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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL

PRODUCT SUPRAX 400 mg coated

tablets
SUPRAX 100 mg/5ml granules for oral suspension SUPRAX
400 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE

COMPOSITION SUPRAX 400 mg coated tablets
One 400 mg coated tablet contains:
Active ingredient: 400 mg cefixime

SUPRAX 100 mg/5ml granules for oral suspension
One bottle of 2% granules for 100 ml oral suspension contains: Active ingredient: 2 mg cefixime

SUPRAX 400 mg dispersible tablets
Each 400 mg dispersible tablet contains:
Active ingredient: 400 mg cefixime
For the complete list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
Granules for oral suspension
Dispersible tablets: The score line in Suprax dispersible tablets is there only to facilitate breaking for ease of dispersal and not to divide the tablet into two equal doses.

4. CLINICAL INFORMATION

4.1. Therapeutic Indications

SUPRAX is indicated for the treatment of infections caused by microorganisms susceptible to cefixime and in particular:
- upper respiratory tract infections (pharyngitis, tonsillitis);
- otorhinolaryngological infections (otitis media, etc.);
- lower respiratory tract infections (pneumonia, bronchitis);
- kidney and urinary tract infections.

4.2. Posology and method of administration

Posology

Adults
In adults, the recommended dosage is a single daily dose (one tablet per day of SUPRAX 400

mg coated tablets or SUPRAX 400 mg dispersible tablets). The SUPRAX 400 mg coated tablet must be swallowed whole.

Add the SUPRAX 400 mg dispersible tablet to a glass of water and mix well until completely dissolved. Then drink it immediately. The score line in Suprax dispersible tablets is there only to facilitate breaking for ease of dispersal and not to divide the tablet into two equal doses.

Paediatric population
In children, the recommended dose of cefixime in 2% suspension is 8 mg/kg/day administered as a single dose, or rather based on the child's weight (see diagram below):

WEIGHT (KG)	DAILY DOSE (MG)	DAILY DOSE (ML)
10	80	4
12.5	100	5
15	120	6
17.5	140	7
20	160	8
22.5	180	9
25	200	10
27.5	220	11
30	240	12

Method of administration
SUPRAX can either be taken optionally with meals or between meals.
According to data from clinical trials, 7 days of treatment with SUPRAX may be sufficient to treat most infections. However, in more serious cases, SUPRAX can also be used for 14 days.
A calibrated measuring cup and syringe are attached to the SUPRAX 100 mg/5ml granules pack to permit the precise dosage of the drug in both older and younger children.

Specific dosing schedules
In patients with creatinine clearance values <20 ml/min, in ambulatory peritoneal dialysis or haemodialysis, the recommended maximum dose is 200 mg once a day. In general, no specific dosing schedules are required in patients with creatinine clearance >20 ml/min, in the elderly and in patients with liver failure.
For instructions on opening the bottle and preparing the suspension see section 6.6

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
The medicinal product is moreover contraindicated in patients who are hypersensitive to penicillins and cephalosporins (see section 4.4).

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions
Serious cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug-induced skin rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients treated with cefixime. When severe cutaneous

adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or precautionary measures should be taken.

Hypersensitivity

Before initiating treatment with SUPRAX, an accurate medical history needs to be obtained to highlight any previous reactions evidencing hypersensitivity to cephalosporins, penicillins or other drugs.

SUPRAX should be used with caution in patients allergic to penicillins. There is some clinical (studies on humans) and laboratory evidence of partial cross-allergenicity between penicillin and cephalosporins and, although rare, cases of patients presenting anaphylactic reactions have been reported, especially after parenteral administration.

Antibiotics should be administered with caution to all patients who have previously shown allergic symptoms, especially to drugs. If any allergic reaction occurs, the treatment should be discontinued.

Alterations in intestinal bacterial flora

Prolonged use of antibiotics may lead to the growth of non-susceptible microorganisms and in particular to an alteration in the normal flora of the colon, with clostridia responsible for pseudomembranous colitis possibly being singled out. Mild cases of pseudomembranous colitis may regress with discontinuation of the treatment. If the colitis does not regress following the adoption of these measures, vancomycin per os, the antibiotic of choice for pseudomembranous colitis, should be administered.

In moderate or severe forms of the disease, treatment will be supplemented by the administration of electrolytic solutions and proteins.

The simultaneous use of drugs that reduce peristalsis must be completely avoided.

Broad-spectrum antibiotics should be administered with caution in patients with a history of gastrointestinal diseases, particularly colitis.

Laboratory tests

The use of SUPRAX has occasionally led to the detection of some albeit slight and reversible variations in parameters linked to liver, kidney and blood crasis functionality (thrombocytopenia, leukopenia, and eosinophilia).

Acute renal failure

As with other cephalosporins, cefixime can cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. If acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Renal impairment

In patients with severe renal failure, or on haemodialysis or peritoneal dialysis, the dose of SUPRAX should be reduced accordingly (see section 4.2).

Convulsions in renally impaired patients

Many cephalosporins have been involved in the development of convulsions, particularly in renally impaired patients, when the dose has not been reduced. Whenever convulsions occur, the administration of cefixime must be discontinued and appropriate treatment and/or measures should be taken.

Antimicrobial resistance

Treatment with cefixime may increase the risk of developing bacterial resistance with or without obvious clinical superinfection.

Superinfection:
Just like other antibiotics, prolonged use may occasionally result in the overgrowth of non-susceptible organisms. If superinfection occurs, appropriate therapy should be initiated.

Anaemia
Cases of haemolytic anaemia, including severe cases with a fatal outcome, have been described following treatment with drugs belonging to the class of cephalosporins. Recurrent episodes of haemolytic anaemia after the re-administration of cephalosporins in patients who had previously developed haemolytic anaemia following an initial administration of cephalosporins (including cefixime) have also been reported.

Paediatric population
The safety of cefixime in children weighing less than 10 kg has not been established.

Suprax 400 mg dispersible tablets contain azo dyes (E110), which may cause allergic reactions.

4.5 Interactions with other medicinal products and other forms of interaction

Coumarin anticoagulants
Cefixime should be administered with caution in patients treated with coumarin anticoagulants, e.g. warfarin. Since cefixime may enhance the effects of anticoagulants, there may be an increase in prothrombin time with or without bleeding.

Other forms of interaction
The administration of cephalosporins, such as cefixime, can interfere with the results of some laboratory tests, causing a false positive reaction for glucose in the urine with the Benedict, Fehling and "Clinitest" methods (but not with enzymatic methods). We recommend the use of glucose tests based on enzymatic glucose oxidase reactions. A (sometimes false) positive reaction from the Coombs test has been reported during treatment with cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy
In pregnant and breastfeeding women, the product should be administered where really necessary, under direct medical supervision, .
In particular, and although there is no evidence of embryotoxicity, the administration of SUPRAX should be avoided, as a precaution, during the first three months of pregnancy.

Breastfeeding
There are no data on the drug passing into breast milk.

4.7 Effects on the ability to drive and use machinery

The medicinal product does not affect the ability to drive vehicles or use machinery.

4.8 Undesirable effects

With cephalosporins, undesirable effects are essentially limited to gastrointestinal disorders and, occasionally, symptoms of hypersensitivity.
The likelihood of the latter is greater in individuals who have previously had hypersensitivity reactions and those with a history of allergies, hay fever, urticaria and allergic asthma.
The following reactions have been reported rarely during cefixime therapy:

- *Infections and infestations:* pathogen resistance, pseudomembranous colitis.
- *Blood and lymphatic system disorders*: transient neutropenia, granulocytopenia, thrombocytopenia and eosinophilia. Cases of haemolytic anaemia have been reported following treatment with cephalosporins.
- *Immune system disorders:* to serum sickness-like reactions, anaphylaxis, arthralgia and drug fever.
- *Nervous system disorders:* headache, dizziness.
- *Respiratory, thoracic and mediastinal disorders:* dyspnoea
- *Gastrointestinal disorders:* glossitis, nausea, vomiting, gastric heartburn, abdominal pain, diarrhoea and dyspepsia. Switching to daily administration (200 mg twice a day) may remedy the problem of diarrhoea. Experiencing severe and prolonged diarrhoea has been linked to the use of different classes of antibiotics If the diagnosis is confirmed by a colonoscopy, the antibiotic in use should be discontinued immediately and treatment with vancomycin per os should be initiated. Peristalsis inhibitors are contraindicated.
- *Hepatobiliary disorders:* jaundice.
- *Skin and subcutaneous tissue disorders:* urticaria, skin rash, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-induced rash with eosinophilia and systemic symptoms (DRESS).
- *Renal and urinary disorders:* acute renal failure including tubulointerstitial nephritis as an underlying pathological condition.
- *General disorders and administrative site conditions:* fever, face oedema.
- *Diagnostic tests:* transient increase in serum transaminases (ALT, AST), alkaline phosphatase and total bilirubin levels, transient increase in urea nitrogen and serum creatinine concentrations.

Other reactions reported included: anorexia, Candida's vaginitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important, as it allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction via the national reporting system at the following address: http://www.agenziafarmaco.gov.it/content/comesegnalare-una-sospetta-reazione-avversa.

4.9 Overdose

No specific antidote exists. General supportive measures are recommended. Cefixime is not removed from the circulation in significant quantities by dialysis.
In healthy volunteers, at up to 2 grams per day, the drug presented the same tolerability profile as that observed in patients treated at the recommended doses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterial for systemic use, belonging to the class of cephalosporins. ATC code: J01DD08

Mechanism of action:
SUPRAX is a new oral cephalosporin marked by a broad-spectrum bactericidal activity and high resistance to the hydrolytic activity of beta-lactamases.
The bactericidal activity of cefixime is due to its inhibition of bacterial cell wall synthesis. It is active in vitro against a wide range of clinically significant Gram- positive and Gram-negative pathogens. Cefixime is particularly active against the following types: Streptococcus (excluding enterococci), Haemophilus, Branhamella, Neisseria, Escherichia, Klebsiella, Proteus, Enterobacter, Pasteurella, Providencia, Salmonella, Shigella, Citrobacter, Serratia. The following are on the other hand mostly resistant to cefixime: Pseudomonas sp., Staphilococcus sp., Listeria monocytogenes, Bacteroides fragilis and Clostridium sp.

5.2 Pharmacokinetic properties

Following a single oral administration of 200 mg the maximum serum concentration of cefixime is 3 μg/ml and this level is obtained within 3 or 4 hours.
Following a single oral administration of 400 mg the maximum serum concentration is higher (3.5 to 4 μg/ml), although there is no direct proportionality with the dose taken.
Following repeated administration of 400 mg/day per os (one or two doses per day) for 15 days, serum levels and bioavailability are not changed, which is evidence of the fact that there is no accumulation of the drug in the body.
Following administration of 8 mg/kg of cefixime suspension in paediatric patients, serum concentrations similar to those achieved in adults following a dose of 400 mg are obtained. The absolute bioavailability of cefixime is about 50% and is not modified by the presence of food. In this case, the time needed to reach peak concentration is delayed by about 1 hour.
The apparent volume of distribution is 17 litres.
In animals, the distribution of cefixime in most tissues (excluding the brain) results in higher tissue concentrations than the M.I.C. of sensitive strains (0.20 μg/ml).
The elimination kinetics of cefixime is marked by a half-life of between 3 and 4 hours.
The drug is excreted unchanged (16 to 25%) renally. Extra-renal elimination is mainly biliary. No serum or urinary metabolites have been detected in humans or animals.
Pharmacokinetic parameters are slightly modified in the elderly population. The slight increase in serum concentrations, bioavailability and quantity of the drug excreted (15 to 25%) do not necessitate changes to the daily dose in this particular population.
In cases of severe renal failure (creatinine clearance <20 ml/min), the increased plasma elimination, half-life and peak serum concentrations render necessary a reduction in the dose from 400 to 200 mg/day.
In case of liver failure, elimination is slowed down ($t_{½}$ = 6.4 h), but it is not necessary to change the daily dose.

Protein binding is about 70%, mainly to albumin and independent of concentration (at clinical dose levels).

5.3 Preclinical safety data

Following oral administration the LD_{50} values were above 10 g/kg in mice, rats and rabbits. Following administration ev, ip, sc, the LD_{50} values were higher than 3, 7 and 10 g/kg in mice and 5, 8, 10 g/kg in rats respectively.
Cefixime has been shown to have no teratogenic effects and did not affect fertility in the animals tested.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

SUPRAX 400 mg coated tablets
One coated tablet contains:
microcrystalline cellulose, pregelatinised starch, dibasic calcium phosphate dihydrate, magnesium stearate.
Coating: hydroxypropyl methylcellulose, sodium lauryl sulphate, titanium dioxide (E171), liquid paraffin.

SUPRAX 100 mg/5ml granules for oral suspension
One bottle of 2% granules for 100 ml oral suspension contains: sucrose,
xanthan gum, sodium benzoate, strawberry flavouring.

SUPRAX 400 mg dispersible tablets
One divisible tablet contains:
microcrystalline cellulose, hydroxypropyl cellulose, anhydrous colloidal silica, povidone, strawberry aroma FA 15757, strawberry flavouring PV 4284, magnesium stearate, calcium saccharin, orange-yellow dye (E110)

6.2 Incompatibilities

None.

6.3 Shelf life

SUPRAX 400 mg coated tablets
Unopened, 36 months
SUPRAX 100 mg/5ml granules for oral suspension
Unopened, 24 months *SUPRAX 400 mg dispersible tablets* unopened, 24 months.

6.4 Special precautions for storage

SUPRAX 100 mg/5ml granules for oral suspension:
Do not store at a temperature above 30°C.
After reconstitution, the suspension must not be stored at a temperature above 25°C. The suspension, once reconstituted, must be used within 14 days.

Do not store in the refrigerator.

SUPRAX 400 mg coated tablets:
Do not store at a temperature above 30°C.

SUPRAX 400 mg dispersible tablets:
Do not store at a temperature above 30°C.

6.5 Nature and content of the container

SUPRAX 400 mg coated tablets;
Five 400 mg tablets in PVDC-PVC aluminium foil blister packs;

SUPRAX 100 mg/5ml granules for oral suspension
100 ml (100 mg/5 ml) in an amber glass bottle + Measuring cup + dosing syringe.

SUPRAX 400 mg dispersible tablets:
7 divisible 400 mg tablets in aluminium-PVDC-PVC blisters;

SUPRAX 400 mg dispersible tablets:
5 divisible 400 mg tablets in PVDC-PVC aluminium foil blisters;

6.6 Special precautions for disposal

Bottle opening instructions
The bottle is equipped with a "child-proof" safety cap. To open the bottle, press the cap firmly and simultaneously turn counterclockwise.

Instructions for the preparation of the suspension

Add water to the granules contained in the bottle up to the point indicated by the arrow.
After adding water, shake well until the powder is completely dispersed.
Wait a few minutes; if the level of suspension is lower than that indicated by the arrow, add more water to bring the level back up to the level indicated by the arrow.
Shake again energetically.
When the suspension is prepared in this way, it can be kept for up to 14 days, during which time it is still usable.
Shake well before use.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma S.p.A.
Via del Bosco Rinnovato, 6 – U7
20090 Assago (Milan)

8. MARKETING AUTHORISATON NUMBER(S)

027127036 - SUPRAX 400 mg coated tablets - 5 Tablets 027127101 -
SUPRAX 100 mg/5ml granules for oral suspension

027127087 - SUPRAX 400 mg dispersible tablets - 5 Tablets 027127075 - SUPRAX 400 mg dispersible tablets - 7 Tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTORISATION First authorisation:

SUPRAX 400 mg coated tablets: 28/03/92.
SUPRAX 100 mg/5 ml granules for oral suspension: 19/6/00. SUPRAX 400 mg dispersible tablets: 5 and 7 tablets: 25/10/01.

Renewal of authorisation: June 2010

10. TEXT REVISION DATE