Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
SANTRIAX S-1000mg injection

2. Qualitative and quantitative composition
Ceftriaxone and Sulbactam for Injection 1.5 gm Each vial contains: Sterile Ceftriaxone Sodium USP Equivalent to anhydrous Ceftriaxone 1000mg Sterile Sulbactam Sodium USP Equivalent to Sulbactam 500mg Sterilised Water for Injections BP.....10 ml

3. Pharmaceutical form
Powder for Injection

4. Clinical particulars

4.1 Therapeutic indications
Sulbactam is a beta (β)-lactamase inhibitor and a derivative of the basic penicillin nucleus. When given in combination with β-lactam antibiotics such as ceftriaxone, sulbactam produces a synergistic effect as it blocks the enzyme responsible for drug resistance by hydrolyzing β-lactams.
Sulbactam is used in combination with other antibacterial agents. It is used to treat skin and skin structure infections, intra-abdominal infections, and gynaecological infections caused by susceptible bacteria.

Ceftriaxone is indicated for the treatment of the following infections in adults and children including term neonates (from birth):
• Bacterial Meningitis
• Community acquired pneumonia
• Hospital acquired pneumonia
• Acute otitis media
• Intra-abdominal infections
• Complicated urinary tract infections (including pyelonephritis)
• Infections of bones and joints
• Complicated skin and soft tissue infections
• Gonorrhoea
• Syphilis
• Bacterial endocarditis
Ceftriaxone may be used:
• For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults
• For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age
• For Pre-operative prophylaxis of surgical site infections
• In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
• In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above Ceftriaxone should be co-administered with other antibacterial

agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).
Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults

The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams. For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously, 1 /2 to 2 hours before surgery is recommended.
The total dose of Sulbactam should not exceed 4 grams per day.

Pediatric:

For the treatment of skin and skin structure Infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams. In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

Renal or Hepatic Impairment:

Dosage regimens of Ceftriaxone sodium & Sulbactam sodium injection therapy should be adjusted In patients with marked decrease In renal function (creatinine clearance of less than 30 ml/min) to compensate for the reduced clearance of Sulbactam. Patients with creatinine clearance between 15 and 30 ml/ min should receive a maximum of 1 g of Sulbactam administered every 12 hours (maximum daily dosage of 2 g Sulbactam), while patients with creatinine clearance of less than 15 mL/min should receive a maximum of 500 mg of Sulbactam every 12 hours (maximum daily dosage of 1 g Sulbactam).

Direction for use:

Intramuscular administration: administration reconstitute the whole content of vial with 6 ml sterile water for injection.

Intravenous Administration: administration reconstitute whole content with 10 ml of sterile water for injection

4.3 Contraindications

Ceftriaxone sodium & sulbactam sodium injection is contraindicated in patients with known allergy to pencillin, any other type of beta-lactam drug, cephalosporin class of antibiotics, beta-lactamase inhibitors or any other ingredients of this formulation.

4.4 Special warnings and precautions for use

Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.
Pseudomembranous colitis has been reported with nearly all-antibacterial agents including ceftriaxone, and may range in severity from mild to life threatening. Therefore, It is Important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia.
After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of Pseudomembranous colitis usually respond to drug discontinuation alone, in moderate to severe cases, consideration should be given to management with effective against clostridium difficile colitis.
Ceftriaxone should therefore not be used In Jaundiced new-born or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired.

Precaution:

Transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone is similar to that of other cephalosporins. Ceftriaxone is excreted via both billiary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of ceftriaxone are administered, but concentrations of drug in the serum should be monitored periodically.
Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Ceftriaxone dosage should not exceed 2 g dally without dose monitoring of serum concentrations.
Prolong use of ceftriaxone may result in overgrowth of nonsusceptible organisms. Ceftriaxone sodium and sulbactam sodium Injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.
Cases of pancreatitis, possibly secondary to biliary obstruction, have been rarely reported in patients treated with ceftriaxone. Most patients presented with risk factors for billiary stasis and billiary sludge

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics: No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.
Aminoglycosides: No interference with the action or increase in nephrotoxicity of aminoglycoside has been observed during simultaneous administration with ceftriaxone.
Alcohol: The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent, which has been associated with a disulfiram-like effect, when alcohol is taken during therapy with certain cephalosporins.
Chloramphenicol: In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The

clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with Chloramphenicol is proposed.
Oral contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.
Probenecid: Probenecid decreases the renal tubular secretion of sulbactam, concurrent use of probenecid with Ceftriaxone sodium & sulbactam sodium Injection may result in increased and prolonged blood levels of sulbactam.

4.6 Pregnancy and Lactation

Pregnancy

Ceftriaxone and Sulbactam crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development (see section 5.3). Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone and Sulbactam is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common (≥ 1/10)

Common (≥ 1/100 - < 1/10)

Uncommon (≥ 1/1000 - < 1/100)

Rare (≥ 1/10000 - < 1/1000)

Not known (cannot be estimated from the available data)

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known** [a]
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytos
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivi Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b]

				Toxic epiderm necrolysis[b] Erythema multiforme Acute generalised exanthematou pustulosis Drug reaction with eosinophilia a systemic symptoms (DRESS)[b]
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive[b] Galactosaemia test false positive[b] Non enzymati methods for glucose
				determination false positive[b]

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

[b] See section 4.4

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in preterm and full-term neonates (aged < 28 days) who had been

treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

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 products. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board

Pharmacovigilance Electronic Reporting System (PvERS);

https://pv.pharmacyboardkenya.org

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins.

ATC code: J01DD04.

Sulbactam being highly specific Inhibitor of wide variety of beta-lactamases produced by gram negative and gram positive aerobes and anaerobes, It blocks the destructive hydrolytic activity of beta-lactamases sparing Ceftriaxone from hydrolysis.

A wide range of beta lactamases found in microorganisms resistant to penicillins and cephalosporins have been shown in biochemical studies with cell free bacterial systems to be irreversibly inhibited by Sulbactam. Although Sulbactam alone possesses little useful antibacterial activity except against the Neisseriaceae. In particular, Sulbactam has good Inhibitory activity against the clinically important plasmid medicated beta-lactamases most frequently responsible for transferred drug resistance.

The presence of Sulbactam in the SANTRIAX S-1000 formulation effectively extends the antibiotic spectrum of Ceftriaxone to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, SANTRIAX S-1000 injection possesses the properties of a broad-spectrum antibiotic and a beta-lactamase Inhibitor.

Mode of action

Ceftriaxone 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.

Resistance

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

• hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.

• reduced affinity of penicillin-binding proteins for ceftriaxone. • outer membrane impermeability in Gram-negative organisms.

• bacterial efflux pumps.

Susceptibility testing breakpoints

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

	Dilution Test (MIC, mg/L)	
Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1	> 2
Staphylococcus spp.	a.	a.
Streptococcus spp. (Groups A, B, C and G)	b.	b.

Streptococcus pneumoniae	≤ 0.5[c.]	> 2
Viridans group *Streptococci*	≤ 0.5	>0.5
Haemophilus influenzae	≤ 0.12[c.]	> 0.12
Moraxella catarrhalis	≤ 1	> 2
Neisseria gonorrhoeae	≤ 0.12	> 0.12
Neisseria meningitidis	≤ 0.12 [c.]	> 0.12
Non-species related	≤ 1[d.]	> 2

a. Susceptibility inferred from cefoxitin susceptibility.

b. Susceptibility inferred from penicillin susceptibility.

c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.

d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

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 ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes *Staphylococcus aureus* (methicillin-susceptible)[£] Staphylococci coagulase-negative (methicillin-susceptible)[£]
Streptococcus pyogenes (Group A) *Streptococcus agalactiae* (Group B) *Streptococcus pneumoniae* Viridans Group *Streptococci* Gram-negative aerobes *Borrelia burgdorferi* *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis* *Neisseria gonorrhoea* *Neisseria meningitidis* *Proteus mirabilis Providencia* spp. *Treponema pallidum*
Species for which acquired resistance may be a problem
Gram-positive aerobes *Staphylococcus epidermidis*[+] *Staphylococcus haemolyticus*[+] *Staphylococcus hominis*[+] Gram-negative aerobes

Citrobacter freundii *Enterobacter aerogenes* *Enterobacter cloacae Escherichia coli*% *Klebsiella pneumoniae*% *Klebsiella oxytoca*% *Morganella morganii* *Proteus vulgaris* *Serratia marcescens* Anaerobes *Bacteroides* spp. *Fusobacterium* spp. *Peptostreptococcus* spp. *Clostridium perfringens*
Inherently resistant organisms
Gram-positive aerobes *Enterococcus* spp. *Listeria monocytogenes* Gram-negative aerobes *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* Anaerobes *Clostridium difficile* Others: *Chlamydia* spp. *Chlamydophila* spp. *Mycoplasma* spp. *Legionella* spp. *Ureaplasma urealyticum*

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

+ Resistance rates >50% in at least one region

% ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration. The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g,

the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone. In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory

increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

In older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Paediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

6. Pharmaceutical Particulars

6.1 List of Excipients

Not Applicable

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and Content of container

Ceftriaxone and Sulbactam For Injection 1.5 gm packed in USP type III clear glass vial stopper with bromobutyl rubber stopper and sealed with flip/ off aluminium seal. Such 1 vial packed in a carton along with an insert and WFI.

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. Marketing Authorization Holder

BLISS GVS PHARMA LTD
102, Hyde Park,
Saki vihar road, Andheri Mumbai-72

8. Marketing Authorization Number

CTD10441

9. Date of first authorization/renewal of the authorization

12/09/2023

10. Date of revision of the text

11/05/2025