants with jaundice, and of hemolysis in infants with glucose-6-phosphate dehydrogenase deficiency. The possible use of this medication during lactation should be evaluated and decided by the physician.

4.7. Effects on the ability to drive and use machines

Clinical experience indicates that it is unlikely for this medication to affect the ability of the patient to drive or use machines.

4.8. Adverse reactions

Gastrointestinal disorders
The most common adverse reactions are of a gastrointestinal nature: nausea, vomiting, glossitis, stomach pain and diarrhea.

Skin and subcutaneous tissue disorders
Skin reactions to sulfamide administration can occur, generally in the form of rash, urticaria and pruritus. In rare isolated cases involving elderly patients with intense hypersensitivity, erythema multiforme (Stevens-Johnson syndrome) or epidermal necrolysis (Lyell syndrome) can be observed. Administration is to be **suspended immediately** in the event of skin eruptions in the course of treatment.
With an unknow frecuency, plum-coloured, raised, painful sores on the limbs and sometimes on the face and neck with a fever (Sweets syndrome) are observed.

Blood and lymphatic system disorders
There have been reports of hematological changes, fundamentally leukopenia, neutropenia, thrombocytopenia and, less frequently, megaloblastic anemia, agranulocytosis and purpura - particularly in elderly people and in patients with liver or kidney problems, or with folic acid deficiency. These alterations are reversible after suspending the treatment. In the case of folic

acid deficiency, appropriate supplementing should be provided.

Prolonged treatments can give rise to signs of megaloblastic anemia secondary to folic acid deficiency, which revert upon supplementing with folic acid.

There have also been rare reports of metahemoglobinemia.

Renal and urinary disorders
There have been rare reports of crystalluria, hematuria, interstitial nephritis or tubular necrosis.

Endocrine disorders
There have been rare reports of goiter or thyroid gland dysfunction.

Rare fatalities have been documented due to serious reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant liver necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Adverse reactions are more common in elderly patients, individuals with renal failure, and in HIV-infected subjects.

Treatment should be suspended at the first signs of skin rash or symptoms of folic acid deficiency.

4.9. Overdose

The symptoms of overdose include vomiting, nausea, diarrhea, vertigo, confusion and bone marrow depression. In very severe cases, hematuria, anuria and crystalluria have been described. It is advisable to suspend treatment, with the induction of vomiting if the latter does not occur spontaneously. Gastric lavage (pumping) is indicated, despite the fact that absorption in the gastrointestinal tract is rapid and complete within about two hours. Urine acidification facilitates trimethoprim elimination, while alkalinization increases the elimination of sulfamethoxazole.
Patient monitorization is required. Hemodialysis is only able to eliminate moderate amounts of the drug. Peritoneal dialysis is not effective in increasing elimination of the product.

In the case of overdose or accidental ingestion, consult the Toxicological Information Service. Telephone (91) 562 04 20.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Trimethoprim / sulfamethoxazole is one of the few commercially available antibiotic combinations. This fixed combination is known as cotrimoxazole.

Sulfamethoxazole is a broad spectrum bacteriostatic antiseptic and a structural analog of para-aminobenzoic acid (PABA) that inhibits the bacterial synthesis of dihydrofolic acid through competition with PABA.

Trimethoprim is a lipophilic diaminopyrimidine that also possesses bacteriostatic action, and which is structurally related to pyrimethamine. It binds to and reversibly inhibits the bacterial enzyme dihydrofolate reductase, selectively blocking the conversion of dihydrofolic acid into its functional form, tetrahydrofolic acid. Such binding depletes the bacterial reserves of folate, an essential cofactor in the biosynthesis of nucleic acids, thereby interfering with bacterial protein and nucleic acid production.

These two drug substances act sequentially in the inhibition of folic acid synthesis and produce a synergic bactericidal effect against a great variety of both gram-positive and gram-negative

bacteria.

Trimethoprim / sulfamethoxazole is active against a great variety of gram-positive and gram-negative organisms: streptococci, *Haemophilus influenzae, Neisseria gonorrhoeae,* Brucella*, Chlanrydia trachomatis, Haemophilus ducreyi, Moraxella catarrhalis, Pneumocystis carinii, Mycobacterium balnei, Pseudomonas pseudomallei, Yersimia pestis and enterocolitica, Salmonella typhi and paratyphi, Shingella, Klebsiella oxytoca,* Enterobacter*, Klebsiella pneumoniae, Escherichia coli and Serratia marcescens*. Non-susceptible organisms include *Mycobacterium tuberculosis, Treponema pallidum, Pseudomonas aeruginosa* and Mycoplasma.

Bromhexine is an antitussive and mucolytic agent with bronchial secretion clearing action that is obtained from a plant that was used in India for the treatment of asthma. Bromhexine facilitates expectoration via two mechanisms: a) sputum fluidification and b) increased bronchial secretion. In this way the drug clears airways that are plugged with mucus and thus reduces airway resistance. The effect is complemented by the balsamic-expectorant action of sodium benzoate and balsamic syrup of Tolu.

The administration of an antibiotic with mucolytic-expectorant agents fluidifies the bronchial secretions, facilitating their elimination, thus reducing bronchial tree plugging and increasing the availability of the antibiotic in the bronchial secretions - thereby ensuring faster and better therapeutic action.

5.2. Pharmacokinetic properties

Following oral administration, absorption is very effective, and the maximum serum concentrations are reached after 2 and 4 hours for trimethoprim and sulfamethoxazole, respectively. The plasma concentrations ratio after reaching plateau levels following repeated oral dosing is 20/1. Trimethoprim and sulfamethoxazole are bound to plasma proteins in proportions of 45% and 66%, respectively. Trimethoprim shows better tissue penetration than sulfamethoxazole, particularly as refers to adipose tissue, since its distribution volume is 9-fold greater than that of sulfamethoxazole. The drug is widely distributed in body tissues and fluids, including bronchial secretions and middle ear fluids. It crosses the placental barrier and is excreted in breast milk.

The elimination half-life of trimethoprim is 8-11 hours, versus 10-13 hours in the case of sulfamethoxazole - this justifying administration of the combination in two daily doses. Cotrimoxazole is metabolized in the liver, followed by excretion of its two components in urine, through glomerular filtration and active tubular secretion. Patients with renal failure will require dose adjustments proportional to the decrease in creatinine clearance. Small amounts of trimethoprim can be detected in stools, as a result of biliary excretion of a small proportion of the circulating drug substance.

Bromhexine is quickly absorbed in the gastrointestinal tract, and 85-90% is excreted in urine, fundamentally as metabolites (ambroxol). The maximum serum concentrations are reached after one hour. The plasma half-life is 12-25 hours, and binding to plasma proteins is extensive (90-99%). Due to intense first pass metabolization in the liver, the bioavailability of bromhexine is only 20%.

5.3. Preclinical safety data

Trimethoprim shows no mutagenic activity as established from the Ames test.
No chromosomal abnormalities have been observed in the peripheral blood lymphocytes of patients administered 320 mg of trimethoprim in combination with 1600 mg of sulfamethoxazole a day during 112 weeks.
No long term studies in animals have been carried out to evaluate the carcinogenic potential of cotrimoxazole.

At doses in excess of the therapeutic range, trimethoprim has shown teratogenic effects in rats,

behaving as a folate antagonist. No malformations have been recorded in rabbits, though doses 10-fold the therapeutic doses revealed an increase in fetal mortality.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol (E-422)
Sucrose
Xanthane gum
Sodium saccharin
Methyl parahydroxybenzoate (E-218)
Polysorbate 80
Propyl parahydroxybenzoate (E-216)
Dimethicone anti-foaming agent
Anisette essence
Water

6.2. Incompatibilities

No data are available.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

No special storage conditions are required.

6.5. Nature and contents of container

Glass bottle containing 150 ml of suspension and supplied with a dosing measure.

6.6. Special precautions for disposal and other handling

Shake the bottle well before use.

Any unused medicinal product and all materials that have come into contact with it shall be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

FAES FARMA, S.A.
c/ Máximo Aguirre, 14
48940 - Leioa (Spain)

8. MARKETING AUTHORIZATION NUMBER

BRONQUIDIAZINA C.R. Oral suspension: E.N.33.618

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization 11 March 1960
Date of latest renewal: September 2009

10. DATE OF REVISION OF THE TEXT

October 2016