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

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 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.

For oral use.

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 the active supstance, to any of the cephalosporins or penicillin, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens Johnson syndrome and rash with eosinophilia and systemic symptoms (DRESS) have been observed in some patients when taking cefixime. If severe skin reactions appear, treatment with cefixime must be discontinued immediately and appropriate measures depending on the patient's condition should be implemented.

In patients with allergic diathesis or asthma, special attention should be payed when beta-lactam antibiotics are used.

Cefixime should be used with caution in patients with known hypersensitivity to other drugs, especially penicillin (cross allergic reaction between penicillins and cephalosporins is possible). 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.

EXPERT/DATA dbs/22.09.17 /28.09.2017

Cefixime should be administered with caution in patients with markedly impaired renal function, so cefixime dosage should be adjusted. (See section 4.2 "Dosage in patients with renal impairment").

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. Treatment of pseudomembranous colitis 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.

During long-term use of high doses of cefixime regular monitoring of renal function and liver and blood counts are required.

As with any long-term use of antibiotics, attention should be payed to the possibility of increased growth of insensitive bacteria or fungi.

Renal function should be closely monitored in case of combination of cefixime with aminoglycosides, polymyxin B, colistin, viomycin or high doses of loop diuretics (eg. Furosemide) (see section 4.5). This is especially intended for patients with impaired renal function.

In some cases, concomitant use of cefixime and nifedipine (blocker of Ca + channels) may increase the bioavailability of cefixime for 70% (see section 4.5).

In individual cases, in patients receiving concomitant cefixime and anticoagulants (eg. Coumarin) prolongation of the prothrombin time with or without bleeding is established, and constant monitoring of coagulation parameters is recommended.

Important information on some of the excipients
Pancef powder for oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is required with concomitant use of:

- potentially nephrotoxic drugs (aminoglycoside and duretici with strong effect such as furosemide or ethacrynic acid): an increased risk of renal impairment can be expected (see section 4.8);
- colistin, polymyxin, viomycin: worsening of renal function is possible;
- nifedipine (calcium blocker): may increase the bioavailability of cefixime for 70% (see section 4.4).

A false positive reaction for the amount of 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 you need to know that a positive Coombs test may be due to the use of the drug.
As with other cephalosporins, in some patients, an increase in prothrombin time is noticed. Therefore, caution is needed in patients receiving anticoagulant therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and controlled studies in pregnant women. Animal studies show no evidence of teratogenic effect of cefixime (see section 5.3). Cefixime crosses the placenta. Due to lack of clinical experience, especially in the first three months of pregnancy, Pancef should only be used after careful assessment of the situation taking into account the risk of its use.

Breastfeeding
The presence of cefixime in breast milk is not revealed. However, due to insufficient clinical experience the drug should not be used during breastfeeding. If treatment is necessary, using of pumps for milking and removal of milk during the treatment is recommended.

4.7 Effects on ability to drive and use machines

Cefixime does not affect the driving ability or operating machinery.

4.8 Undesirable effects

Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and individual.
Their frequency is defined using the following classification: 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). Within each organ system, adverse drug reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
Rare: eosinophilia, granulocytopenia;
Very rare: leukopenia, agranulocytosis, pancytopenia, or thrombocytopenia (these side effects normalize after discontinuation of the treatment), hemolytic anemia, coagulation disorders.

Immune system disorders
Rare: Hypersensitivity reactions in the form of flushing, palpitations, dyspnea, hypotension, bronchospasm, angioedema.
Very rare: Anaphylactic shock, serum sickness.

Nervous system disorders
Uncommon: headache;
Rare: dizziness;
Very rare: temporary hyperactivity.

Gastrointestinal disorders
Common diarrhea, soft stools;
Uncommon: abdominal pain, indigestion nausea and vomiting;
Rare: decreased appetite, flatulence;
Very rare: inflammation of the colon caused by the antibiotic (eg. Pseudomembranous colitis), which can be life threatening.

Hepato-biliary disorders
Uncommon: transient elevations in ALT, AST and alkaline phosphatase and bilirubin;
Very rare: hepatitis and cholestatic jaundice.

Renal and urinary disorders
Rare: transient increase in the values of urea;
Very rare: increase of serum creatinine, interstitial nephritis. High doses of cephalosporins should be given with caution in patients receiving concomitant diuretics (eg. Furosemide) or potentially nephrotoxic drugs (eg. Aminoglycosides), since there is a possibility of deterioration of the renal function (see section 4.5).

Infections and infestations
Rare: use of cefixime on long term may lead to superinfections with resistant bacteria or fungi (genital pruritus, vaginitis / candidiasis).

Skin and subcutaneous tissue disorders
Uncommon: Rash (erythema, exanthema)
Rare: pruritus, inflammation of the mucosa

Very rare: Erythema multiforme, Stevens Johnson syndrome, Lyle syndrome, urticarial
Not known: DRESS syndrome (rash accompanied with eosinophilia and systemic symptoms) - see section 4.4.

General disorders and administration site conditions
Rare: hyperthermia.

4.9 Overdose

There is no experience with cefixime overdose.
Hemodialysis or peritoneal dialysis does not remove significant amounts of cefixime from the circulation.
In case of anaphylactic reaction appropriate measures should be taken when first signs and symptoms appear.
In case of overdose, gastric lavage is indicated.

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 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%. The presence of food does not modify significantly the absorption. Therefore, cefixime can be applied regardless of food intake.

Studies in vitro have shown that serum or urinary levels of 1 mcg / ml or more, are considered effective for most of the pathogens sensitive on cefixime. Usually, the maximum serum values at recommended doses for adults or children are between 1.5 and 3 mcg / mL. Small amount or no accumulation of cefixime occurs after repeated dosing.

After applying the oral suspension, achieved are approximately 25-50% higher concentrations versus the same, after administration of the same doses in tablet form. Use of 200 mg and 400 mg in the form of oral suspension achieves a concentration of 3 mcg / ml (1,0-4,5 mcg / ml) and 4,6 mcg / ml (1,9-7,7 mcg / ml) respectively, when administered to healthy volunteers. What refers to the values of the area under the curve, values obtained after applying the oral suspension are 10-25% higher than after administration of tablets in the same doses. These pharmacokinetic differences must be taken into consideration in a possible substitution of oral suspension with tablets.
Maximal serum concentrations are reached within 2-6 hours.

Distribution
Binding to the serum proteins it is well known in the serum of humans and animals; cefixime is almost exclusively bounded to the albumin fraction, the mean free fraction is approximately 30%. Binding of cefixime to the proteins it is just a concentration dependent in the human serum in a high doses which do not appear in the clinical dosing.

Transfer of ^{14}C-labeled cefixime to rats which are breastfeeding to their infants through the excreted milk in quantitative was small (approximately 1.5% of the amount of the mother of the baby rats) there are no data on secretion of cefixime in human 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 is 3-4 hours, but in some individuals was extended by up to 9 hours. Longevity elimination half-life allows one-day dosing.

Older people
Cefixime pharmacokinetics 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 can receive same doses as the general population.

Patients with renal impairment
In case of moderate impairment of renal function (creatinine clearance of 20-40 ml/min) serum elimination half-life is extended and is, on average, 6.4 hours, while in severe impairment (creatinine clearance from 5 to 20 ml/min) is 11,5 hours.

5.3 Preclinical safety data

The acute toxicity of cefixime is low. In studies with repeated administration determined are dose-dependent changes 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. In rats is not determined any impact on perinatal or postnatal development and fertility.

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 made.

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°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

ALKALOID AD Skopje
Blvd. Aleksandar Makedonski 12,
1000 Skopje, Republic of Macedonia
Tel: + 389 2 31 04 000
Fax: + 389 2 31 04 021
www.alkaloid.com.mk

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT