Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefixime Nectar Lifesciences 100 mg/5 ml Powder for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted suspension contains cefixime trihydrate equivalent to 100 mg of cefixime.

Excipient(s): This medicine contains approximately 2.33g of sucrose in each 5 ml after reconstitution.
This medicine contains 10.0 mg of sodium benzoate in each 5 ml after reconstitution.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral suspension.

Off-white to pale yellow coloured granular powder with strawberry guarana flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms (see sections 4.4 and 5.1):

- Acute exacerbations of chronic bronchitis (AECB)
- Acute otitis media (AOM)
- Uncomplicated acute cystitis
- Uncomplicated pyelonephritis.
- Acute bacterial pharyngitis
- Uncomplicated acute gonorrhoea

The use of cefixime should be reserved for infections in which the causative organism is known or suspected to be resistant to other commonly used antibacterial agents.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Route of Administration: Oral

Adults and adolescents older than 12 years (or more than 50 kg body weight):
The recommended dose is 400 mg daily, given either as a single dose or in two divided doses of 200 mg every 12 hours. (see section 4.4 and 5.1).
The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

- 400 mg (in 1-2 doses) 7 up to 10 days for Acute otitis media (AOM) and Acute bacterial pharyngitis
- 400 mg (in 1-2 doses) 1 to 3 days for uncomplicated acute cystitis in female patients
- 400 mg (in 1 dose), 1 day for uncomplicated gonorrhoea

Elderly patients
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment (See above and section 4.4).

Children from 6 months to 11 years of age

The recommended dose of Cefixime oral suspension is 8 mg/Kg/day in a single dose or divided in two doses based on weight (as a general guide see following table):
Dosage recommendations are given in the table below.

Body weight (kg)	Daily dose of cefixime (mg)	Daily dose (ml) using the graduated syringe (dose can be given as a single dose or divided in 2 doses)
10.0	80	4 ml or 2 x 2 ml
12.5	100	5 ml or 2 x 2.5 ml
15.0	120	6 ml or 2 x 3ml
17.5	140	7 ml or 2 x 3.5
20.0	160	8 ml or 2 x 4 ml
22.5	180	9 ml or 2 x 4.5 ml
25.0	200	10 ml or 2 x 5 ml
27.5	220	11 ml or 2 x 5.5 ml
30.0	240	12 ml or 2 x 6 ml
37.5	300	15 ml or 2 x 7.5 ml
> 37.5 (and patients 12 years and older)	400	20 ml or 2 x 10 ml

For exact dosing the pack is supplied with a 5 ml plastic oral syringe graduated in 0.25 ml divisions.
1 ml of Cefixime oral suspension is equal to 20 milligram (mg) of cefixime,
5 ml of Cefixime oral suspension are equal to 100 milligram (mg) of cefixime.

Children less than 6 months of age

The safety and efficacy of cefixime has not been established in children less than 6 months of age.

Renal insufficiency

Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

There are insufficient data regarding use of cefixime in children < 12 years old in the presence of renal insufficiency: the use of cefixime in these patients is not recommended.

Duration of treatment

The usual course of treatment is 7 days. This may be continued for up to 14 days if required.
Cefixime may be taken with or without food (see section 5.2).

Instructions for the preparation of the suspension

See section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, other cephalosporin antibiotics or to any of the excipients listed in section 6.1.

Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use

Encephalopathy
Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken.
Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs.

Hypersensitivity to penicillin's
As with other cephalosporins, Cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs.

If an allergic reaction occurs with Cefixime; the use of cefixime should be discontinued and the patient treated with appropriate agents if necessary.

Haemolytic anaemia
Drug-induced haemolytic anaemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia has also been reported.

Acute renal failure
As with other cephalosporins, Cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, Cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Renal Impairment:
Cefixime should be administered with caution in patients with markedly impaired renal function (See section 4.2 under Dosage in Renal Impairment).

Paediatric Use
Safety of cefixime in premature or newborn infant has not been established.
Resistance rates of *Streptococcus pneumoniae* (> 20 %) have been reported for cefixime in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Prolonged use of cefixime may result in the overgrowth of non-susceptible organisms.

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins including cefixime); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment.

In patients who develop severe diarrhoea during or after use of cefixime, the risk of life threatening pseudo-membranous colitis should be taken into account. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated

pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded. The use of medicinal products inhibiting the intestinal peristalsis is contra-indicated.

This medicine contains approximately 2.33 g of Sucrose in each 5ml after reconstitution. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth when the medicinal product may be intended for chronic use, e.g. for two weeks or more.

This medicine contains 10.0 mg of sodium benzoate in each 5ml after reconstitution. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interactions

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

A false positive direct Coombs' test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognised that a positive Coombs' test may be due to the drug.

In common with other cephalosporins, increases in prothrombin time have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There is no sufficient data from the use of cefixime in pregnant women. Animal data revealed no undesirable effects on pregnancy, embryonal/ fetal development, parturition or postnatal development (see section 5.3). However, these have also showed that cefixime reaches the embryo/fetus via the placenta.

As a precautionary measure, cefixime should only be used during pregnancy after careful benefit/risk assessment by the physician.

Breastfeeding:
It is unknown whether cefixime is excreted in human milk. Non-clinical studies have shown excretion of cefixime in animal milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the benefit of cefixime therapy to the woman. However, until further clinical experience is available, Cefixime should not be prescribed to breast-feeding mothers.

Fertility:
Reproduction studies performed in mice and rats have revealed no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Cefixime has no known influence on the ability to drive and use machines. However, side effects (for example *vertigo*) may occur (See also section 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects

In this section, the following convention has been used for the classification of undesirable effects (for example *vertigo*) in terms 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 and
Very rare: < 1/10,000
Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse Drug Reaction	Frequency
Infections and infestations	Superinfection bacterial, superinfection fungal	Rare
	Antibiotic-associated colitis (see section 4.4)	Very rare
Blood and lymphatic system disorders	Eosinophilia	Rare
	Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia	Very rare
	Thrombocytosis, neutropenia	Not Known
Immune system disorders	Hypersensitivity	Rare
	Anaphylactic shock, serum sickness	Very rare
Metabolism and nutrition disorders	Anorexia	Rare
Nervous system disorders	Headache	Uncommon
	Vertigo	Rare
	Psychomotor hyperactivity	Very rare
	Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.	Not known
Gastrointestinal disorders	Diarrhoea	Common
	Abdominal pain, nausea, vomiting	Uncommon
	Flatulence	Rare
Hepatobiliary disorders	Hepatitis, cholestatic jaundice	Very rare
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Angioneurotic oedema, pruritus	Rare
	Stevens-Johnson syndrome, toxic epidermal necrolysis	Very rare
	Drug rash with eosinophilia and systemic symptoms (DRESS) (see section 4.4.), erythema multiforme	Not known
Renal and urinary disorders	Interstitial nephritis	Very rare
General disorders and administration site conditions	Mucosal inflammation, pyrexia	Rare
Investigations	Hepatic enzyme increased (transaminase, alkaline phosphatase)	Uncommon
	Blood urea increased	Rare
	Blood creatinine increased	Very rare
	Direct and indirect positive Coombs tests (see section 4.4)	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no experience with overdoses with cefixime.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third generation cephalosporins. ATC Code: J01DD08

Mode of Action

Cefixime is an antibacterial agent of the cephalosporin class. Like other cephalosporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

PK/PD relationship

The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

Mechanisms of resistance

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

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or de-repressed in certain aerobic gram-negative bacterial species
- Reduced affinity of penicillin-binding proteins
- Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins
- Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell.
Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and / or antibacterial drugs of other classes.

Breakpoints

Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2018) for cefixime are:

- *Haemophilus influenzae*: sensitive ≤ 0.125 mg/L, resistant > 0.125 mg/L
- *Moraxella catarrhalis*: sensitive ≤ 0.5 mg/L, resistant > 1.0 mg/L
- *Neisseria gonorrhoeae*: sensitive ≤ 0.125 mg/L, resistant > 0.125 mg/L
- *Enterobacterales*: sensitive ≤ 1.0 mg/L, resistant > 1.0 mg/L (for uncomplicated urinary tract infections only)
- Non-species related breakpoints: insufficient evidence.

Susceptibility

The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections.
As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobes, Gram positive:
Streptococcus pyogenes°
Aerobes, Gram negative:
Haemophilus influenza
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis[%]
Species for which resistance may be a problem
Aerobes, Gram positive:
Streptococcus pneumoniae
Aerobes, Gram negative:
Citrobacter freundii[$]
Enterobacter cloacae[$]
Escherichia coli[%&]
Klebsiella oxytoca[%]
Klebsiella pneumoniae[%]
Morganella morganii[$]
Serratia marcescens[$°]
Resistant species
Aerobes, Gram positives:

Enterococcus spp. *Staphylococcus* spp. *Streptococcus pneumoniae* (Penicillin-intermediate and resistant)
Aerobes, Gram-negative Pseudomonas aeruginosa
Other micro-organism *Chlamydia* spp. *Chlamydophila* spp. *Legionella pneumophila* *Mycoplasma* spp.

° No current data was available when the table was published. In literature and actual therapy recommendations, susceptibility is assumed.
$ Natural susceptibility of most isolates is intermediate.
% Extended spectrum beta-lactamase (ESBL) producing isolates are always resistant
& In isolates of patients with uncomplicated Cystitis, the rate of resistance is < 10 %, in other isolates ≥ 10 %.

5.2 Pharmacokinetic properties

Absorption:
The absolute oral bioavailability of cefixime is in the range of 22-54 %. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

Distribution:
Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30 %. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations which are not seen following clinical dosing.

From *in vitro* studies, serum or urine concentrations of 1 mg/L or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

Metabolism and elimination:
Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.
Transfer of ^{14}C-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5 % of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

Special age groups:
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean C_{max} and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population (see section 4.2).

5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, *in vivo* and *in vitro* studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted.

Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death, which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum
Sodium benzoate (E211)
Silica colloidal, anhydrous
Sucrose
Flavour Strawberry Guarana which contains nature identical flavourings, natural flavours, maize maltodextrin and propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 6 months

After reconstitution: The reconstituted suspension may be stored for 14 days.

6.4 Special precautions for storage

Unopened: Store below 25ºC. Do not refrigerate or freeze.

After reconstitution, the suspension can be stored below 25ºC for 14 days. Do not refrigerate or freeze.

6.5 Nature and contents of container

Type III amber coloured glass bottle with white child-resistant closure with pilfer-proof cap.

Pack Sizes:
25 g powder for preparation of 50 ml oral suspension.
50 g powder for preparation of 100 ml oral suspension

Bottles are supplied with a measuring cup that have the marking of 35 ml and 69 ml; which can measure 35 ml and 69 ml of water for reconstitution.

Bottles are supplied with a single 5 ml plastic oral syringe graduated in 0.25 ml divisions.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for the preparation of the oral suspension:

Cefixime Nectar Lifesciences 100 mg/ 5 ml Powder for oral Suspension	**Pack size**	**Directions for Reconstitution**
100 mg/ 5ml	50 ml	Add 35 ml of water in two portions to the dry mixture in the bottle. Shake well after each addition. Further dilution is not recommended.
	100 ml	Add 69 ml of water in two portions to the dry mixture in the bottle. Shake well after each addition. Further dilution is not recommended.

The reconstitution results light yellow suspension with strawberry guarana flavor.

After reconstitution, the suspension can be stored below 25ºC for 14 days without significant loss of potency. Do not refrigerate or freeze. Keep bottles tightly closed and shake well before use. Discard any unused portion after 14 days.

Any antibiotic residual solution as well as all materials that have been used for administration should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

NECLIFE PT UNIPESSOAL LDA
Rua Brito Pais nº8C
1495-028 Algés
Portugal

8 MARKETING AUTHORISATION NUMBER

PA22914/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2018

10 DATE OF REVISION OF THE TEXT

November 2019