# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Adaluzis 500mg Powder for concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of ceftobiprole (as 666.6 mg of ceftobiprole medocaril sodium). After reconstitution, each mL of concentrate contains 50 mg of ceftobiprole (as 66.7 mg of ceftobiprole medocaril sodium).

Excipient(s) with known effect:

Each vial contains approximately 1.3 mmol (29 mg) sodium.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White, yellowish to slightly brownish, cake to broken cake or powder.

The pH of the reconstituted solution is between 4.5 and 5.5.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Adaluzis is indicated for the treatment of the following infections in adults (see sections 4.4, 5.1):

- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

Posology
The recommended dose of Adaluzis is 500 mg administered as a 2-hour intravenous infusion every 8 hours. For CAP, a switch to an appropriate oral antibiotic may be considered after completion of at least 3 days of intravenous ceftobiprole medocaril sodium treatment, depending on the patient's clinical response.

*Paediatric population*
The safety and efficacy of Adaluzis in children aged birth to < 18 years have not yet been established. Adaluzis is not recommended for use in children or adolescents below 18 years of age.

*Elderly patients*
No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see below and section 5.2).

*Renal impairment*
In patients with mild renal impairment (i.e., creatinine clearance [$CL_{CR}$] 50 to 80 mL/min), no dosage adjustment is necessary. In patients with moderate renal impairment ($CL_{CR}$ 30 to < 50 mL/min), the recommended dose of Adaluzis is 500 mg administered every 12 hours as a 2-hour intravenous infusion. In patients with severe renal impairment ($CL_{CR}$ < 30 mL/min), the recommended dose of Adaluzis is 250 mg administered every 12 hours as a 2-hour intravenous infusion. Due to limited clinical

data and an expected increased exposure of Adaluzis and its metabolite, Adaluzis should be used with caution in patients with severe renal impairment (see section 5.2).

*End-stage renal disease requiring dialysis*
Ceftobiprole medocaril sodium is haemodialysable. The recommended dose for patients with end-stage renal disease with or without intermittent haemodialysis is 250 mg once every 24 hours.

*Patients with creatinine clearance > 150 mL/min*
At start of treatment the prescribing physician should assess the renal function of the patient based on creatinine clearance expressed in mL/minute.

In patients with a supra-normal creatinine clearance (> 150 mL/min), based on pharmacokinetic/pharmacodynamic considerations, prolongation of the infusion duration to 4 hours is recommended (see section 5.2).

*Hepatic impairment*
There is no experience in patients with hepatic impairment. However, as ceftobiprole undergoes minimal hepatic metabolism and is eliminated predominantly by the kidneys, no dosage adjustment is considered necessary in patients with hepatic impairment.

Method of administration
Adaluzis must be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous infusion over a period of 2 hours.

Precipitation can occur when Adaluzis is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, Adaluzis and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line (see sections 4.4, 6.2).

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to the cephalosporin class of antibacterials.
Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

**4.4 Special warnings and precautions for use**

Hypersensitivity reactions
As With all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported. In case of severe hypersensitivity reactions, treatment with Adaluzis 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 Adaluzis, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if Adaluzis is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Dosing above the recommended dose range
There is no clinical experience with Adaluzis doses higher than the recommended 500 mg administered every eight hours.

Patients with pre-existing seizure disorders
Seizures have been associated with the use of Adaluzis. Seizures occurred most commonly in patients with pre-existing CNS/seizure disorders during treatment with Adaluzis. Therefore caution is advised when treating these patients.

*Clostridium difficile*-associated diarrhoea
Antibacterial agent-associated colitis and pseudomembranous colitis have been reported with the use of Adaluzis 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 Adaluzis (see section 4.8). Discontinuation of therapy with Adaluzis and t the

administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Superinfection with non-susceptible organisms
The use of Adaluzis may result in overgrowth of non-susceptible organisms, including fungi.
Appropriate measures should be taken if evidence of superinfection occurs during therapy.

Renal toxicity in animals
In animals, reversible renal toxicity was observed at high doses of Adaluzis and was associated with precipitation of drug-like material in the distal tubules (see section 5.3). Although the clinical significance of this observation is unknown, it is advisable to correct hypovolaemia to maintain normal urinary output in patients receiving Adaluzis.

Precipitation with calcium-containing solutions
Precipitation can occur when Adaluzis is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, Adaluzis and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line (see section 6.2).

Limitations of clinical data
There is no experience with ceftobiprole in the treatment of HAP (excluding VAP) and CAP in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression. Caution is advised when treating such patients.

*Patients with ventilator-associated pneumonia (VAP)*
Adaluzis has not been shown to be effective in the treatment of patients with VAP. Adaluzis should not be initiated in patients with VAP (see Section 5.1). In addition, on the basis of a post-hoc analysis showing a trend in favour of ceftobiprole, it is recommended that in patients with hospital-acquired pneumonia (HAP) who subsequently require ventilation, Adaluzis should be used with caution.

Clinical efficacy against specific pathogens
*Susceptibility to Enterobacteriaceae*
Ceftobiprole, like other cephalosporins is susceptible to hydrolysis that may be produced by Enterobacteriaceae including many of the extended-spectrum beta-lactamases (ESBLs), serine carbapenemases, class B metallo-beta-lactamases (among others). Therefore, information on the prevalence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) should be taken into consideration when selecting Adaluzis for treatment (see section 5.1).

Interference with serological testing
*Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia*

The development of a positive direct antiglobulin test may occur during treatment with a cephalosporin. In clinical studies there was no evidence of haemolytic anaemia. However, the possibility that haemolytic anaemia may occur in association with Adaluzis treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Adaluzis should be investigated for this possibility.

Potential interference with serum creatinine test
It is not known whether ceftobiprole, like some other cephalosprins, interferes with the alkaline picrate assay to measure serum creatinine (Jaffé reaction), which may lead to erroneously high creatinine measurements. During treatment with Adaluzis it is recommended that an enzymatic method of measuring serum creatinine be used.

Potential interference with urine glucose test
During treatment with Adaluzis it is recommended that an enzymatic method to detect glucosuria be used, because of potential interference with tests using the copper reduction technique.

This medicinal product contains approximately 1.3 mmol (29 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

**4.5 Interaction with other medicinal products and other forms of interactions**

*In vitro* studies have been carried out to investigate potential interactions at the level of CYP enzymes. However, as the concentrations of ceftobiprole used in these studies were limited by solubility, the potential for CYP drug interactions cannot be ruled out.

*In vitro* studies showed that ceftobiprole inhibits OATP1B1 and OATP1B3 with $IC_{50}$s of 67.6 micromole and 44.1 micromole respectively. Adaluzis may increase concentrations of drugs eliminated by OATP1B1 and OATP1B3, such as statins (pitavastin, pravastatin, rosuvastatin), glyburide, and bosentan.

No clinical interaction studies have been performed. Caution is advised when Adaluzis is administered together with drugs with narrow therapeutic index.

**4.6 Fertility, pregnancy and lactation**

Pregnancy
There are no adequate and well-controlled studies with Adaluzis in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

As no data in exposed human pregnancies are available, Adaluzis should not be used during pregnancy unless strictly necessary.

Breast-feeding
Animal studies have shown the excretion of ceftobiprole/metabolites in milk at low concentrations. It is unknown whether ceftobiprole is excreted in human milk and the risk of diarrhoea and fungal infection of the mucous membranes in the breast-fed infant 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 Adaluzis therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
The effects of ceftobiprole medocaril on fertility in humans have not been studied. Animal studies with ceftobiprole medocaril do not indicate harmful effects with respect to fertility.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, since dizziness is a common undesirable effect, driving and using machines is not recommended while on treatment with Adaluzis.

**4.8 Undesirable effects**

Summary of the safety profile
In therapeutic clinical studies, 1,668 subjects received Adaluzis. Within these trials there were a total of 1,239 subjects (696 subjects in community-acquired pneumonia and nosocomial pneumonia, and 543 subjects in complicated skin and soft tissue infections, cSSTIs) who received 500 mg three times daily, 389 subjects (cSSTIs) who received 500 mg twice daily and 40 subjects (cSSTIs) who received 750 mg twice daily.

The most common adverse reactions occurring in ≥ 3% of patients treated with Adaluzis were nausea, vomiting, diarrhoea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity) and dysgeusia.

Less frequently reported, but more serious, adverse reactions include thrombocytopenia, agranulocytosis, anaphylaxis, *Clostridium difficile*, colitis, convulsion, agitation (including anxiety, panic attacks and nightmares), and renal failure.

Tabulated list of adverse reactions
The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to 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); not known (cannot be estimated from the available data):

| **System Organ Class** | **Frequency:** |
|---|---|

| | **adverse events** |
|---|---|
| *Infections and infestations* | Common: Fungal infection (including vulvovaginal, oral and cutaneous fungal infections)<br>Uncommon: *Clostridium difficile* colitis** |
| *Blood and lymphatic system disorders* | Uncommon: Eosinophilia***, leukopenia, anaemia, thrombocytosis, thrombocytopenia<br>Not known: Agranulocytosis* |
| *Immune system disorders* | Common: Hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity)<br>Uncommon: Anaphylaxis** |
| *Metabolism and nutrition disorders* | Common: Hyponatraemia<br>Uncommon: Hypokalaemia |
| *Psychiatric disorders* | Uncommon: Insomnia, agitation (including anxiety, panic attacks and nightmares) |
| *Nervous system disorders* | Common: Dysgeusia, headache, dizziness, somnolence***<br>Not known: Convulsions*,** |
| *Respiratory, thoracic and mediastinal disorders* | Uncommon: Dyspnoea, pharyngolaryngeal pain***, asthma |
| *Gastrointestinal disorders* | Common: Nausea, vomiting , diarrhoea, abdominal pain, dyspepsia |
| *Hepatobiliary disorders* | Common: Hepatic enzymes increased (including AST, ALT, LDH and alkaline phosphatase) |
| *Skin and subcutaneous tissue isorders* | Common: Rash (including macular, papular, |

| | |
|---|---|
| | maculo-papular and generalised rash), pruritus |
| *Musculoskeletal and connective tissue disorders* | Uncommon: Muscle spasms*** |
| *Renal and urinary disorders* | Uncommon: Renal failure |
| *General disorders and administration site conditions* | Common: Infusion site reactions<br>Uncommon: Peripheral oedema |
| *Investigations* | Uncommon: Blood triglycerides increased, blood creatinine increased, blood glucose increased<br>Not known: Coombs Direct Test Positive (see section 4.4) |

* Based on post-marketing reports. Since these reactions were spontaneous reports post-marketing, it is not possible to reliably estimate their frequency which is therefore categorised as not known.
** See section 4.4
*** Seen in cSSTI studies only

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**

Information on overdosage with Adaluzis in humans is not available. The highest total daily dose administered in Phase 1 trials was 3 g (1 g every 8 hours). If overdosage should occur, it should be treated symptomatically. Ceftobiprole plasma concentrations can be reduced by haemodialysis.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other cephalosporins, ATC code: J01DI01

Mechanism of Action
Ceftobiprole exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs) in susceptible species. In Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), Ceftobiprole binds to PBP2a. Ceftobiprole has demonstrated in vitro activity against strains with divergent *mecA* homolog (*mecC or mecA*LGA251). Ceftobiprole also binds to PBP2b in *Streptococcus pneumoniae* (penicillin-intermediate), PBP2x in *S. pneumoniae* (penicillin resistant), and to PBP5 in *Enterococcus faecalis*.

Mechanisms of Resistance
Ceftobiprole is inactive against strains of Enterobacteriaceae that express Ambler class A β-lactamases, especially TEM, SHV and CTX-M type extended-spectrum β-lactamases (ESBL) and the KPC-type carbapenemases, Ambler class B β-lactamases and Ambler class D β-lactamases, especially ESBL variants and carbapenemases (OXA-48). Ceftobiprole is also inactive against strains that have high levels of expression of Ambler class C β-lactamases.
Ceftobiprole is inactive against strains of *P. aeruginosa* that express enzymes belonging to Ambler class A (e.g., PSE-1), Ambler class B (e.g., IMP-1, VIM-1, VIM-2) and Ambler class D (e.g., OXA-10). It is also inactive against isolates that have acquired

mutations in regulatory genes leading to de-repressed levels of expression of the chromosomal Ambler class C β-lactamase, or over-expression of the Mex XY efflux pump.
Ceftobiprole is inactive against strains of *Acinetobacter* spp. that express enzymes belonging to Ambler class A (e.g., VEB-1), Ambler class B (e.g., IMP-1, IMP-4) Ambler class D (e.g., OXA-25, OXA-26), or that have de-repressed levels of expression of the chromosomal Ambler class C β-lactamase.

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

| | **MIC breakpoints (mg/mL)** | |
|---|---|---|
| **Pathogen** | Susceptible (≤ S) | Resistant (R >) |
| *Staphylococcus aureus* (including MRSA) | 2 | 2 |
| *Streptococcus pneumoniae* | 0.5 | 0.5 |
| Enterobacteriaceae | 0.25 | 0.25 |
| *Pseudomonas aeruginosa* | IE[a] | IE[a] |
| Non-species specific breakpoint[b] | 4 | 4 |
| [a] Insufficient evidence.<br>[b] Based on the PK/PD target for Gram-negative organisms. | | |

PK/PD relationship
As with other beta-lactam antimicrobial agents, the percent time above the minimum inhibitory concentration (MIC) of the infecting organism over the dosing interval (%T > MIC) has been shown to be the parameter that best correlates with the efficacy of ceftobiprole

Clinical efficacy against specific pathogens
Efficacy has been demonstrated in clinical studies against the following pathogens in patients with HAP (not including VAP) and CAP that were susceptible to ceftobiprole in vitro:

*Staphylococcus aureus* (including MRSA)
*Streptococcus pneumoniae* (including MDRSP)
*Escherichia coli*
*Klebsiella pneumoniae*

Antibacterial activity against other relevant pathogens
Clinical efficacy has not been established against the following pathogens, although in vitro studies suggest that they would often be susceptible to ceftobiprole in the absence of an acquired mechanism of resistance:

*Acinetobacter* spp.
*Citrobacter* spp.
*Enterobacter* spp.
*Haemophilus influenzae*
*Klebsiella oxytoca*
*Moraxella catarrhalis*
*Morganella morganii*
*Proteus mirabilis*
*Providencia* spp.
*Pseudomonas* spp.
*Serratia* spp.

*In vitro* data indicate that the following species are not susceptible to ceftobiprole:

*Chlamydophila (Chlamydia) pneumoniae*
*Burkholderia cepacia complex*
*Mycoplasma pneumoniae*
Mycobacteria
*Nocardia* spp
*Stenotrophomonas maltophilia*

Data from clinical studies

*Nosocomial pneumonia*

Adaluzis demonstrated efficacy in a well-controlled randomised Phase 3 study in patients with HAP. Non-inferiority between Adaluzis and the comparator group could not be demonstrated in patients with VAP (i.e., patients who develop pneumonia > 48 hours after onset of ventilation). In VAP, clinical cure rates in Adaluzis treated patients were 37.7% in the Adaluzis group (20 out of 53 patients) compared to 55.9% in the ceftazidime plus linezolid group (33 out of 59 patients), see also sections 4.1 and 4.4.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adaluzis in one or more subsets of the paediatric population in the treatment of pneumonia (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

Plasma concentrations

The mean pharmacokinetic parameters of Adaluzis in adults for a single 500 mg dose administered as a 2-hour infusion and multiple 500 mg doses administered every 8 hours as 2-hour infusions are summarised in Table 1. Pharmacokinetic characteristics were similar with single and multiple dose administration.

**Mean (standard deviation) pharmacokinetic parameters of Adaluzis in adults**

| **Parameter** | **Single 500 mg dose administered as a 120-minute infusion** | **Multiple 500 mg doses administered every 8 hours as 120 minute infusions** |
|---|---|---|
| $C_{max}$ (microgram/mL) | 29.2 (5.52) | 33.0 (4.83) |
| AUC (microgram· h/mL) | 90.0 (12.4) | 102 (11.9) |
| $t_{1/2}$ (hours) | 3.1 (0.3) | 3.3 (0.3) |
| CL (mL/min) | 4.89 (0.69) | 4.98 (0.58) |

Distribution

Ceftobiprole binds minimally (16%) to plasma proteins and binding is independent of concentration. Ceftobiprole steady-state volume of distribution (18 litres) approximates extracellular fluid volume in humans.

Metabolism

The active substance of Adaluzis is ceftobiprole medocaril sodium, which is the pro-drug of the active moiety ceftobiprole. Conversion from the prodrug ceftobiprole medocaril sodium, to the active moiety ceftobiprole, occurs rapidly and is mediated by non-specific plasma esterases. Prodrug concentrations are negligible and are measurable in plasma and urine only during infusion. The metabolite resulting from the cleavage of the prodrug is diacetyl which is an endogenous human compound.

Ceftobiprole undergoes minimal metabolism to the open-ring metabolite, which is microbiologically inactive. Systemic exposure of the open-ring metabolite was considerably lower than for ceftobiprole, accounting for approximately 4% of the parent exposure in subject with a normal renal function.

*In vitro* studies demonstrated that ceftobiprole is an inhibitor of the hepatocyte uptake transporters OATP1B1 and OATP1B3, but is not an inhibitor of PgP, BCRP, MDR1, MRP2, OAT1, OAT3, OCT1 or OCT2. Ceftobiprole is potentially a weak substrate of the renal tubule cells uptake transporters OAT1 and OCT2.

Ceftobiprole protein binding is low (16%) and is not a PgP inhibitor or substrate. The potential for other drugs to interact with ceftobiprole is minimal, since only a small fraction of ceftobiprole is metabolised. Therefore, no relevant drug-drug interactions are anticipated (see section 4.5).

Since ceftobiprole does not undergo tubular secretion and only a fraction is reabsorbed, renal drug-drug interactions are not expected.

Elimination

Ceftobiprole is eliminated primarily unchanged by renal excretion, with a half-life of approximately 3 hours. The predominant mechanism responsible for elimination is glomerular filtration, with some active reabsorption. Following single dose

administration in human, approximately 89% of the administered dose is recovered in the urine as active ceftobiprole (83%), the open-ring metabolite (5%) and ceftobiprole medocaril (<1%).

Linearity/non-linearity
Ceftobiprole exhibits linear and time-independent pharmacokinetics. The $C_{max}$ and AUC of Adaluzis increase in proportion to dose over a range of 125 mg to 1 g. Steady-state active substance concentrations are attained on the first day of dosing; no appreciable accumulation occurs with every-8-hour dosing in subjects with normal renal function.

Pharmacokinetic/Pharmacodynamic Relationship
Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of Adaluzis exceeds the minimum inhibitory concentration of the infecting organism (%T>MIC) has been shown to best correlate with efficacy in clinical and pre-clinical pharmacokinetic/pharmacodynamic studies.

Special Populations

*Renal impairment*
The estimation of creatinine clearance should be based on the Cockcroft-Gault formula using actual body weight. During treatment with ceftobiprole it is recommended that an enzymatic method of measuring serum creatinine be used (see section 4.4).

The pharmacokinetics of ceftobiprole are similar in healthy volunteers and subjects with mild renal impairment ($CL_{CR}$ 50 to 80 mL/min). Ceftobiprole AUC was 2.5- and 3.3-fold higher in subjects with moderate ($CL_{CR}$ 30 to < 50 mL/min) and severe ($CL_{CR}$ < 30 mL/min) renal impairment, respectively, than in healthy subjects with normal renal function. Dosage adjustment is recommended in patients with moderate to severe renal impairment (see section 4.2).

*End-stage renal disease requiring dialysis*
AUCs of ceftobiprole and of the microbiologically inactive ring-opened metabolite are substantially increased in patients with end stage renal disease who require haemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease on haemodialysis received a single dose of 250 mg Adaluzis by intravenous infusion, ceftobiprole was demonstrated haemodialysable with an extraction ratio of 0.7 (see section 4.2).

*Patients with creatinine clearance > 150mL/min*
Ceftobiprole systemic clearance ($CL_{SS}$) was 40% greater in subjects with a $CL_{CR}$ > 150 mL/min compared to subjects with a normal renal function ($CL_{CR}$ = 80-150 mL/min). Volume of distribution was 30% larger. In this population, based on pharmacokinetic/pharmacodynamic considerations, prolongation of duration of infusion is recommended (see section 4.2).

*Hepatic impairment*
The pharmacokinetics of ceftobiprole in patients with hepatic impairment have not been established. As ceftobiprole undergoes minimal hepatic metabolism and is predominantly excreted unchanged in the urine, the clearance of Adaluzis is not expected to be affected by hepatic impairment (see section 4.2).

*Elderly*
Population pharmacokinetic data showed that age as an independent parameter has no effect on the pharmacokinetics of ceftobiprole. Dosage adjustment is not considered necessary in elderly patients with normal renal function (see section 4.2).

*Gender*
Systemic exposure to ceftobiprole was higher in females than males (21% for $C_{max}$ and 15% for AUC), however the %T>MIC was similar in both males and females. Therefore, dosage adjustments based on gender are not considered necessary.

*Race*
Population pharmacokinetic analyses (including Caucasians, Black and Other groups) and a dedicated pharmacokinetic study in healthy Japanese subjects showed no effect of race on the pharmacokinetics of ceftobiprole. Therefore, dosage adjustments based on race are not considered necessary.

*Body weight*
A study was performed in morbidly obese subjects. No dose adjustments based on body weight are required.

**5.3 Preclinical safety data**

Reversible renal toxicity in the distal tubules due to precipitation of drug-like material was observed at high doses only in small animals such as rats and marmosets and after bolus administration. Absence of kidney toxicity was observed in animals at urinary concentrations up to 12 times higher than those observed in humans at the therapeutic dose. Convulsions were observed after both single and multiple doses at exposures of six times the human exposure and higher, based on $C_{max}$.

Infusion-site irritation leading to thrombus formation was observed in small animals (rats and marmosets) but not in dogs. In a pre- and post-natal development study in rats, litter size and survival up to 4 days postpartum were decreased at maternally toxic doses. The relevance of all these findings for humans is unknown.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Citric acid monohydrate
Sodium hydroxide

**6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

This medicinal product must not be mixed or administered simultaneously with calcium-containing solutions (except Lactated Ringer's solution for injection). See sections 4.2, 4.4, 6.6.

This medicinal product should not be simultaneously administered via a Y site with:
Acyclovir sodium, Amikacin sulphate, Amiodarone hydrochloride, Amphotericin B (colloidal), Calcium gluconate, Caspofungin acetate, Ciprofloxacin, Cisatracurium besylate, Diazepam, Diltiazem hydrochloride, Diphenhydramine hydrochloride, Dobutamine hydrochloride, Dopamine hydrochloride, Esomeprazole sodium, Famotidine, Filgrastim, Gentamicin sulphate, Haloperidol lactate, Hydromorphone hydrochloride, Hydroxyzine hydrochloride, Insulin human regular, Insulin lispro, Labetalol hydrochloride, Levofloxacin, Lidocaine hydrochloride, Magnesium sulphate, Meperidine hydrochloride, Metoclopramide hydrochloride, Midazolam hydrochloride, Milrinone lactate, Morphine sulphate, Moxifloxacin hydrochloride, Ondansetron hydrochloride, Pantoprazole sodium, Potassium phosphates, Promethazine hydrochloride, Remifentanil hydrochloride, Sodium phosphates, Tobramycin sulphate.

**6.3 Shelf life**

Powder vial
4 years

After reconstitution
Chemical, and physical in-use stability of the reconstituted solution (50 mg/mL) has been demonstrated for 1 hour at 25°C and up to 24 hours at 2°C–8°C.

After dilution
Chemical and physical in-use stability data support the total times for reconstitution and infusion(2.67 mg/mL) described in the table below:

**Total time by which reconstitution and infusion (including a 2-hour period of infusion, see Section 4.2) must be completed**

| **Infusion solution diluent** | **Infusion solutions stored at 25°C** | | **Infusion solutions stored at 2°C–8°C (refrigerator)** |
|---|---|---|---|
| | Protected from light | NOT protected from light | Protected from light |
| Sodium chloride 9 mg/mL (0.9%) solution | 24 hours | 8 hours | 96 hours |

| | | | |
|---|---|---|---|
| for injection | | | |
| Dextrose 50 mg/mL (5%) solution for injection | 12 hours | 8 hours | 96 hours |
| Lactated Ringer's solution for injection | 24 hours | 8 hours | Do not refrigerate |

From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The reconstituted and infusion solutions should not be frozen or exposed to direct sunlight.

If the infusion solution is stored in the refrigerator, it should be equilibrated to room temperature prior to administration. The infusion solution does not need to be protected from light during administration.

The infusion solution should be prepared and used as defined in section 6.6.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C–8°C). Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted and/or diluted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

20 mL clear type I glass vials fitted with a grey bromobutyl elastomeric closure and an aluminium seal with a blue plastic flip-off cap.

Pack size: 10 vials.

**6.6 Special precautions for disposal and other handling**

Each vial is for single use only.

Adaluzis must be reconstituted and then further diluted prior to infusion.

**Step 1. Reconstitution**

10 mL of sterile water for injections or dextrose 50 mg/mL (5%) solution for injection should be added to the vial and the vial should be shaken vigorously until complete dissolution, which in some cases may take up to 10 minutes. The volume of the resulting concentrate is approximately 10.6 mL. Any foam should be allowed to dissipate and the reconstituted solution should be inspected visually to ensure the product is in solution and particulate matter is absent. The reconstituted concentrate contains 50 mg/mL of ceftobiprole and must be further diluted prior to administration. It is recommended that the reconstituted solution be further diluted immediately. However, if this is not possible the reconstituted solution can be stored at room temperature for up to one hour, or in a refrigerator for up to 24 hours.

**Step 2. Dilution**

Preparation of 500 mg dose of Adaluzis solution for infusion
10 mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5-10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 500 mg dose of Adaluzis.

Preparation of 250 mg dose of Adaluzis solution for infusion for patients with severe renal impairment
5 mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 125 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5-10

times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 250 mg dose of Adaluzis.

The solution for infusion should be clear to slightly opalescent and yellowish in colour. The solution for infusion should be inspected visually for particulate matter prior to administration, and discarded if particulate matter is visible.

Detailed information on the time by which reconstitution, dilution and infusion must complete is provided in section 6.3.

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

**7 MARKETING AUTHORISATION HOLDER**

Correvio
15 Rue du Bicentenaire
92800 Puteaux
France

**8 MARKETING AUTHORISATION NUMBER**

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