SUMMARY OF PRODUCT CHARACTERISTICS

SANFUROX - 250

Cefuroxime Axetil Tablets USP 250 mg

1. NAME OF THE MEDICINAL PRODUCT

SANFUROX - 250 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 250 mg cefuroxime (as cefuroxime axetil).

3. PHARMACEUTICAL FORM

White to off white coloured caplet shaped film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SANFUROX - 250 is indicated for the treatment of the infections listed below in adults and children from the age of 3 months.

- Acute streptococcal tonsillitis and pharyngitis.
- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Cystitis.
- Pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Treatment of early Lyme disease.

4.2 Posology and method of administration

The usual course of therapy is seven days (may range from five to ten days).

Adults and children (≥40 kg)

Adult Dose:

Uncomplicated Urinary Tract Infections – 125 mg twice daily

Respiratory tract infection – 250 to 500 mg twice daily

Children Dose:

Children more than 3 months of age – 125 mg twice daily (10 mg/kg body weight up to a maximum of 250 mg

Children over 2 years of age in case of Acute Otitis Media – 250 mg twice daily (15 mg/kg body weight) or as directed by the physician.

There is no experience of using Cefuroxime axetil tablets in children under the age of 3 months.

Renal impairment

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Creatinine clearance	T1/2 (hrs)	Recommended dosage
≥30 mL/min/1.73 m^2	1.4–2.4	no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 mL/min/1.73 m^2	4.6	standard individual dose given every 24 hours
<10 mL/min/1.73 m^2	16.8	standard individual dose given every 48 hours
Patients on haemodialysis	2–4	a further standard individual dose should be given at the end of each dialysis

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Method of administration

Oral use

SANFUROX - 250 tablets should be taken after food for optimum absorption.

4.3 Contraindications

SANFUROX - 250 Tablets are contraindicated in patients with hypersensitivity to cefuroxime, other cephalosporin antibiotics, beta-lactam antibacterial agent (penicillins, monobactams and carbapenems) or to any of the excipients.

4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

As with other antibiotics, use of cefuroxime axetil may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms, which may require interruption of treatment.**4.5 Interaction with other medicinal products and other forms of interaction**

Drugs which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime. Concomitant use with oral anticoagulants may give rise to increased INR.

4.6 Fertility, pregnancy and lactation

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of

sensitisation should be taken into account. Cefuroxime should only be used during pregnancy and breastfeeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects

The most common adverse reactions are Candida overgrowth, eosinophilia, headache, dizziness, gastro-intestinal disturbances such as diarrhoea, nausea, abdominal pain and transient rise in liver enzymes.

Other uncommon side effects observed are Clostridium difficile overgrowth, positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound), haemolytic anaemia, drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction, vomiting, pseudomembranous colitis, jaundice (predominantly cholestatic), hepatitis, skin rashes, urticaria, pruritus, erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) and angioneurotic oedema.

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment. Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins

Mechanism of action

Cefuroxime axetil undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime. Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases; including (but not limited to) by extended spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria species
- reduced affinity of penicillin-binding proteins for cefuroxime
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria
- bacterial efflux pumps

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime.

Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

Cefuroxime axetil breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microorganism	**Breakpoints (mg/L)**	
	S	R
Enterobacteriaceae[1,2]	≤8	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤0.25	>0.5
Moraxella catarrhalis	≤0.125	>4
Haemophilus influenzae	≤0.125	>1
Non-species related	IE[5]	IE[5]

[1]The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or

infection control
purposes
Uncomplicated UTI (cystitis)
only
Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections
The beta-lactam susceptability of beta-haemolytic streptococci groups A, B, C and G is

inferred from the penicillin susceptibility insufficient evidence that the species in question is a good target for therapy with the drug. An MIC with a comment but without an accompanying S or R-categorization may be reported

S=susceptible,
R=resistant

Microbiological
susceptibility

The prevalence of acquired 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 cefuroxime axetil in at least some types of infections is questionable. Cefuroxime is usually active against the following microorganisms in vitro.

Commonly susceptible
species

Gram-positive aerobes: Staphylococcus aureus (methicillin susceptible)*, Streptococcus pyogenes, Streptococcus agalactiae

Gram-negative aerobes: Haemophilus influenza, Haemophilus parainfluenzae, Moraxella catarrhalis

Spirochaetes: Borrelia
burgdorferi

Microorganisms for which acquired resistance may be a
problem

Gram-positive aerobes: Streptococcus
pneumonia

Gram-negative aerobes: Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Proteus spp. (other than P. vulgaris), Providencia spp.

Gram-positive anaerobes: Peptostreptococcus spp., Propionibacterium spp. Gram-negative anaerobes: Fusobacterium spp., Bacteroides spp.

Inherently resistant microorganisms

Gram-positive aerobes: Enterococcus faecalis, Enterococcus faecium

Gram-negative aerobes: Acinetobacter spp., Campylobacter spp., Morganella morganii, Proteus vulgaris, Pseudomonas aeruginosa, Serratia marcescens

Gram-negative anaerobes: Bacteroides fragilis

Others: *Chlamydia spp., Mycoplasma spp., Legionella spp.*

* All methicillin-resistant *S. aureus* are resistant to cefuroxime.

5.2 Pharmacokinetic properties

Absorption: After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to releas cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal.

Following administration of cefuroxime axetil tablets peak serum levels (2.9 µg/mL for a 125 mg dose, 4.4 µg/mL for a 250 mg dose, 7.7 µg/mL for a 500 mg dose and 13.6 µg/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with food. The rate of absorption of cefuroxime from the suspension is reduced compared with the tablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17% less). Cefuroxime axetil oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults and therefore is not substitutable on a milligram-per-milligram basis (see section 4.2).The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution: Protein binding has been stated as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV%=28%). Concentrations of cefuroxime

in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation: Cefuroxime is not metabolised.

Elimination: The serum half-life is between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 mL/min/1.73 m^2.

Special patient populations

Gender: No differences in the pharmacokinetics of cefuroxime were observed between males and females.

Elderly: No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly (see section 4.2).

Paediatrics: In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults. There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

Renal impairment: The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <30 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). Cefuroxime is effectively

removed by dialysis.

Hepatic impairment: There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

PK/PD relationship: For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the

percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e.%T>MIC).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose (PH-200), Magnesium Sterate, Colloidal Anhydrous Silica Super-D33 CL, Crosscarmellose Sodium, Doshion 544 DS, Hypermellose (E-5), Microcrystalline Cellulose (PH-200), Super- D33CL, Crosscarmellose Sodium, Doshion 544DS, Magnesium Stearate, Colloidal Anhydrous Silica.

6.2 Incompatibilities

A positive Coombs' test has been reported during treatment with cephalosporins - this phenomenon can interfere with cross-matching of blood.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature below 30^0C. Protected from light. Keep out of reach of children.

6.5 Nature and contents of container

1 alu alu blister of 10 tablets in a monocarton along with an insert.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

-Bliss GVS Pharma Ltd.