SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANCEF® 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg cefixime (in a form of cefixime trihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Film-coated tablets.

White to slightly cream, oblong, biconvex, film coated tablets with bisection line on one side of the tablet

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pancef is indicated for the treatment of infections caused by microorganisms susceptible 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

Adults and Children (weighing more than 50 kg or older than 10 years of age).
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.

For the treatment of uncomplicated cervical/urethral gonococcal infection, a single one day oral dose of 400 mg is recommended.
For the treatment of lower urinary infections in women a single dose of 400 mg or 3 day treatment is 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 in cases with severe renal impairment (See "Dosage in patients with renal Impairment").

Dosage in patients with renal impairment
Pancef 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 lower than 20 ml/min.

Duration
Usual duration of the therapy is 7 days. In some cases, treatment may be extended to 14 days, depending on the severity of the infection.
Infections with *Streptococcus Pyogenes* should be treated at least 10 days.

Method of Administration
For oral administration.
Food does not significantly impair the absorption of cefixime.

4.3 Contraindications

Hypersensitivity to the active supstance, to any of the cephalosporins or penicilline 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 medicines 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 undertaken.

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is required with concomitant use of:

- potentially nephrotoxic drugs (aminoglycosides and duretics 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, urticaria;
Not known: DRESS syndrome (rash accompanied with eosinophilia and systemic symptoms) - see section 4.4.

General disorders and administration site conditions
Rare: hyperthermia.

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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.

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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 application of 400 mg, in a form of tablet, concentration of 3,7 mcg/ml (1,3 -7,7 mcg/ml) is achieved. Peak serum concentrations are reached in 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

Tablet core:
Microcrystalline Cellulose;
Starch, pregelatinized;
Calcium hydrogen phosphate dihydrate;
Magnesium stearate.
Film-coating:
Hypromellose 5 cP E464; Macrogol 400; Titanium dioxide E171.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 (three) years.

6.4 Special precautions for storage

The drug should be stored at the temperature below 25°C.

6.5 Nature and contents of container

The film coated tablets are blister-packed in transparent PVC/PVdC/Al foil.Each blister contains 5 tablets or 7 tablets.
Cardboard box contains 1 blister with 5 tablets (5 tablets) or 1 blister with 7 tablets (7 tablets) or 2 blisters with 5 tablets (10 tablets) and a leaflet inside.

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.

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