1. Name of the medicinal product

Coptrine® Suspension

2. Qualitative and quantitative composition

Each 5ml of Coptrine® Suspension contains Sulphamethoxazole 200 mg and Trimethoprim 40mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Suspension

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of urinary tract infections (UTI); ear, nose and throat infections (ENT); acute otitis media in children; lower respiratory tract infection (acute exacerbation of chronic bronchitis in adults); traveller's diarrhea in adult; shigellosis and enteritis; pneumocystis carrinii pneumonia.

4.2 Posology and method of administration

Posology

Children:

Children 6 weeks to 5 months - 2.5 ml every 12 hours

Children 6 weeks to 5 years – 5ml every 12 hours

Children 6 years to 12 years – 10 ml every 12 hours

Method of administration

For oral administration only

It is important to **shake the bottle** for at least 10 seconds before use

4.3 Contraindications

Hypersensitivity to trimethoprim or sulphonamides, hepatic or renal failure, megaloblastic anaemia due to folate deficiency; pregnancy, breastfeeding, premature infants less than two months old.

4.4 Special warnings and precautions for use

Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.

This medicine may cause serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), or acute febrile neutrophilic dermatosis (AFND). Check with your doctor if you have a skin rash, blistering, peeling, loosening of the skin, chills, cough, diarrhea, itching, joint or muscle pain, red irritated eyes, red skin lesions, often with a purple center, sore throat, sores, ulcers, white spots in the mouth or on the lips, black, tarry stools, chest pain, or painful or difficult urination.

Check with your doctor right away if you have dark urine, clay-colored stools, stomach pain, or yellow eyes or skin. These may be symptoms of a serious liver problem.

This medicine, especially if you are receiving high doses or for a long period of time, may lower the number of platelets in your body, which are necessary for proper blood clotting. Because of this, you may bleed or get infections more easily. Talk with your doctor if you have black, tarry stools, bleeding gums, blood in urine or stools, pinpoint red spots on the skin, unusual bleeding or bruising.

This medicine may cause diarrhea, and in some cases it can be severe. It may occur 2 months or more after you stop taking this medicine. Do not take any medicine to treat diarrhea without first checking with your doctor. If you have any questions or if mild diarrhea continues or gets worse, check with your doctor.

Check with your doctor right away if you or your child have stomach cramps, bloating, watery and severe diarrhea, which may also be bloody, nausea or vomiting, or unusual tiredness or weakness. These may be symptoms of a serious intestinal infection.

This medicine may cause serious allergic reactions, including anaphylaxis, which can be life-threatening and require immediate medical attention. Check with your doctor right away if you or your child have a rash, itching, swelling of the face, tongue, and throat, trouble breathing, or chest pain after you use the medicine.

This medicine may cause electrolyte problems, including high potassium in the blood (hyperkalemia) and low sodium in the blood (hyponatremia). Tell your doctor right away if you have confusion, weakness, muscle twitching, an irregular heartbeat, numbness or tingling in the hands, feet, or lips, or trouble breathing.

This medicine may cause hypoglycemia (low blood sugar) in some patients. Check with your doctor if you have anxiety, behavior change similar to being drunk, blurred vision, cold sweats, confusion, cool pale skin, difficulty with concentrating, drowsiness, excessive hunger, headache, nausea, nervousness, rapid heartbeat, shakiness, or unusual tiredness or weakness.

Before you have any medical tests, tell the medical doctor in charge that you or your child are taking this medicine. The results of some tests may be affected by this medicine.

Patients receiving anticonvulsant treatment (medicines to prevent seizures) may be at risk for a folate (vitamin B9) deficiency, which may increase the risk for side effects. Talk with your doctor if you have concerns about this.

Do not use this medicine for Pneumocystis jiroveci pneumonia (PCP) if you are also using leucovorin. Using these medicines together may cause these medicines to not work as well for you.

Do not take other medicines unless they have been discussed with your doctor. This includes leucovorin, other prescription or nonprescription (over-the-counter [OTC]) medicines and herbal or vitamin supplements.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with laboratory tests: trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

Rifampicin: concurrent use of rifampicin and Co-Trimoxazole results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co- trimoxazole be prescribed concurrently.

Warfarin: co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites in vitro. Careful control of the anticoagulant therapy during treatment with Co-Trimoxazole is advisable.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

Digoxin: concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If Co-Trimoxazole is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

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

Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.

Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, 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 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant women has not been established. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see section 5.3). Co-Trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Co-Trimoxazole is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when Co-Trimoxazole is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Breast-feeding

The components of Co-Trimoxazole (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Co-Trimoxazole should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of Co-Trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Summary of the safety profile

As co-trimoxazole contains trimethoprim and a sulphonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency. In addition, adverse events may vary in their incidence depending on the indication.

Tabulated list of adverse reaction

The following convention has been used for the classification of adverse events in terms of frequency: Very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000, not known - cannot be estimated from the available data.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Infections and infestations	Common	Overgrowth fungal.
	Very rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.
Immune system disorders	Very rare	Serum sickness, anaphylactic reactions,allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus. Severe hypersensitivity reactions associated with PJP*, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.

Metabolism and nutrition disorders	Very common	Hyperkalaemia.
	Very rare	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination.
	Not known	Psychotic disorder.
Nervous system disorders	Common	Headache.
	Very rare	Meningitis aseptic *, seizure, neuropathy peripheral, ataxia, dizziness
Ear and Labyrinth disorders	Very rare	Vertigo, tinnitus
Eye disorders	Very rare	Uveitis.
Respiratory, thoracic and mediastinal disorders	Very rare	Cough*, dyspnoea*, lung infiltration*
Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	Very rare	Jaundice cholestatic *, hepatic necrosis*. Transaminases increased, blood bilirubin increased.
Skin and subcutaneous tissue disorders*	Common	Rash.
	Very rare	Photosensitivity reaction, dermatitis exfoliative, 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)*
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis.

Description of selected adverse reactions

Aseptic meningitis

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

Pulmonary hypersensitivity reactions

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Hepatobiliary disorders

Jaundice cholestatic and hepatic necrosis may be fatal.

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)

As with any other drug, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the drug. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days. Rhabdomyolysis has been reported in HIV positive patients receiving co-tromixazole for prophylaxis or treatment of PJP.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment:

If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependant on the status of renal function administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use - Sulphonamides and trimethoprim, ATC code: J01EE01.

Mechanism of Action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out-compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

Trimethoprim binds to plasmodial DHFR but less tightly than to bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Many common pathogenic bacteria are susceptible in vitro to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, in vitro activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

Susceptibility testing breakpoints

EUCAST (European Committee on 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

Hemophilus influenza: S≤ 0.5 R> 1

Moraxella catarrhalis: S≤0.5 R >1

Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant. *These are CLSI breakpoints since no

EUCAST breakpoints are currently available for these organisms.

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

Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 66% of sulfamethoxazole in the plasma is protein bound. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in elderly patients compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function.

There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of Co-Trimoxazole should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Elderly patients

In elderly patients, a slight reduction in renal clearance of sulfamethoxazole but not trimethoprim has been observed.

Paediatric population

5.3 Preclinical safety data

At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. Pharmaceutical particulars

6.1 List of excipients

Sulfamethoxazole,

Trimethoprim micronized powder

Sucrose

Sodium saccharin methyl paraben

Propylene glycol

Sodium carboxyl methyl cellulose

Aerosol

Xanthan gum

Sodium citrate

Polysorbate

Banana flavor

Ethanol

Aniseed oil

Purified water

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30^{o}C. Protect from light and moisture.

6.5 Nature and contents of container

60ml Amber glass bottle

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7.0 APPLICANT/MANUFACTURER

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