**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

IXINE 200 mg, film-coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IXINE Tablet
Cefixime as cefixime trihydrate 200 mg

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

They are limited to infections caused by germs defined as sensitive, when these infections enable an oral antibiotherapy, and among others:

- Acute pyelonephritis without uropathies
- Low urinary tract infection, complicated or not, except for prostatitis
- Bacterial superinfections of acute bronchitis and exacerbation of chronic bronchitis
- Pneumopathies from suspected bacterial origin
- Masculine gonococcal urethritis

It is required to take the official recommendation concerning the appropriate use of antibacterial agents into account.

### 4.2 Posology and method of administration

Posology

*Adult*
The posology of IXINE is 400 mg/day in 2 administrations of a 200 mg tablet, with 12-hour spacing.

In gonococcal urethritis, the efficacy is observed with a single administration of two 200 mg tablets.

*Elderly subjects*
When the kidney function is normal, it is not required to modify the posology in elderly subjects.

*Kidney failure*
When the creatinine clearance values are over 20 ml/min, no posology modification is required. For lower values, including patients undergoing haemodialysis, the posology of cefixime should not be more than 4 mg/kg/day in one administration.

*Liver failure*
No posology modification is required.

Method of administration

Oral route

The suspension is reconstituted by adding water up to the mark to make up a total volume of 40 ml and to shake before use.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Special warnings

- Any allergic manifestation imposes stopping the treatment.
- Prescription of cephalosporin requires prior questioning. Allergy to penicillins being crossed to allergy to cephalosporins in 5 to 10 % of cases:
  - The use of cephalosporins should be extremely careful in patients with sensitivity to penicillins; a strict medical monitoring is required as of the time of the first administration.
  - The use of cephalosporin is formally proscribed in patients with history of immediate type allergy to cephalosporins. In doubt, presence of a doctor by the patient is essential at time of the first administration, in order to treat the potential anaphylactic accident.
- Hypersensitivity reactions (anaphylaxis) observed with these 2 types of substances might be serious and sometimes fatal.
- Cases of colitis related to the administration of antibacterial products and pseudo membranous colitis, have be reported with almost all antibacterial products, including cefixime with seriousness ranging from mild to life-threatening. Therefore, it is important to take this diagnosis into account in patients with diarrhoea during or after the administration of cefixime. Stopping the treatment with cefixime and the administration of a treatment against *Clostridium difficile* should be considered. Any administration of peristaltism inhibitors is proscribed.
- Serious skin reactions as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or bullous skin reactions (Lyell syndrome, Stevens-Johnson syndrome) have been reported in patients treated with cefixime (see section 4.8).
- Betalactams including cefixime predispose the patients to a risk of encephalopathy (that can include convulsions, confusion, conscience disorders or abnormal movements), and, particularly, in case of overdose or of altered kidney function.
- Excipients with known effects:
  - IXINE tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
  - IXINE Kid and IXINE 1st age contain sucrose. Their use is discouraged in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltase insufficiency.

Precautions for use

- In patients with allergies to other betalactams, the possibility of cross-allergy should be taken into account.
- In case of severe renal failure, daily dosage adaptation in terms of creatinine clearance should be considered (cf. Pharmacokinetics – Posology and method of administration).
- In patients below 6-year-old, in the absence of specific studies, it is recommended not to use cefixime.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Drug-drug interactions:*
No clinically significant interaction has been reported during the clinical trials. In terms of pharmacokinetics, it was demonstrated that combining 1 g of probenecid and cefixime results in a 25 % decrease in total product clearance. In man, the combination with an antacid does not decrease the absorption of cefixime.

*Interaction with laboratory exams:*
False positive reaction in the test for ketones in urines (nitroprussiate method).
False positive reaction in the test for glycosuria (preferably use the methods using glucose oxidase).
False positivation of Coombs test was described during treatment with cephalosporins.

*Specific problems of INR imbalance:*
Number of cases of increase in the activity of oral anticoagulants were reported in patients treated with antibiotics. The marked infectious or inflammatory context, the age and the general state of the patient appear as risk factors. In these circumstances, it seems difficult to differentiate between the infectious pathology and its treatment in the appearance of INR imbalance. However, some classes of antibiotics are more implicated than others: notable the fluoroquinolones, macrolides, cyclins, cotrimoxazole and some cephalosporins.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Because of the expected benefit, the use of cefixime can be considered during pregnancy, if required. Indeed, despite the clinical data being insufficient, the animal data did not show any malformative effect of foetotoxicity.

Breast-feeding
There is no data on the excretion of cefixime into breast milk. However, breast-feeding is possible in case of treatment with this antibiotic. Nevertheless, breast-feeding (or treatment) in case of appearance of diarrhoea, candidiasis or skin rash in the infant should be interrupted.

## 4.7 Effects on ability to drive and use machines

In case of appearance of undesirable effect as encephalopathy (that might include convulsions, confusion, conscience disorders or abnormal movements) (see sections 4.4, 4.8, 4.9), the patient should drive or use machines.

## 4.8 Undesirable effects

**Haematological and lymphatic system disorders**
- Hypereosinophilia, thrombocytosis, thrombocytopenia, leucopoenia, neutropenia and agranulocytosis

**Gastro-intestinal disorders**
- Abdominal pains, diarrhoea (see section 4.4), nausea, vomiting, dyspepsia

**General disorders and administration site conditions**
- Fever

**Infections and infestations**
- Pseudo-membranous colitis

**Immune system disorders**
- Skin rash, rare cases of anaphylactic reactions as urticarial or angioedema

**Investigations**
- Moderate increase in transaminases AST and AST and alkaline phosphatases.
- Low increase in blood urea and creatinine.

**Nervous system disorders**
- Headaches, dizziness

- Unknown frequency: cases of convulsions were reported with cephalosporins, including cefixime

Betalactams including cefixime predispose the patients to the risk of encephalopathy (that can include convulsions, confusion, conscious disorders or abnormal movements) and, particularly, in case of overdose or of altered kidney function.

**Kidney and urinary function disorders**
- Acute kidney failure by interstitial nephritis

**Skin and subcutaneous disorders**
- Very rare cases of bullous eruption (erythema multiform, Stevens-Johnson syndrome, Lyell syndrome), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4).

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 the national reporting system.

### 4.9 Overdose

Betalactams, including cefixime, predispose the patients to the risk of encephalopathy and, particularly, in case of overdose or of altered kidney function.
In case of ingestion of high doses of cefixime, a symptomatic treatment shall be initiated. There is no specific antidote. Haemodialysis or peritoneal dialysis does not enable to eliminate cefixime from the plasma.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporins, ATC code: J01DD08

As other cephalosporins, the mechanism of action of cefixime relies on the inhibition of bacterial wall synthesis.
Cefixime presents an *in vivo* bactericidal activity against numerous Gram positive or negative germs.

ANTIBACTERIAL SPECTRUM OF ACTIVITY
Critical concentrations segregate sensitive strains from intermediate and resistant strains:
$S \leq 1$ mg/l et $R > 2$ mg/l
Prevalence of acquired resistance may vary in terms of geographical parameters and time for certain species. It is then required to have information on local prevalence of resistance, especially to treat severe infections. These data can bring an orientation on probabilities of the sensitivity of a bacterial strain to this antibiotic.
When the variability of the prevalence of the resistance in France is known for a specific bacterial strain, it is indicated in the table below:

| **Categories** | **Frequency of acquired resistance in France (> 10 %) (extreme values)** |
|---|---|
| **SENSITIVE SPECIES** | |
| **Gram positive Aerobes** | |
| *Streptococcus* | |
| *Streptococcus pneumoniae* | 30 – 70 % |
| **Gram negative Aerobes** | |

| | |
|---|---|
| *Branhamella catarrhalis* | |
| *Citrobacter koseri* | |
| *Escherichia coli* | 5 – 15 % |
| *Haemophilus influenzae* | |
| *Klebsiella* | 0 – 20 % |
| *Neisseria gonorrhoeae* | |
| *Pasteurella* | |
| *Proteus mirabilis* | |
| *Proteus vulgaris* | |
| *Providencia* | |
| **Anaerobes** | |
| *Fusobacterium* | 10 – 20 % |
| *Prevotella* | 30 – 70 % |
| **RESISTANT SPECIES** | |
| **Gram positive Aerobes** | |
| *Corynebacterium diphtheriae* | |
| Enterococcus | |
| *Listeria* | |
| *Staphylococcus* | |
| **Gram negative Aerobes** | |
| *Acinetobacter* | |
| *Citrobacter freundii* | |
| *Pseudomonas* | |
| *Serratia* | |
| **Anaerobes** | |
| Except for *Prevotella and Fusobacterium* | |

## 5.2 Pharmacokinetic properties

Absorption

- After oral administration, a single dose of 200 mg, maximal serum concentrations ($C_{max}$) are, on average, 3 µg/ml and are reached ($T_{max}$) in about 3 to 4 hours.
- After administration of a dose of 400 mg, maximal serum concentrations are increased (3,4-5 µg/ml), but not proportionally to the dose increase.
- After repeated administrations for 15 days of doses of 400 mg/day in one or two administrations, serum concentrations and bioavailability are not modified, showing the absence of accumulation of the active ingredient.
- the bioavailability of cefixime is about 50 % of the 200 mg dose. It is not modified by a meal. The time of appearance of the maximal serum concentration is though delayed by about an hour.

Distribution

- The apparent volume of distribution if about 15 L. in animal, cefixime diffuses in a large majority of the studied tissues, except for the brain. In man, after intakes of 200 mg with 12 hours spacing, the pulmonary concentration, 4 to 8 hours after the last intake, are about 1 µg/g of tissue, these concentrations being greater to C.M.I. of 90 % of the sensitive germs causing pulmonary infections.

Elimination

- The elimination of cefixime is characterised by a half-life ($T_{1/2}$) ranging between 3 and 4 hours (average: 3.3 hours). The product is eliminated renally unchanged (16 to 20 % of the administered dose), the extra-renal elimination is essentially biliary (25 %).
- No metabolite from the serum or the urine, could be detected in animal or man.

- In case of kidney impairment (creatinine clearance < 20 ml/min) the increase in elimination plasmatic half-life and in maximal serum concentrations make it necessary to reduce the daily posology from 400 to 200 mg/day.
- In hepatic impaired patients, the elimination is slowed down ($T_{1/2}$ = 6.4 hours), but it is not necessary to modify the dose.
- Serum proteins binding is about 70 % and is involves mainly albumin, independently from the concentration (at therapeutic doses).

Pharmacokinetics characteristics of cefixime are slightly modified in elderly subjects. The weak increase in maximal serum concentrations, bioavailability and the weak decrease in excreted quantity (15 to 25 %) do not require any decrease in posology in this population.

**Children**
- Serum concentrations obtained after administration, in a single dose, of 4 mg/kg of cefixime (granules) range between 1,7 and 2,5 µg/ml.
- Five hours after an intake of 4 mg/kg of cefixime, the concentration in the non-fibrous tonsils are in average 0.6 to 0.8 µg/g for a concomitant serum concentration of 1.24 ± 0.94 µg/ml.

### 5.3 Preclinical safety data

Not applicable.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

IXINE tablet: lactose, microcrystalline cellulose, talc, magnesium stearate, sodium croscarmellose, hypromellose, titanium dioxide (E171), macrogol 6000, povidone K30.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original container, below 30 °C.
The reconstituted suspensions of IXINE kid and IXINE first age can be stored at room temperature for 7 days.

### 6.5 Nature and contents of container

IXINE Tablet
Aluminium/aluminium blister containing 10 film-coated tablets.

Not all pack sizes might be marketed

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

## 8. MARKETING AUTHORISATION HOLDER

Exphar s.a.
Zoning Industriel de Nivelles Sud, zone II – Avenue Thomas Edison 105 – 1402 Thines
BELGIUM
Phone: +32 2(0)67 68 84 05
Fax: +32 2(0)67 68 84 19

## 9. MANUFACTURER

Gracure Pharmaceuticals Ltd.,
E-1105, Industrial Area, Phase-III, Bhiwadi, Dist. Alwar (Raj.)
INDIA

Phone: 91+11+25920748
Fax: 91+11+25920747

## 10. DATE OF REVISION OF THE TEXT

02/2019