SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
BACTRIM 200 mg + 40 mg/5 mL Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One scoop (5 mL):
Active substance:
Sulfamethoxazole (SMZ).....200 mg
Trimethoprim (TMP).....40 mg

Excipient(s):
Methyl paraben.....2.5 mg
Propylparaben.....0.5 mg
Sorbitol 70% (non-crystallising).....4.5 g
Propylene glycol.....17.5 mg
Dispersible cellulose (Avicel RC 591).....80 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension
A homogeneous suspension between yellowish white and orange

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
BACTRIM should only be used when the benefits of treatment outweigh the potential risks, as advised by a physician; the use of a single effective antibacterial agent should be considered.

BACTRIM is an antibacterial agent. BACTRIM is effective in vitro against a wide range of Gram-positive and Gram-negative organisms. It is not active against *Mycobacterium tuberculosis*, mycoplasma or *Treponema* pallidum, and *Pseudomonas aeruginosa* is generally resistant to BACTRIM.

BACTRIM is indicated for the treatment of the following infections caused by susceptible organisms in children aged 12 years and younger (6 weeks or older) (see Section 5.1):
- Prevention and treatment of *Pneumocystis jiroveci (P. carinii)* pneumonitis
- Prophylaxis and treatment of toxoplasmosis
- Treatment of nocardiosis

If there is evidence of bacterial susceptibility to BACTRIM and there is a good reason to prefer the antibiotic combination in BACTRIM over a single antibiotic, the following infections may be treated with BACTRIM:

- Acute uncomplicated urinary tract infection caused by
- Acute otitis media
- Acute exacerbation of chronic bronchitis caused by
- Official guidelines on the appropriate use of antibacterial agents should be taken into account.

4.2. Posology and method of administration
Dosage/frequency and duration of administration:
Standard dosage recommendations for acute infections
Treatment should be continued until the patient remains symptom-free for two days; most patients will require at least 5 days of treatment. If clinical improvement is not observed after 7 days of treatment, the patient should be re-evaluated.

Children aged 12 years and under:
The standard dose for children is approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram of body weight per day, administered in two equally divided doses.
A programme showing the use according to the child's age, prepared for children, is provided in the table below:

STANDARD DOSAGE	
Age	**Paediatric Suspension**
6–12 years	10 mL (2 scoops) every 12 hours
6 months – 5 years	5 mL (1 scoop) every 12 hours
6 weeks – 5 months	Every 12 hours, 2.5 mL (1/2 scoop)

For acute uncomplicated lower urinary tract infections, short-term treatment for 1–3 days has been shown to be effective as an alternative to the standard dose.

Route of administration:
It is taken orally.
BACTRIM should be taken after meals with sufficient liquid. It is recommended to take it with food and drink to reduce gastrointestinal complaints.

Additional information on specific populations
Liver impairment:
There is no dose-related data in patients with impaired liver function.
It is contraindicated in patients with significant parenchymal liver damage.

Renal impairment:
Dosage recommendation:
Adults and children over 12 years of age:

Creatinine clearance (ml/min)	Recommended dose
>30	10 ml every 12 hours
15–30	5 ml every 12 hours
<15	Not recommended

No information is available for children aged 12 years and under with renal impairment. For the pharmacokinetics of both active ingredients of BACTRIM, trimethoprim (TMP) and sulfamethoxazole (SMZ), in the paediatric population with normal renal function, see section 5.2.

It is recommended that the plasma concentration of sulfamethoxazole be measured at 2 to 3 day intervals from samples obtained 12 hours after administration of BACTRIM. If the total sulfamethoxazole concentration exceeds 150 micrograms/ml, treatment should be discontinued until the value falls below 120 micrograms/ml.

Pneumocystis jiroveci (P. carinii) pneumonia:
Treatment - Children aged 12 years and under:
A higher dose is recommended; 20 mg trimethoprim and 100 mg sulfamethoxazole per kg body weight per day, administered in two or more divided doses over a 2-week period. The aim is to achieve peak plasma or serum trimethoprim levels of 5 micrograms/ml or higher (confirmed in patients receiving a 1-hour intravenous BACTRIM infusion) (see Section 4.8 Undesirable Effects).

Prevention - Children aged 12 years and under:
The standard dose for children is approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram of body weight per day, administered in two equally divided doses. The following dosage schedule may be used for children during the risk period, prepared according to the child's age:
- Standard dose divided into two doses over seven days
- Standard dose divided into two doses every other day, three times a week
- Standard dose divided into two doses on three consecutive days per week
- Standard dose as a single dose on three consecutive days per week

Age	**Paediatric Suspension**
6-12 years	10 ml every 12 hours, 7 days a week
6-12 years	10 ml every 12 hours, 3 times a week on alternate days
6–12 years	10 ml every 12 hours, 3 times a week on consecutive days

6-12 years	20 ml once daily, 3 times a week on consecutive days
6 months to 5 years	5 ml every 12 hours, 7 days a week
6 months–5 years	5 ml every 12 hours, 3 times a week on alternate days
6 months to 5 years	5 ml every 12 hours, 3 times a week on consecutive days
6 months to 5 years	10 ml once daily, 3 times a week on consecutive days
6 weeks–5 months	2.5 ml every 12 hours, 7 days a week
6 weeks–5 months	2.5 ml every 12 hours, 3 times a week on alternate days
6 weeks to 5 months	2.5 ml every 12 hours, 3 times a week on consecutive days
6 weeks to 5 months	5 ml once daily, 3 times a week on consecutive days

The daily dose administered on a treatment day is approximately equivalent to 150 mg trimethoprim/m²/day and 750 mg sulfamethoxazole/m²/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Nocardiosis:
There is no consensus on the optimal dose. Adult doses of 6-8 tablets per day (one tablet contains 400 mg of sulfamethoxazole and 80 mg of trimethoprim) have been used for up to 3 months.

Toxoplasmosis:
There is no consensus on the most appropriate dose for the treatment or prophylaxis of this disease. The decision should be based on clinical experience. However, the doses recommended for the prevention of *Pneumocystis jiroveci* pneumonia may be appropriate for prophylaxis.

4.3. Contraindications

- BACTRIM should not be administered to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole, or any of the excipients in BACTRIM.
- It is contraindicated in patients with severe hepatic dysfunction.
- It is contraindicated in patients with severe renal impairment where repeated measurements of plasma concentrations cannot be performed.
- It should not be administered to newborn infants within the first 6 weeks of life.
- It is contraindicated in patients with a history of drug-induced immune thrombocytopenia associated with the use of sulfamethoxazole and/or trimethoprim.
- BACTRIM should not be administered to patients with acute porphyria.

4.4. Special warnings and precautions for use

Life-threatening adverse reactions
Although extremely rare, deaths have been reported due to severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis,

aplastic anaemia, other blood dyscrasias, and hypersensitivity of the respiratory tract.

Life-threatening skin reactions associated with the use of BACTRIM, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported.

Patients should be advised of the signs and symptoms of skin reactions and monitored closely ( ). The highest risk for SJS or TEN occurs during the first weeks of treatment.

BACTRIM treatment should be discontinued if symptoms or signs of SJS or TEN (e.g., progressive skin rash with blisters and mucosal lesions) or symptoms or signs of DRESS (e.g., fever, eosinophilia) occur (see Section 4.8 Undesirable effects).

The best outcomes in the treatment of SJS, TEN, and DRESS are achieved with early diagnosis and immediate discontinuation of the suspected drug. Early discontinuation of treatment is associated with a better prognosis.

If SJS, TEN, or DRESS develops in a patient using BACTRIM, the patient should never use BACTRIM again.

At the onset of treatment, the appearance of generalised febrile erythema associated with pustules should raise suspicion of Acute Generalised Exanthematous Pustulosis (AGEP) (see section 4.8); this condition requires discontinuation of treatment, and a new course of BACTRIM, either alone or in combination with other drugs, is contraindicated.

Haemophagocytic lymphohistiocytosis (HLH)
Very rare cases of HLH have been reported in patients treated with BACTRIM. HLH is a life-threatening pathological immune activation syndrome characterised by clinical signs and symptoms of excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenemia, elevated serum ferritin, cytopenia, and haemophagocytosis). Patients showing early signs of pathological immune activation should be evaluated immediately. If HLH is diagnosed, BACTRIM treatment should be discontinued.

Respiratory toxicity
Very rarely, cases of severe respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during BACTRIM treatment. The onset of pulmonary symptoms such as cough, fever, and dyspnoea, along with radiological findings of pulmonary infiltrates and deterioration in pulmonary function, may be early signs of ARDS. In such cases, BACTRIM should be discontinued and appropriate treatment initiated.

Elderly patients
Particular caution is always advised when treating elderly patients, as this group is more susceptible to adverse reactions and the likelihood of serious effects is higher, especially if there are complicating factors (impaired liver and/or kidney function and/or concomitant use of other drugs).

Patients with renal impairment
Special precautions should be taken in patients with known renal impairment (see Section 4.2).
Urinary output
Adequate urine output should always be maintained. Although sulphonamide crystals have been observed in the cooled urine of treated patients, *in vivo* crystalluria is rare. The risk may be higher in patients with nutritional deficiencies.

Folate
When BACTRIM is administered for prolonged periods, to patients with folate deficiency, or to the elderly, regular monthly blood counts are recommended, as asymptomatic changes in haematological laboratory parameters may occur due to existing folate deficiency. Folic acid supplementation may be considered during treatment but should be initiated with caution as it may affect antimicrobial efficacy (see Section 4.5).

Patients with glucose-6-phosphate dehydrogenase deficiency
Haemolysis may occur in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Patients with severe atopy or bronchial asthma
In patients with severe atopy or bronchial asthma, BACTRIM should be administered with caution.

Treatment of streptococcal pharyngitis caused by Group A beta-haemolytic streptococcus
BACTRIM should not be used in the treatment of streptococcal pharyngitis caused by Group A beta-haemolytic streptococcus; it is less effective than penicillin in eradicating these organisms from the oropharynx.

Phenylalanine metabolism
Trimethoprim has been reported to interfere with phenylalanine metabolism, but this is not significant in patients with phenylketonuria who follow an appropriate dietary restriction .

Patients with porphyria or at risk of porphyria

BACTRIM should be avoided in patients suspected of having acute porphyria or known to have acute porphyria. Both trimethoprim and sulphonamides (especially sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Patients with hyperkalaemia and hyponatraemia
Serum potassium and sodium levels should be closely monitored in patients at risk of hypokalaemia and hyponatraemia.

Metabolic acidosis
BACTRIM has been associated with metabolic acidosis when other possible causes have been ruled out. Close monitoring is recommended if metabolic acidosis is suspected.

Patients with severe haematological disorders
BACTRIM should not be administered to patients with serious haematological disorders without careful monitoring (see Section 4.8 Undesirable effects). BACTRIM has been administered to patients receiving cytotoxic therapy ( ) without additional or minimal effects on bone marrow or peripheral blood.

The antibiotic combination in BACTRIM should only be used when, in the doctor's judgement, the benefits of treatment outweigh the potential risks; the use of a single effective antibacterial agent should be considered.

Sulphamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Fatal or life-threatening cases of severe thrombocytopenia have been reported. Thrombocytopenia usually resolves within a week after discontinuation of sulphamethoxazole/trimethoprim therapy.

Excipients
Methylparaben in this medicinal product may cause allergic reactions (possibly delayed).

Propyl paraben in this medicinal product may cause allergic reactions (possibly delayed).

This medicine contains 4500 mg of sorbitol per scoop. The additive effect of concomitant use of products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The sorbitol content in medicinal products for oral use may affect the bioavailability of other medicinal products administered orally at the same time.
This medicine should not be administered to patients with hereditary fructose intolerance/patients should not take this medicine.
Sorbitol may cause gastrointestinal discomfort and a mild laxative effect.

This medicine contains 17.5 mg of propylene glycol per scoop. Co-administration with any substrate for alcohol dehydrogenase, such as ethanol, may cause serious adverse effects in newborns.

This medicine contains less than 1 mmol sodium (23 mg) per scoop, i.e. essentially 'sodium-free'.

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

Interaction with laboratory tests: Trimethoprim may cause incorrect calculation of serum/plasma creatinine values when the alkaline picrate reaction is used. As a result, serum/plasma creatinine levels may be found to be 10% higher than they actually are. Creatinine clearance decreases: creatinine renal tubular secretion decreases from 23% to 9%, while glomerular filtration remains unchanged.

Zidovudine: In some cases, concomitant treatment with zidovudine may increase the risk of developing haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, monitoring of haematological parameters should be considered.

Cyclosporine: Reversible impairment of renal function has been observed in patients treated concomitantly with co-trimoxazole and cyclosporine following renal transplantation.

Rifampicin: Concomitant use of rifampicin and BACTRIM results in a shortening of the plasma half-life of trimethoprim after a one-week period. This is not considered to be clinically significant.

When trimethoprim is used concomitantly with drugs that form cations at physiological pH and are partially excreted by active renal secretion (e.g., procainamide, amantadine), competitive inhibition of this process ( ) is possible ( ), leading to increased plasma concentrations of one or both drugs.

Diuretics (thiazides): In elderly patients taking diuretics (primarily thiazides) concomitantly, there is an increased risk of thrombocytopenia, with or without purpura.
Primetamine: According to some reports, when co-trimoxazole is prescribed concomitantly, megaloblastic anaemia may develop in patients receiving more than 25 mg of primetamine per week.

Warfarin: It has been demonstrated that co-trimoxazole potentiates the anticoagulant effect of warfarin by stereoselectively inhibiting its metabolism. Sulfamethoxazole can displace warfarin from plasma albumin protein binding sites in vitro. Careful monitoring of anticoagulant therapy is recommended during BACTRIM treatment.

Phenytoin: Co-trimoxazole prolongs the half-life of phenytoin and, if administered concomitantly, may result in excessive phenytoin effects. Close monitoring of the patient's condition and serum phenytoin levels is recommended.

Digoxin: Concomitant use of trimethoprim and digoxin has been shown to increase plasma digoxin levels in some elderly patients.

Methotrexate: Co-trimoxazole may increase free plasma levels of methotrexate. If BACTRIM is considered appropriate treatment in patients receiving other anti-folate drugs such as methotrexate, folate supplementation should be considered (see Section 4.4).

In the test, trimethoprim interferes with serum methotrexate level tests when *Lactobacillus* casei dihydrofolate reductase is used. There is no interference when methotrexate is measured by radioimmunoassay.

Lamivudine: Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure due to the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Interactions with sulphonylurea hypoglycaemic agents are rare, but potentiation has been reported.

Hyperkalaemia: Caution is required in patients taking other drugs that may cause hyperkalaemia, such as ACE inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically significant hyperkalaemia.

Repaglinide: Trimethoprim may increase repaglinide exposure and cause hypoglycaemia.

Folic acid: Folic acid supplements have been shown to alter the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in the prophylaxis and treatment of *Pneumocystis jiroveci* pneumonia.

Contraceptives: Contraceptive failures have been reported during antibiotic treatment. The mechanism of action is not fully understood. Women undergoing antibiotic treatment should use a temporary barrier method in addition to oral contraceptives or choose another method of contraception.

Azathioprine: There are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulfamethoxazole resulting in serious haematological abnormalities.

4.6. Pregnancy and lactation
General Recommendation
Pregnancy category: C

Women of childbearing potential/Contraception
Women of childbearing potential should use appropriate contraceptive methods when BACTRIM is administered due to the risk of neonatal hyperbilirubinaemia, exacerbation, or theoretically kernicterus.

Contraceptive failures have been reported during antibiotic treatment. The mechanism of action is not fully understood. Women receiving antibiotic treatment should use a temporary barrier method in addition to oral contraceptives or choose another method of contraception.

Pregnancy
There is insufficient data on the use of BACTRIM in pregnant women.

Animal studies are inadequate with respect to effects on pregnancy and/or embryonic/foetal development/birth/postnatal development (see Section 5.3). The potential risk to humans is not known.

BACTRIM crosses the placenta and there is insufficient data on the use of BACTRIM in pregnant women. Case-control studies have suggested a possible relationship between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist, and animal studies have shown that both agents cause folate disorders (see Section 5.3 Preclinical Safety Data).

BACTRIM should not be used during pregnancy, particularly in the first trimester, unless clearly necessary. If BACTRIM is used during pregnancy, folate supplementation should be considered.

Sulfamethoxazole competes with bilirubin for plasma albumin binding. As significant maternal drug levels persist for several days in the newborn, there is a risk of neonatal hyperbilirubinaemia or exacerbation when BACTRIM is administered to the mother close to delivery (theoretically with the risk of kernicterus). This theoretical risk is particularly important in infants at high risk of hyperbilirubinaemia, such as preterm infants and those with glucose-6-phosphate dehydrogenase deficiency.

Lactation
The components of BACTRIM (trimethoprim and sulfamethoxazole) pass into breast milk. BACTRIM should be avoided in late pregnancy and in lactating mothers if the mother or infant has hyperbilirubinaemia or is at risk of developing hyperbilirubinaemia. Furthermore, considering the predisposition to hyperbilirubinaemia in young infants, BACTRIM should be avoided in infants younger than eight weeks of age.

Reproductive ability/Fertility
There is no data available on the potential risk to humans. Animal studies have shown reproductive toxicity (see Section 5.3).

4.7. Effects on the ability to drive and use machines
No studies have been conducted on the effect of BACTRIM on the ability to drive and use machines. An adverse effect on these activities cannot be predicted from the pharmacology of the drug. Nevertheless, when considering a patient's ability to drive, the patient's clinical condition and the adverse event profile of BACTRIM should be taken into account.

4.8. Undesirable effects
The frequency categories associated with the following adverse events are estimated calculations. Suitable data are not available to calculate the incidence for most events. Furthermore, adverse events may vary in incidence depending on the indication.
Due to its composition of co-trimoxazole, trimethoprim, and a sulphonamide, the type and frequency of adverse reactions associated with these compounds are expected to be consistent with comprehensive historical experience.

Data from extensive clinical trials were used to determine the frequency of adverse events ranging from very common to rare. Very rare adverse events were primarily identified from post-marketing experience data and therefore reflect the reporting rate rather than the "true" frequency.
The frequency ranking of adverse effects reported in clinical trials is as follows:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Infections and infestations
Common: Excessive fungal overgrowth
Very rare: Pseudomembranous colitis

Blood and lymphatic system disorders

Very rare: In patients with specific G-6-P D deficiency, leukaopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis

Deaths have been reported in at-risk patients, and such patients should be closely monitored (see Section 4.3 Contraindications).

Immune system disorders
Very rare: Serum sickness, anaphylaxis, allergic myocarditis, allergic vasculitis resembling Henoch-Schönlein purpura, periarteritis nodosa, systemic lupus erythematosus. Serious hypersensitivity reactions associated with PCP, rash, pyrexia, neutropenia, thrombocytopenia, increased hepatic enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis.

Metabolic and nutritional disorders
Very common: Hyperkalaemia
Very rare: Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis

When co-trimoxazole is used in elderly patients or in patients receiving high doses of co-trimoxazole, close monitoring is recommended as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

Psychiatric disorders
Very rare: Depression, hallucinations
Not known: Psychotic disorders

Nervous system disorders
Common : Headache
Very rare: Aseptic meningitis, convulsions/seizures, peripheral neuropathy, ataxia, dizziness

When the drug was discontinued, aseptic meningitis rapidly resolved, but it reappeared in a number of cases upon re-exposure to co-trimoxazole or trimethoprim alone.

Eye disorders
Very rare: Uveitis

Ear and inner ear disorders
Very rare: Vertigo, tinnitus

Vascular disorders
Not known: Shock (circulatory)

Respiratory, thoracic disorders and mediastinal disorders
Very rare: Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates, although very rare, may be early indicators of fatal respiratory hypersensitivity.

Gastrointestinal disorders
Common: Nausea, diarrhoea
Rare: Vomiting
Very rare: Glossitis, stomatitis, pancreatitis

Hepatobiliary disorders
Very rare: Elevated serum transaminases, elevated bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders
Common: Skin rashes
Very rare: Photosensitivity, exfoliative dermatitis, angioedema, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Acute Generalised Exanthematous Pustulosis (AGEP)
Not known: Acute febrile neutrophilic dermatosis (Sweet's syndrome), drug reaction with eosinophilia and systemic symptoms (DRESS)

As with other drugs, allergic reactions such as pruritic rash and urticaria may occur in patients with hypersensitivity to the drug's components. Very rarely, cases of acute generalised exanthematous pustulosis (AGEP) have been observed (see Section 4.4)
Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening (see Section 4.4).

Musculoskeletal disorders, connective tissue and bone diseases
Very rare: Arthralgia, myalgia

Renal and urinary tract disorders
Very rare: Impaired renal function (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis.

Effects associated with the treatment of Pneumocystis jiroveci (P. carinii) pneumonia (PCP)
Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, elevated liver enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis

Serious hypersensitivity reactions leading to discontinuation of treatment have been reported with high doses used in PCP treatment. Serious hypersensitivity reactions have been reported in PCP patients upon re-exposure to co-trimoxazole (sometimes after a few days' interval between doses). Rhabdomyolysis has been reported in HIV-positive patients using the combination of sulfamethoxazole and trimethoprim for PCP treatment or prophylaxis.

Definition of selected adverse reactions
Shock (circulatory): Cases of shock (circulatory) associated with fever, unresponsive to standard treatment for hypersensitivity, have been reported with sulfamethoxazole+trimethoprim, mostly in immunocompromised patients.

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 and Treatment
Nausea, vomiting, dizziness and confusion are possible signs and symptoms of overdose. Bone marrow depression has been reported in acute trimethoprim overdose.

If vomiting has not occurred, it may be desirable to induce vomiting. Gastric lavage may be useful, but absorption from the gastrointestinal tract is normally very rapid and is completed in approximately two hours. This may not be the case with very large overdoses. Depending on the state of renal function, fluid administration is recommended if urine output is low.
Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is ineffective.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, sulphonamides and trimethoprim combinations (including derivatives)
ATC code: J01EE01

Mechanism of action:

BACTRIM is an antibacterial drug consisting of two active substances (sulfamethoxazole and trimethoprim). Sulfamethoxazole is a competitive inhibitor of the dihydropteroate synthase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) by bacterial cells in dihydrofolate synthesis, resulting in bacteriostasis. Trimethoprim binds to bacterial dihydrofolate reductase (DHFR), reversibly inhibits it, and blocks tetrahydrofolate production. Depending on the conditions, the effect may be bactericidal. In this way, trimethoprim and sulfamethoxazole block two consecutive steps in purine biosynthesis and thus block nucleic acids essential for many bacteria. This effect causes a marked potentiation of activity between the two agents in vitro.

Trimethoprim binds to plasmodial DHFR, but less tightly than it binds to the bacterial enzyme. Its affinity for mammalian DHFR is 50,000 times lower than its affinity for the relevant bacterial enzyme.

Resistance mechanisms:
In vitro studies have shown that bacterial resistance may develop more slowly to the combination of sulfamethoxazole and trimethoprim (compared to sulfamethoxazole alone or trimethoprim alone).

Resistance to sulfamethoxazole can develop through different mechanisms. Bacterial mutations cause an increase in PABA concentration, which competes with sulfamethoxazole and thus reduces its inhibitory effect on the dihydropteroate synthase enzyme. Another resistance mechanism is plasmid-dependent and results from the production of an altered dihydropteroate synthase enzyme. This altered enzyme has a lower affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs via a plasmid-dependent mutation. This mutation results in the production of a different dihydrofolate reductase (DHFR) enzyme, which has a lower affinity for trimethoprim compared to the wild-type enzyme.

Many common pathogenic bacteria are susceptible to trimethoprim and sulfamethoxazole in vitro (at concentrations well below those achieved in blood, tissue fluids, and urine after administration of recommended doses). However, as with other antibiotics, *in vitro* activity does not always translate into clinical efficacy, and it should be noted that satisfactory susceptibility testing is performed using media that do not contain inhibitory substances (particularly thymidine and thymine).

Breakpoints:
EUCAST (European Confederation of Antimicrobial Susceptibility Testing) limits
Enterobacteriaceae: S ≤ 2 R > 4

S. maltophilia: S ≤ 4 R > 4
Acinetobacter: S ≤ 2 R > 4
Staphylococcus: S ≤ 2 R > 4
Enterococcus: S ≤ 0.032 R > 1
Streptococcus ABCG: S ≤ 1 R > 2
Streptococcus pneumoniae: S ≤ 1 R > 2
Haemophilus influenzae: S ≤ 0.5 R > 1
Moraxella catarrhalis: S ≤ 0.5 R>1
Pseudomonas aeruginosa and other non-Enterobacteriaceae: S ≤ 2* R > 4*

S = susceptible, R = resistant. * As EUCAST breakpoints are not yet available for these organisms, CLSI breakpoints are used.

Trimethoprim: sulfamethoxazole is in a 1:19 ratio. Breakpoints are expressed as trimethoprim concentration.

Antibacterial spectrum:
Resistance prevalence may vary geographically and may vary over time for certain species. Knowledge of local resistance patterns is important, particularly when treating serious infections. Where the local prevalence of resistance indicates that the use of the agent may be questionable, at least for some types of infection, expert advice should be sought when necessary. This information provides only an indicative guide as to the likelihood of microorganisms being susceptible to trimethoprim/sulfamethoxazole.

The susceptibility of a range of bacteria to trimethoprim/sulfamethoxazole is shown in the table below:

Generally susceptible species:
Gram-positive aerobes: *Staphylococcus aureus* *Staphylococcus saprophyticus* *Streptococcus pyogenes*
Gram-negative aerobes: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Salmonella* species *Stenotrophomonas maltophilia* *Yersinia* species
Species where acquired resistance may pose a problem:

Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium* *Nocardia* spp. *Staphylococcus epidermidis* *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter* spp. *Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella pneumonia* *Proteus mirabilis* *Proteus vulgaris* *Providencia* species *Serratia marcescens*
Naturally resistant organisms:
Gram-negative aerobes: *Pseudomonas aeruginosa* *Shigella spp.* *Vibrio cholera*

5.2. Pharmacokinetic properties

General characteristics

Absorption:

Following oral administration, trimethoprim and sulfamethoxazole are rapidly and almost completely absorbed. The presence of food does not delay absorption. Peak blood levels occur one to four hours after administration, and the levels achieved are dose-related. Therapeutic levels in the blood persist for up to 24 hours after a therapeutic dose. In adults, steady-state levels are reached 2-3 days after dosing. Neither component has a significant effect on the concentration of the other in the blood.

Distribution:

Approximately 50% of trimethoprim in plasma is protein-bound.

Trimethoprim tissue levels are generally higher than the corresponding plasma levels (the lungs and kidneys show particularly high concentrations). Trimethoprim concentrations exceed plasma concentrations in bile, prostatic fluid and tissue, saliva, sputum, and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid, and tissue (intestinal) fluid are sufficient for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues (reaching concentrations close to maternal serum concentrations).

Approximately 66% of sulfamethoxazole in plasma is bound to proteins.

The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, saliva, synovial fluid, and tissue (intestinal) fluid is 20-50% of the plasma concentration.

Biotransformation:
Renal excretion of sulfamethoxazole accounts for 15-30% of the dose. Sulfamethoxazole is metabolised to a greater extent than trimethoprim by acetylation, oxidation or glucuronidation. Over periods exceeding 72 hours, approximately 85% of the dose may be found in the urine as unchanged drug and its major metabolite (N4-acetyl).

Elimination:
The half-life of trimethoprim in humans is 8.6 to 17 hours when renal function is normal. If creatinine clearance is less than 10 ml/min, the half-life increases by 1.5-3.0 times. There is no significant difference between elderly patients and younger patients.

The primary route of elimination for trimethoprim is renal, and approximately 50% of the dose is excreted unchanged in the urine within 24 hours. Some metabolites have been identified in the urine. Urinary concentrations of trimethoprim are highly variable.

The half-life of sulfamethoxazole is approximately 9 to 11 hours when renal function is normal. There is no change in the half-life of active sulfamethoxazole with decreased renal function, but the half-life of the major acetylated metabolite is prolonged when creatinine clearance is below 25 ml/min.

The primary route of elimination of sulfamethoxazole is renal; 15-30% of the dose (obtained in urine) is in the active form. In elderly patients, renal clearance of sulfamethoxazole is low.

The pharmacokinetics of both active ingredients of BACTRIM, TMP and SMZ, in the paediatric population with normal renal function are age-dependent. The elimination of TMP-SMZ decreases in newborns during the first two months of life, after which both TMP and SMZ show higher elimination with a higher body clearance and a shorter elimination half-life. Differences are most pronounced in infants (from >1.7 months to 24 months of age) and decrease with increasing age when compared to young children (1 to 3.6 years), children (7.5 years and <10 years), and adults ( ) (see Section 4.2).

Elderly patients:
A slight decrease in the renal clearance of sulfamethoxazole, except for trimethoprim, has been observed in elderly patients.

5.3. Preclinical safety data

At doses above the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities (typical findings for folate antagonism) in rats. The effects of trimethoprim were prevented by dietary folate supplementation. In rabbits, foetal losses have been observed at doses above the human therapeutic dose of trimethoprim.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Purified water
Sorbitol 70% (non-crystallising)
Methyl paraben
Propyl paraben
Polysorbate 80
Propylene glycol
Banana flavouring
Vanilla flavouring
Dispersible cellulose (Avicel RC 591):
    Microcrystalline cellulose
    Sodium carboxymethylcellulose

6.2. Incompatibilities

None.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at a room temperature below 25°C.

6.5. Nature and contents of container

Our product, BACTRIM 200 mg+40 mg/5 mL suspension, is supplied in a 100 mL glass bottle containing the suspension, along with the package leaflet.

6.6. Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORISATION HOLDER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05.05.2009

10. DATE OF REVISION OF THE TEXT