SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANCEF® 100 mg/5 ml powder for oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml (1 graduated spoon) of prepared suspension contains 111.9 mg of cefixime trihydrate, corresponding to 100 mg of cefixime.).
Excipients with known effect:
Sucrose 2.517 g/5 ml
Sodium benzoate (E 211) 2.5 mg/5 ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Powder for oral suspension.

Almost white to pale yellow powder.
The reconstituted suspension appears as almost white to pale yellow viscous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pancef is indicated for the treatment of infections caused by microorganisms sensitive to cefixime, as follows:
- acute upper respiratory tract infections (pharyngo-tonsillitis, sinusitis);
- otitis media acuta;
- lower respiratory tract infections (acute bronchitis, acute exacerbation of chronic bronchitis, tracheobronchitis, pneumonia);
- uncomplicated and complicated urinary tract infections, including acute pyelonephritis;
- uncomplicated gonorrhea (cervical/urethral);

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

4.2 Posology and method of administration

Posology
Paediatric population

Children below 10 years old or weighing less than 50 kg: 8 mg/kg daily administered as a single oral dose, or divided in two equal doses of (4 mg/kg every 12 hours).

As a general guide for prescribing in children the following daily doses in terms of volume of oral suspension are suggested:
6 months up to 1 year: 2.5 ml to 5.0 ml daily.
Children 1-4 years: 5 ml daily
Children 5-10 years: 10 ml daily
The safety and efficacy of cefixime has not been established in children under 6 months.

Children weighing more than 50 kg or older than 10 years should be treated with the recommended dose for adults.
The recommended dosage is 400 mg daily, administered as single oral dose or divided in two equal oral doses of 200 mg every 12 hours.

It is recommended otitis media acuta to be treated with suspension and replacement of the suspension with tablets is not recommended.

Older people
Older people may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in cases with severe renal impairment (See "Dosage in Renal Impairment").

Dosage in patients with renal impairment
Pancef may be administered also in the presence of impaired renal function. Normal doses and method of administration can be applied 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.

Duration
The usual course of treatment is 7 days. This may be continued for up to 14 days according the severity of the infection.
Streptoccocal (Streptococcus Pyogenes) infections should be treated at least 10 days.

Method of Administration
See section 6.6 for further instructions on medication preparation before use.

The suspension is for oral administration only.

Measuring teaspoon (5 ml) is provided with the bottle to allow proper dosing.

One measuring spoon (5 ml) contains the equivalent of 100 mg cefixime.
Food does not significantly impair the absorption of cefixime.

4.3 Contraindications

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

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 (SCARS) such as toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), rash with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with cefixime. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of skin hypersensitivity. .

Pancef should be given with caution to patients who have shown hypersensitivity to other drugs.

Hypersensitivity to penicillins

As with other cephalosporins, cefixime should be used with caution in patients with known hypersensitivity to penicillin as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins .

In both groups of drugs severe reactions occurred (including anaphylaxis). In case of allergic reaction, the use of the product should be discontinued and if necessary, appropriate measures should be taken.

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 "Dosage in patients with renal impairment").

Paediatric use

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

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

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.

Important information on some of the excipients
Pancef powder for oral suspension contains 2.517 g of sucrose per 5 ml reconstituted suspension. This should be taken into account by patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine.

This medicine contains 2.5 mg sodium benzoate (E 211) per 5 ml reconstituted suspension. Sodium benzoate (E211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml reconstituted suspension, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants

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

Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction

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

A false positive direct Coombs test may occur during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the use of the drug.

4.6 Fertility, pregnancy and lactation

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. There are no adequate and well-controlled studies in pregnant women. Pancef should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

In the case of side effects such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

4.8 Undesirable effects

Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and individual.

The following adverse reaction (Preferred term# or equivalent) will be considered listed:

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia Thrombocytopenia Thrombocytosis

Gastrointestinal disorders:	Abdominal pain Diarrhoea* Dyspepsia Nausea Vomiting Flatulance
Hepatobiliary disorders:	Jaundice
Infections and infestations:	Pseudomembranous colitis
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased
Nervous system disorders:	Dizziness Headache Cases of convulsions have been reported with cephalosporins including cefixime (frequency not known)** 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 (frequency not known)**
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Renal and urinary disorders:	Acute renal failure including tubulointerstitial nephritis as an underlying pathological condition
Immune system disorders, administrative site conditions, skin and subcutaneous tissue disorders:	Anaphylactic reaction Serum sickness-like reaction Drug rash with eaosinophilia and systemic symptoms (DRESS) Pruritus Rash Drug Fever Arthralgia Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-oedema Urticaria Pyrexia Face oedema

	Genital pruritus Vaginitis Acute generalised exanthematous pustulosis(AGEP) (see section 4.4)

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

Preferred term in MedDRA (v.14.0)

*Diarrhoea has been more commonly associated with higher doses. Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Pancef should be discontinued if marked diarrhoea occurs

** Cannot be estimated from available data

Reporting of side effects

If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to the information database on adverse reactions (actions) to medicinal products, including reports of drug inefficiency, identified in the territory of the EAEU member states.

«SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC
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Phone: (+374 60)83-00-73, (+374 10)23-08-96, (+374 10)23-16-82
Hot Line: (+374 10) 20-05-05, (+374 96) 22-05-05
E-mail: naira@pharm.am,vigilance@pharm.am

By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics, including cefixime, particularly in case of overdose or renal impairment.

Adverse reactions seen at dose levels up to 2 g cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses.

Cefixime is not removed from the circulation in significant quantities by dialysis.

No specific antidote exists. General supportive measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Cefixime is an oral third generation cephalosporin which has marked antibacterial activity against a wide variety of Gram-positive and Gram-negative organisms.

Mechanism of action
The mechanism of action is based on the inhibition of bacterial wall synthesis. The drug is stable against hydrolytic action of a great number of beta-lactamases, thus many organisms resistant to penicillins and some cephalosporins (due to the presence of beta-lactamases) may be sensitive on cefixime.

Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Branhamella catarrhalis* (beta-lactamase positive and negative strains) and *Enterobacter* species. It is highly stable in the presence of the enzyme beta-lactamase.

Most strains of enterococci (*Streptococcus faecalis*, group D Streptococci) and Staphylococci (including coagulase positive and negative strains and meticillin-resistant strains) are resistant to cefixime. In addition, most strains of *Pseudomonas, Bacteroides fragilis, Listeria monocytogenes* and *Clostridia* are resistant to cefixime.

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..

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

The administration of oral suspension, produces average peak concentration approximately 25-50% higher than the same dose, administered in a form of tablets. 200 mg and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg / mL (range 1 to 4,5 mcg/mL) and 4,6 mcg/mL (range 1,9 to 7,7 mcg/mL) respectively, when tested in normal adult volunteers. Area under the curve value is greater approximately 10-25% following oral suspension administration than following tablet administration. These pharmacokinetic differences must be taken into consideration whether the oral suspension is to be substituted with tablet formulation.
Maximal serum concentrations are reached within 2-6 hours.

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 is approximately 30%. Protein binding of cefixime is only concentration dependent in the human serum at very high concetrations which are not seen following clinical testing.

Transfer of ^{14}C-labeled 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 in pregnant rats was low.

Biotransformation
Metabolites of cefixime have not been isolated from human serum or urine.

Elimination
Cefixime is predominantly eliminated as unchanged drug in the urine through glomerular filtration.
Elimination half-life in healthy subjects averages 3-4 hours, but may range up to 9 hours in some normal volunteers.The longelimination half-life enables once daily administration.

Older people
The pharmacokinetics of cefixime in healthy elderly (age> 64 years) and in younger volunteers (11-35 years) was compared during the use of a dose of 400 mg once daily for 5 days. The mean Cmax and AUC values were slightly higher in the elderly. Therefore elderly patients can receive same doses as the general population.

Patients with renal impairment
In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance) the average serum elimination half-life of cefixime is prolonged to 6.4 hours, while in severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life is increased to 11,5 hours.

5.3 Preclinical safety data

The acute toxicity of cefixime is low. In studies with repeated administration dose-dependent changes were found in the gastrointestinal system and the kidneys. It is thought that cefixime, like other cephalosporins is potentially nephrotoxic.

Animal studies in mice, rats and rabbits revealed no teratogenic potential of the drug. Cefixime does not have any impact on perinatal or postnatal development and fertility in rats.

Cefixime showed no mutagenic potential in most in vitro and in vivo tests. Because there are no data on carcinogenicity of cefixime and no data on toxicity in long-term use in rats and because cefixime is not intended for use in a longer time frame, studies for carcinogenicity for chronic use of the drug were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose;
Xanthan gum;
Sodium benzoate (E 211);
Flavour durarome orange containing:
- Flavouring ingredients
- Maize maltodextrin
- Sucrose
- Soy-Lecithins (E 322)
- Silicon dioxide (E 551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unreconstituted product: 3 (three) years.
Reconstituted suspension: may be stored for 14 days at ambient conditions (below 25^{o}C) or refrigerated conditions.

6.4 Special precautions for storage

Before reconstitution, powder for oral suspension should be stored below 25°C.
For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

The powder for oral suspension is packed in a 150 ml brown neutral glass bottle supplied with an aluminium cap with a polyethylene sealing.
Each bottle contains 53 g powder for preparing 100 ml oral suspension.
Cardboard box contains one (1) bottle, one plastic 5 ml graduated spoon for dosing and , an instruction leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The suspension is prepared in a pharmacy, just before use, as follows:
Before preparing the suspension the bottle containing powder should be well shaken several times, 66 ml purified water to be added, divided into two parts, and again strongly shaken.
The prepared suspension is almost white to pale yellow viscous liquid.
Before each use, the bottle should be shaken well!

The prepared suspension should be dosed with special graduated spoon.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT