Approved Professional Information for Medicines for Human Use:

AUSTELL CEFTRIAXONE 1 g

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AUSTELL CEFTRIAXONE 1 g (POWDER FOR INJECTION) [VIAL]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains sterile ceftriaxone sodium equivalent to 1 g of anhydrous ceftriaxone base.

3. PHARMACEUTICAL FORM

Powder for injection

White to yellowish orange, crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUSTELL-CEFTRIAXONE is indicated for the treatment of the following infections:

BACTERIAL SEPTICEMIA caused by:

Methicillin-sensitive Staphylococcus aureus (MSSA), Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli or Klebsiella pneumoniae.

MENINGITIS caused by:

Haemophilus influenzae, Neisseria meningitides, or Streptococcus pneumoniae.

INTRA-ABDOMINAL INFECTIONS caused by:

Escherichia coli, Klebsiella pneumoniae, or *Peptostreptococcus* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by:

Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes, Streptococcus viridans group, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Serratia marcescens, or Peptostreptococcus species.*

BONE AND JOINT INFECTIONS caused by:

Methicillin-sensitive *Staphylococcus aureus (MSSA), Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, KIebsiella pneumoniae, or Enterobacter species.*

RENAL AND URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by: *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii or KIebsiella pneumoniae.*

RESPIRATORY TRACT INFECTIONS caused by: -

Streptococcus pneumoniae, Methicillin-sensitive *Staphylococcus aureus (MSSA), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis or Serratia marcescens.*

EAR NOSE AND THROAT INFECTIONS (Acute Bacterial Otitis Media) caused by: *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase producing strains), or *Moraxella catarrhalis* (including beta-lactamase producing strains).

UNCOMPLICATED GONORRHOEA (cervical/urethral and rectal) caused by: *Neisseria gonorrhoeae*, including both beta-lactamase-, and non-beta-lactamase producing strains, and pharyngeal gonorrhoea caused by non-beta-lactamase- producing strains of *Neisseria gonorrhoeae.*

PERIOPERATIVE INFECTION PROPHYLAXIS.

4.2 Posology and method of administration

Posology

See **Incompatibilities** and sections on how **AUSTELL CEFTRIAXONE** should be reconstituted.

Calcium-containing solutions are not among the appropriate solutions described for

reconstitution, due to possible incompatibility.

Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute **AUSTELL CEFTRIAXONE**. Particulate formation can result. **AUSTELL CEFTRIAXONE** and calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites (see sections 4.3 and 4.4).

In the past few years, however, isolated neonatal deaths associated with calcium-ceftriaxone precipitates in the lungs and kidneys have been described worldwide. In some of these cases ceftriaxone and the calcium-containing solutions or medications were administered by different routes and different times.

Standard dosage

Adults and children over 12 years.

The usual dosage is 1 - 2 g **AUSTELL CEFTRIAXONE** once daily. In severe cases or in infections caused by moderately sensitive organisms the dosage may be raised to 4 g, once daily.

Neonates, infants and children up to 12 years.

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days):

20 - 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. It is not necessary to differentiate between premature and term infants.

Infants and children (15 days to 12 years):

20 - 80 mg/kg once daily. For children with bodyweights of 50 kg or more, the usual adult dose should be used. Intravenous doses of ≥ 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

Elderly patients.

No dose modification is needed in the elderly.

Duration of therapy

The duration of therapy varies according to the course of the disease. Administration of **AUSTELL CEFTRIAXONE** should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Special dosage instructions

Meningitis:

In bacterial meningitis in neonates, infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dose can be adapted accordingly. For bacterial meningitis in adults, the recommended dosage is 4 g once daily.

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (both beta-lactamase-producing strains), a single i.m. dose of 125 mg **AUSTELL CEFTRIAXONE** is recommended.

Peri-operative Infection Prophylaxis:

A single dose of 1-2 g **AUSTELL CEFTRIAXONE** administered 30-90 minutes prior to surgery. In colorectal surgery, administration of A**USTELL CEFTRIAXONE** with or without a 5-nitroimidazole, e g. metronidazole, has been proven effective, (separate administration: see 'Method of administration')

Impaired renal and hepatic function:

In patients with impaired renal function, there is no need to reduce the dosage of **AUSTELL CEFTRIAXONE** provided that hepatic function is intact.

In cases of severe renal failure (creatinine clearance, 10 ml/min) the **AUSTELL CEFTRIAXONE** dosage should not exceed 2 g daily.

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal

function is intact.

Method of administration

Ceftriaxone must be reconstituted prior to use. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature or 24 hours in the refrigerator at +5 °C. As a general rule, however, the solutions should be used immediately after preparation. The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection

For i.m. injection, **AUSTELL CEFTRIAXONE** 1 g is dissolved in 3.5 ml of water for injection. **AUSTELL CEFTRIAXONE** dissolved in a 1 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 g be injected at one site. Reconstitution with 1 % lignocaine (without adrenaline) has no effect on the absorption or the elimination of **AUSTELL CEFTRIAXONE**.

Intravenous injection

The lignocaine solution must never be administered intravenously.

For i.v. injection, **AUSTELL CEFTRIAXONE** 1 g is dissolved in 10 ml sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

4.3 Contraindications

Hypersensitivity to cephalosporins or any of the ingredients.

Hypersensitivity to penicillin's due to the possibility of cross-reactivity.

Hyperbilirubinnemic neonates, especially prematures, should not be treated with **AUSTELL CEFTRIAXONE**. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in the patients.

AUSTELL CEFTRIAXONE should not be administered concurrently with calcium-containing solutions or products in newborns because of the risk of precipitation of ceftriaxone-calcium salt

(see section 4.4).

4.4 Special warnings and precautions for use

AUSTELL CEFTRIAXONE must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium-containing solutions or products must not be administered within 48 hours of last administration of ceftriaxone.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed (see section 4.3 and 4.8).

Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute AUSTELL CEFTRIAXONE. Particulate formation can result.

Interaction with Calcium-Containing Products:

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, **AUSTELL CEFTRIAXONE** and calcium-containing solutions, including calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of **AUSTELL CEFTRIAXONE** and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see section 4.2 and 4.3).

No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

Pseudomembranous enterocolitis and coagulation disorders have been reported with **AUSTELL CEFTRIAXONE**. It is important to consider pseudomembranous enterocolitis in patients who present with diarrhoea subsequent to the administration of **AUSTELL CEFTRIAXONE**. Superinfections with non-susceptible micro-organisms may occur. Shadows, which have been mistaken for gallstones have been detected on sonograms of the gallbladder, usually following doses higher than the standard recommended dose. These shadows are, however, precipitates of calcium ceftriaxone, which disappear on completion or discontinuation of **AUSTELL CEFTRIAXONE** therapy. In symptomatic
cases, conservative non-surgical management is recommended.
Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with **AUSTELL CEFTRIAXONE**. Most patients who developed pancreatitis have had risk factors associated with biliary stasis and biliary sludge, e.g. severe illness and total parenteral nutrition.

Ceftriaxone displaces bilirubin from serum albumin.

Caution should be exercised when considering AUSTELL CEFTRIAXONE treatment in hyperbilirubinaemic neonates. AUSTELL CEFTRIAXONE is not recommended for use in neonates (especially premature) at risk of developing bilirubin encephalopathy.

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including AUSTELL CEFTRIAXONE (see section 4.8).
Severe cases of haemolytic anaemia, including fatalities, have been reported during AUSTELL CEFTRIAXONE treatment in both adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Long term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial agent-associated colitis and pseudo-membranous colitis have 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 diarrhoea during or subsequent to the administration of ceftriaxone (see section 4.8).
Discontinuation of therapy with ceftriaxone and the administration of specific treatment for Clostridium
difficile should be considered. Medicinal products that inhibit peristalsis should not be given.
Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Interference with serological testing

Interference with Coombs tests may occur, as AUSTELL CEFTRIAXONE may lead to false-positive test results. AUSTELL CEFTRIAXONE can also lead to false-positive test results for galactosaemia (see section 4.8).
Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with AUSTELL CEFTRIAXONE should be done enzymatically (see section 4.8).

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with AUSTELL CEFTRIAXONE (see
section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of AUSTELL CEFTRIAXONE-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute AUSTELL CEFTRIAXONE vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone (see section 4.8).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

Renal function impairment has not been observed after concurrent administration of **AUSTELL CEFTRIAXONE** and diuretics (e.g. furosemide). There is no evidence that **AUSTELL CEFTRIAXONE** increases renal toxicity of aminoglycosides.
The elimination of **AUSTELL CEFTRIAXONE** is not altered by probenecid.

Interaction with Laboratory Tests:
In patients treated with **AUSTELL CEFTRIAXONE** the Coombs' test and tests for galactosaemia may become false positive.
Non-enzymatic methods for glucose determination in urine may give false-positive results.

4.6 Fertility, pregnancy and lactation
Ceftriaxone crosses the placental barrier, and is excreted in breast-milk.
Safety in pregnancy and lactation has not been established.

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.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known[a]**
Infections and infestations		Genital fungal infection, Pseudo-membranous colitis[a]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia, Leukopenia, Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy	Haemolytic anaemia[b] Agranulocytosis Haematoma or bleeding Lymphopenia Prolongation of prothrombin time. Isolated cases of agranulocytosis (< 500

			mm3) have been reported, most of them following total doses of 20 g or more.
Immune system disorders			Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b] Jarisch-Herxheimer Reaction[b]
Nervous system disorders		Headache, Dizziness, Encephalopathy	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		Gallbladder precipitation[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash (Allergic dermatitis)	Pruritus Urticaria	Oedema Steven Johnson Syndrome[b]

			Toxic epidermal necrolysis Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS)[b]
Renal and urinary disorders		Heamaturia Glycosuria	Oliguria Renal precipitation (reversible)[c] Genital mycosis

General disorders and administration site conditions		Phlebitis[d] Injection site pain Pyrexia Oedema Chills	
Investigations		Blood creatinine increased	Coombs test false positive[b] Galactosaemia test false positive[b] Non enzymatic 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 realibly estimate their frequency which is therefore categorized as not known.

[b] See section 4.4

[c] Cases of drug precipitation in the kidneys have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses

exceeding 10 g and presenting with other risk factors (e.g. fluid restrictions, confinement to bed, etc.). This event may lead to renal insufficiency and is usually reversible upon discontinuation of AUSTELL CEFTRIAXONE.

[d] Phlebitic reactions may occur after i.v. administration. These may be minimized by slow (2 -4 minutes) injection of the medicine.

Intramuscular injection without lignocaine solution is painful, (see DOSAGE AND DIRECTIONS FOR USE).

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 pre-term 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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Post-marketing surveillance is used to confirm or deny the safety of a medicine after it is used in the general population by large numbers of people who have a wide variety of medical conditions. Where possible, following the SAHPRA adverse event reporting, kindly also report any suspected ADRs; new or existing safety, quality or effectiveness concerns occurring as a result of the use of this medicine via email to medsafety@austell.co.za.

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur.

In the case of over-dosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1. 1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins, ATC code: J01DD04.

Ceftriaxone is a third generation cephalosporin. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis.

5.2 Pharmacokinetic properties

Absorption:

The maximum plasma concentration after a single intramuscular (i.m) dose of 1.0 g is about 81 mg/litre and is reached within 2—3 hours after administration. The area under the plasma concentration versus time curve (AUC) after intramuscular (i.m) administration is equivalent to that after intravenous (i.v) administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly administered ceftriaxone.

Distribution:

The apparent volume of distribution of ceftriaxone is 0.13— 0.19 litres/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1—2 g; concentrations well above the minimum inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in body-fluids or tissues including the lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

Protein binding:

Ceftriaxone is reversibly bound to albumin. There is proportionally decreased albumin binding with an increase in plasma concentration of ceftriaxone.

Penetration into particular tissues:

Paediatrics:

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations exceed 1.4 mg/litre in the cerebrospinal fluid (CSF) 24 hours after i.v. injection in doses of 50 mg/kg in neonates to 100 mg/kg in infants. Peak concentration in CSF with a mean of 18 mg/litre is reached about 4 hours after intravenous injection. Mean CSF concentrations are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis.

The mean values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg i.v. dose and after a 75 mg/kg i.v. dose in paediatric patients suffering from bacterial meningitis are shown in the table below.

Mean pharmacokinetic parameters of ceftriaxone in paediatric patients with meningitis:

	50 mg/kg IV	75 mg/kg IV
Maximum Plasma Concentrations (mcg/ml)	216	275
Elimination Half-life (hr)	4,6	4,3
Plasma Clearance (ml/hr/kg)	49	60
Volume of Distribution (ml/kg)	338	373
CSF Concentration-inflamed meninges (mcg/ml)	5,6	6,4
Range (mcg/ml)	1.3 -18.5	1.3 - 44
Time after dose (hr)	3.7 (+1.6)	3.3 (+1.4)

Adults:

In meningitis in adults, administration of 50 mg/kg leads within 2—24 hours to CSF concentrations several times higher than the minimum *in vitro* inhibitory concentrations required for the most common meningitis pathogens.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk in low concentrations.

In healthy, young adult volunteers the total plasma clearance is 10—22 ml/min. The renal clearance is 5—12 ml/min. Fifty to sixty percent of ceftriaxone is excreted unchanged in the urine, while 40 — 50 % is excreted unchanged in the bile. The elimination half-life in adults is about eight hours.

Pharmacokinetics in special clinical situations:

Neonates - urinary recovery accounts for about 70 % of the dose.

Infants less than eight days old and elderly persons aged over 75 years-elimination half-life is usually 2 — 3 times that in young adults.

Patients with renal or hepatic dysfunction — the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased.

Impaired kidney function alone— biliary elimination of ceftriaxone is increased.

Impaired liver function alone — renal elimination of ceftriaxone is increased.

Micro-organisms resistant to ceftriaxone: -

Methicillin-resistant *Staphylococcus* species; *Enterococcus faecum;*

Listeria monocytogenes, Pseudomonas aeruginosa; Ureaplasma urealyticum; Mycoplasma species; Mycobacterium species; some isolates of *Bacteriodes* species (bile-sensitive); and most strains of *Clostridium difficile.*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

AUSTELL CEFTRIAXONE should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution. Ceftriaxone is incompatible with vancomycin, fluconazole and aminoglycosides.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Reconstituted product should be stored in original vials. These maintain potency for at least 6 hours at or below 25 °C in daylight, or 24 hours at 2-8 °C.

KEEP OUT OF REACH OF THE CHILDREN.

6.5 Nature and contents of container

1 x 10 ml Colourless glass vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

1 Sherborne Road,

Parktown,

Johannesburg, 2193

South Africa.

Tel: 011 611 1400 or 0860 287 835

8. REGISTRATION NUMBER(S)

39/20.1.1/0176

9. DATE OF FIRST AUTHORISATION

20 May 2008

10. DATE OF REVISION OF THE TEXT

03/01/2022