Summary of Product Characteristics

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

Trade/Proprietary Name: Gucefor

Approved/Inn/Generic Name: Cefuroxime for injection

1.2 Strength

Each vial contains, as the active ingredient, cefuroxime sodium for injection 789mg equivalent to 750mg of cefuroxime

1.3 Pharmaceutical form

Powder for injection

2. Qualitative and quantitative composition

Each vial contains, as the active ingredient, cefuroxime sodium for injection 789mg equivalent to 750mg of cefuroxime.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection

4. Clinical particulars

4.1 Therapeutic indications

GUCEFOR is an antibiotic used in adults and children. It works by killing bacteria that cause infections. It belongs to a group of medicines called cephalosporin. GUCEFOR is used to treat infections of:

• The lungs or chest

• The urinary tract

• The skin and soft tissue

• The abdomen

GUCEFOR is also used: to prevent infections during surgery. Your doctor may test the type of bacteria causing your infection and monitor whether the bacteria are sensitive to GUCEFOR during your treatment.

4.2 Posology and method of administration

GUCEFUR is usually given by a doctor or nurse.

It can be given as a drip (intravenous infusion) or as an injection directly into a vein or into a muscle.

The usual dose

The correct dose of **GUCEFUR** for you will be decided by your doctor and depends on: the severity and type of infection, whether you are on any other antibiotics; your weight and age; how well your kidneys are working.

Usual dosage for Adults and the Elderly:

Most infections will respond to Cefuroxime 750 mg three times a day. For more severe infections, the dose may be increased to 1.5g three times a day by intravenous injection.

If necessary, the frequency of administration of Cefuroxime can be increased to four times a day up to total daily doses of 3g to 6g.

Infants, toddlers and Children:

The daily dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most infections will respond to a dose of 60 mg/kg/day.

Neonates

The daily dosage range is 30 to 100 mg/kg/day given as two or three divided doses. In the first weeks of life the serum half-life of Cefuroxime can be three or five times that in adults.

For impaired renal function:

It is not necessary to reduce the dose if creatinine clearance is more than 20ml/min. The recommended maintenance doses in

Creatinine clearance (ml/min)	Recommended dosage of Cefuroxime (mg)	Frequency of dosage (hours)
0	Usual dose	
10-20	750	12
<10	750	24
CAPD patients	750	12
Patients on hemodialysis hemofiltration arteriovenous ongoing / continuous hemodialysis arteriovenous hemodialysis.	750	12

Impaired renal functions are as follows:

Special precautions are required if creatinine clearance is <10ml/minute under appropriate expert supervision.

Patients undergoing hemodialysis will require a further 750mg dose of Cefuroxime at the end of each dialysis treatment. A suitable dosage for patients on continuous peritoneal dialysis is usually 750mg twice a daily.

A dosage of 750mg twice daily is recommended for patients in renal failure on continuous arteriovenoushemodialysis or high flux hemofiltration in intensive therapy units. For low flux hemofiltration follow the dosage recommended under impaired renal function.

Cefuroxime is usually effective as a single the therapy in the treatment of the above infections.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Concurrent treatment with potent diuretics or aminoglycosides

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides. Renal impairment has been reported during use of these combinations. Renal function should be monitored in the elderly and those with known pre-existing renal impairment (see section 4.2).

Overgrowth of non-susceptible microorganisms

Use of cefuroxime may result in the overgrowth of *Candida.* Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).

Antibacterial agent–associated pseudomembranous colitis has been reported with use of cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime (see section 4.8). Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Intra-abdominal infections

Due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria (see section 5.1)

Interference with diagnostic tests

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood (see section 4.8).

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

Important information about excipients

Cefuroxime powder for solution for injection and infusion contains sodium. This should be considered for patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Cefuroxime 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 prolongs the excretion of the antibiotic and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics

High-dosage treatments with cephalosporins should be carried out with caution on patients who are taking strong-acting diuretics (such as furosemide) or potential nephrotoxic preparations (such as aminoglycoside antibiotics), since impairment of renal function through such combinations cannot be ruled out.

Other Interactions

Determination of blood/plasma glucose levels: Please refer to section 4.4.

Concomitant use with oral anticoagulants may give rise to increased international normalised ratio (INR).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity (see section 5.3). Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk.

Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of cefuroxime sodium on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of cefuroxime on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse reactions are neutropenia, eosinophilia, transient rise in liver enzymes or bilirubin, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver and injection site reactions.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not known
Infections and infestations			*Candida* overgrowth, overgrowth of *Clostridium difficile*
Blood and lymphatic system disorders	neutropenia, eosinophilia, decreased haemoglobin concentration	leukopenia, positive Coomb's test	thrombocytopenia, haemolytic anaemia
Immune system disorders			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
Gastrointestinal disorders		gastrointestinal disturbance	pseudomembranous colitis
Hepatobiliary disorders	transient rise in liver enzymes	transient rise in bilirubin	
Skin and subcutaneous tissue disorders		skin rash, urticaria and pruritus	erythema multiforme, toxic epidermal necrolysis and

			Stevens-Johnson syndrome, angioneurotic oedema
Renal and urinary disorders			elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4)
General disorders and administration site conditions	injection site reactions which may include pain and thrombophlebitis		
Description of selected adverse reactions Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coomb's test (which can interfere with cross matching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes or bilirubin have been observed which are usually reversible. Pain at the intramuscular injection site is more likely at higher doses. However it is unlikely to be a cause for discontinuation of treatment.			

Paediatric population

The safety profile for cefuroxime sodium in children is consistent with the profile in adults.

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 (see sections 4.2 and 4.4).

Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, Second-generation cephalosporins, ATC code J01DC02

Mechanism of Action:

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.

Mechanisms 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) extended-spectrum beta-lactamases (ESBLs), and Amp-C enzymes, that may be induced or stably de-repressed in certain aerobic Gram-negative bacterial 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 sodium breakpoints

The 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]	<8[2]	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤0.5	>1
Streptococcus (other)	≤0.5	>0.5
Haemophilus influenzae	≤1	>2
Moraxella catarrhalis	≤4	>8
Non-species related breakpoints[1]	≤4[5]	>8[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 absence of an ESBL does not in itself influence the categorisation of susceptibility. In many areas, ESBL detection and characterisation is recommended or mandatory for infection control purposes.

[2] Breakpoint relates to a dosage of 1.5 g × 3 and to *E. coli, P. mirabilis* and *Klebsiella spp* . only.

[3] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidime and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.
[4] The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.
[5] Breakpoints apply to daily intravenous dose of 750 mg × 3 and a high dose of at least 1.5 g × 3.

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 therefore desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is known and the utility of the agent 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* *Streptococcus mitis* (viridans group)
Gram-negative aerobes: *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter freundii* *Enterobacter cloacae* *Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus* spp. (other than *P. vulgaris*) *Providencia* spp. *Salmonella* 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. *Morganella morganii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia marcescens*
Gram-positive anaerobes: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

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

In vitro the activities of cefuroxime sodium and aminoglycoside antibiotics in combination have been shown to be at least additive with occasional evidence of synergy.

5.2 Pharmacokinetic properties

Absorption

After intramuscular (IM) injection of cefuroxime to normal volunteers, the mean peak serum concentrations ranged from 27 to 35 μg/mL for a 750 mg dose and from 33 to 40 μg/mL for a 1000 mg dose, and were achieved within 30 to 60 minutes after administration. Following intravenous (IV) doses of 750 and 1500 mg, serum concentrations were approximately 50 and 100 μg/mL, respectively, at 15 minutes.

AUC and C_{max} appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV administration. There was no evidence of accumulation of cefuroxime in the serum from normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been stated as 33 to 50%, depending on the methodology used. The average volume of distribution ranges from 9.3 to 15.8 L/1.73 m^2 following IM or IV administration over the dosage range of 250 to 1000 mg. 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 humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised.

Elimination

Cefuroxime is excreted by glomerular filtration and renal tubular secretion. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The majority of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m^2 following IM or IV administration over the dosage range of 250 to 1000 mg.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly

Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function (see section 4.2).

Paediatrics

The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment

Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. $C1_{cr}$ <20 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 haemodialysis and peritoneal dialysis.

Hepatic impairment

Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an 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 conventional 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

None

6.2 Incompatibilities

Cefuroxime should not be mixed in the syringe or giving set with aminoglycosides prior to or during administration.

Mixing of Cefuroxime with sodium bicarbonate solutions significantly affects the color of the solution. Therefore, this solution is not recommended for the dilution of Cefuroxime. If required, the Cefuroxime solution in water for injections can be introduced into the tubing of the giving set in patients receiving sodium bicarbonate solution by infusion.

6.3 Shelf life

36 months for the medicinal product as packaged for sale. After reconstitution the product should be used immediately, but if not practicable, the diluted product may be stored for 24 hours at 2 - 8 ° C, after which time unused material should be discarded.

6.4 Special precaution for storage

Store in a dry place at a temperature not above 30°C.

Keep the vial in the outer carton in order to protect from light.

Reconstituted solution: The product should be used immediately.

6.5 Nature and contents of container

10ml tube-type vial and flip off cap containing 750mg of cefuroxime.

10ml ampoule containing sterilised water for injections

Pack of 1 vial and 1ampoule, 200 boxes/carton

or

Pack of 50vials/box, 20boxes/carton.

6.6 Instructions for use and handling <and disposal>

Instruction for constitution

Intravenous route

Dissolve the contents of the vial in 8.3ml of sterile water for injection.

Intramuscular route

Dissolve the contents of the vial in 3ml of sterile water for injection.

Cefuroxime may be given over short periods (30 minutes).

As for all parenteral medicinal products, inspect the reconstituted solution /suspension visually for particular matter and discoloration prior to administration. The reconstituted solution is clear. For single use only. Any remaining solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Guilin Pharmaceutical (Shanghai) Co.,Ltd

Manufacturer

Reyoung Pharmaceutical Co., Ltd.

No.1, Ruiyang Road, Yiyuan County, Shandong Province, China.

8. MARKETING AUTHORISATION NUMBER(S)

Not available currently

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

11/2016