CEFPAN DT – 100 / CEFPANORAL SUSPENSION

Cefixime Dispersible Tablets 100 mg / Cefixime Oral Suspension IP

QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFPAN DT - 100

Each dispersible uncoated tablet contains:
Cefixime IP (as trihydrate) equivalent to anhydrous Cefixime 100 mg
Colour: Lake Sunset Yellow.

CEFPAN ORAL SUSPENSION

Each 5 ml of the reconstituted suspension contains:
Cefixime IP (as trihydrate) equivalent to anhydrous Cefixime 50 mg
Colour: Sunset Yellow FCF.

PHARMACEUTICAL FORM

Dispersible Tablets;

Dry powder for reconstitution in water, at the time of dispensing, to form an oral suspension.

CLINICAL PARTICULARS

Therapeutic Indications

For the treatment of:
• Urinary Tract Infections
• Respiratory Tract Infections
• Biliary Tract Infections

For the treatment of the listed indications due to micro-organisms sensitive to cefixime including pathogens such as Streptococci pneumoniae and pyogenes, E.coli, Proteus, H. influenzae and B. catarrhalis (both beta-lactamase positive and negative), Klebsiella and Enterobacter species.

Most Enterococci, staphylococci, Pseudomonas, Clostridia, Bacteroides fragilis and Listeria monocyctogenes are resistant to cefixime.
Posology and Method of Administration

For oral use.

Adults

- The usual daily dose is 200-400 mg in single or twice daily dosage regimen.
- In uncomplicated upper respiratory tract infections or urinary tract infections a daily dose of 200 mg may be sufficient

Children

An appropriate formulation must be used to ensure proper dosage. The usual dosage is provided in Table 1:

Table 1: Usual dosage of cefixime in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants less than 6 months of age</td>
<td>The safety and efficacy of use in infants less than 6 months of age has not been established.</td>
</tr>
<tr>
<td>Children aged 6 months to 2 years</td>
<td>The usual total daily dose is 8 mg/kg in single or twice daily regimen.</td>
</tr>
<tr>
<td>Children aged 2 to 4 years</td>
<td>The usual total daily dose is 100 mg in single or twice daily dosage regimen.</td>
</tr>
<tr>
<td>Children aged 5 to 8 years</td>
<td>The usual total daily dose is 200 mg in single or twice daily dosage regimen.</td>
</tr>
<tr>
<td>Children aged 9 to 12 years</td>
<td>The usual total daily dose is 300 mg in a single or twice daily regimen.</td>
</tr>
<tr>
<td>Children aged 12 years and over (or more than 50 kg body weight)</td>
<td>Posology in children over 12 years (or more than 50 kg body weight) is the same as for adults.</td>
</tr>
</tbody>
</table>

Elderly

The usual dosage is as per the adult dosage with appropriate modifications on the basis of renal impairment (see Section Posology and Method of Administration).

Renal Impairment

Dosage does not require modification in patients with a creatinine clearance of 20 ml/minute or greater.

In patients with a creatinine clearance less than 20 ml/minute a dose of 200 mg once daily should not be exceeded. The same dosage regimen is applied to those patients maintained on
chronic ambulatory peritoneal dialysis or haemodialysis (see Section Special Warnings and Special Precautions for Use).

**Hepatic Impairment**

There are no relevant data available.

**Contraindications**

Cefixime is contraindicated in:

- patients hypersensitive to cephalosporins or to any of the excipients of this medicinal product.

**Special Warnings and Special Precautions for Use**

*Microbiological overgrowth and colitis*

Prolonged use of an anti-infective may result in overgrowth of non susceptible organisms. With an oral medication the normal colonic flora may be altered allowing the overgrowth by clostridia with consequent pseudomembranous colitis.

*Severe cutaneous adverse reactions*

Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

*Antibiotic resistance*

Emergence of resistance to cefixime has not been shown to be clinically significant to date. Nevertheless it is recommended that newer antibiotics such as cefixime should usually be reserved for infections which are recurrent or resistant to other agents.

*Patients with gastrointestinal disturbances*

Particular care should be exercised in patients with severe gastrointestinal disturbances involving vomiting and diarrhoea. The product should be discontinued if severe diarrhoea develops.

*Acute renal failure*

As with other cephalosporins, cefixime may cause acute renal failure including tubulo-interstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.
Patients with renal impairment
The product should be used with caution in patients with renal functional impairment. Renal function should be monitored with particular care when combining cefixime with aminoglycoside antibiotic, polymyxin B, colistin or high-dosed loop diuretics (e.g. furosemide). This applies especially to patients with pre-existing renal impairment (see Section Posology and Method of Administration).

Cephalosporins/penicillins cross-allergy
Cross allergenicity may exist between cephalosporins and penicillins. Use of the product should be cautious in patients allergic to penicillins.

Patients predisposed to allergic reactions
Particular care should be exercised in patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria.

Malnutrition
Particular care should be exercised in patients with poor oral nutrition, patients receiving parenteral nutrition, elderly patients or patients in a debilitated state.

Elderly patients
Adverse reactions to drugs are liable to occur more frequently in the elderly patients since they usually have physiological hypofunction. Bleeding tendency due to Vitamin K deficiency may occur in the elderly.

Premature or newborn infants
The safety of cefixime in premature or newborn infant has not been established.

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.

Typhoid vaccine
Cefixime, like other antibiotics with antibacterial activity against Salmonella typhi organisms, may interfere with the immunological response to the live typhoid vaccine. The appropriate period of time should elapse between the administration of the last dose of the antibiotic and the live typhoid vaccine.

Excipients
Sunset Yellow
Contains Sunset Yellow which may cause allergic-type reactions.
Aspartame
Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

Interaction with Other Medicaments and Other Forms of Interaction

Alternations in laboratory test results
The administration of cefixime may result in false-positive results for glucose in the urine using Benedict's solution, Fehling's solution, or Clinitest. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (e.g. Tes-Tape) be used.

A false positive direct Coomb's test may occur with cefixime.

Anticoagulants of the coumarin-type
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.

Pregnancy and Lactation

Fertility
There are no relevant data available.

Pregnancy
The product should only be used during pregnancy if considered essential by the physician. Safety of cefixime in pregnant women has not been established.

Lactation
The product should only be used during lactation if considered essential by the physician. It is not known whether cefixime is excreted in human milk.

Effects on Ability to Drive and Use Machines
There are no relevant data available.

Undesirable Effects

Clinical Trial and Post Marketing Data
Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as:

- Very common $\geq 1/10$
- Common $\geq 1/100$ to $<1/10$
- Uncommon $\geq 1/1000$ to $<1/100$
- Rare $\geq 1/10000$ to $<1/1000$
- Very rare $<1/10000$
- Not known (cannot be estimated from the available data).

**Infections and infestations**
*Not known:* pseudomembranous colitis, vaginitis

**Blood and lymphatic system disorders**
*Not known:* eosinophilia, granulocytopenia, haemolytic anaemia, thrombocytopenia, prolongation in prothrombin time and blood coagulation disturbances

**Immune system disorders**
*Not known:* anaphylactic reaction, serum sickness-like reaction

**Metabolism and nutrition disorders**
*Not known:* anorexia

**Nervous system disorders**
*Not known:* headache, dizziness, convulsions

**Respiratory, thoracic and mediastinal disorders**
Not known: dyspnoea

**Gastrointestinal disorders**
*Not known:* diarrhoea, abdominal pain, vomiting, nausea, dyspepsia, flatulence

**Hepatobiliary disorders**
*Not known:* hepatitis, jaundice, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased.

**Skin and subcutaneous tissue disorders**
*Not known:* drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pruritus, rash, urticaria

**Renal and urinary disorders**
*Not known:* blood urea increased, blood creatinine increased, renal failure acute including tubulointerstitial nephritis as an underlying pathological condition
Reproductive system and breast disorders
Not known: pruritus genital

General disorders and administration site conditions
Not known: pyrexia, face oedema

Overdose

No specific antidote exists. General supportive measures are recommended.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Third-generation cephalosporins; ATC Code: J01DD08.

Mechanism of Action and Pharmacodynamic Effects

Cefixime inhibits the cell wall synthesis of various bacteria. Cefixime has high affinity for penicillin binding proteins (PBP) 1 (1a, 1b and 1c) and 3 and prevents cross-linking reaction. Cefixime has broad spectrum activity against Gram-positive and Gram-negative bacteria. Sensitivity will vary according to area, and local prescribing guidelines should always be consulted. Where possible microbiological sensitivity tests should guide treatment as resistance can emerge. Its mechanism of action is bactericidal.

Pharmacokinetic Properties

Absorption

Following oral administration of cefixime to healthy volunteers, peak serum concentrations are generally attained in 3 to 4 hours. After a single oral dose of 50, 100 and 200 mg mean peak serum concentrations were 1.02, 1.46 and 2.63 mg/L respectively in 12 healthy volunteers of Western origin and 0.69, 1.13 and 1.95 mg/L respectively in 12 healthy Japanese volunteers.

Paediatric Populations
Following a single oral dose of 1.5, 3.0 and 6.0 mg/kg of cefixime in Japanese paediatric patients, maximum serum concentrations at around 3 to 4 hours were 1.14, 2.01 and 3.97 mg/L, respectively.
**Distribution**

In human plasma, cefixime is approximately 70% protein bound, a value not concentration dependent in the range 0.5 to 30mg/L. Cefixime is distributed to target organs/tissues such as tonsils, maxillary sinus mucosal tissue, lung tissue and gallbladder tissue.

**Metabolism**

No biologically active metabolites of cefixime were identified in plasma or urine following oral administration to healthy volunteers.

**Elimination**

Around 20% of a 200 mg dose of cefixime is recovered unchanged over 24 hours in the urine of healthy volunteers. The elimination half-life is 2-4 hours.

**Renal Impairment**

Studies in patients with various degrees of renal dysfunction administered single 400mg oral doses of cefixime indicated that elimination half-life, oral clearance (CL/F), renal clearance and AUC were altered in patients with severe renal dysfunction (creatinine clearance < 20 mL/min) and in those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as compared with healthy subjects (see Section Special Warnings and Special Precautions for Use).

<table>
<thead>
<tr>
<th>Pharmacokinetic properties (mean values) of cefixime in healthy volunteers and patients with various degrees of renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study group</strong></td>
</tr>
<tr>
<td>Healthy Volunteers</td>
</tr>
<tr>
<td><strong>Renal dysfunction</strong></td>
</tr>
<tr>
<td>Very mild</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>CAPD</td>
</tr>
</tbody>
</table>

Difference statistically significant compared with healthy volunteers

Abbreviations: CLcr = creatinine clearance, T1/2_β = elimination half life, CL/F = oral clearance, CAPD = continuous ambulatory peritoneal dialysis
Clinical Studies

Not relevant for this product.

Preclinical Safety Data

There are no relevant data available.

PHARMACEUTICAL PARTICULARS

List of Excipients

*CEFSPAN DT - 100*

Microcrystalline Cellulose, Hydroxy Propyl Cellulose, Dibasic Calcium Phosphate Anhydrous, Aspartame, Powdarome Orange 4153, Colloidal Silicon Dioxide, Crospovidone, Starch, Magnesium Stearate, Lake Sunset Yellow.

*CEFSPAN ORAL SUSPENSION*

Sucrose, Microcrystalline Cellulose and Sodium Carboxymethylcellulose, Sodium Benzoate, Sunset Yellow FCF, Powdarome Orange 4153, Colloidal Silicon Dioxide, Aspartame, Saccharin Sodium.

Incompatibilities

There are no relevant data available.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Keep out of reach of children.

*CEFSPAN DT - 100*

Store below 25°C. Protect from light and moisture.

*CEFSPAN ORAL SUSPENSION*
Dry Powder: Store below 25°C in a dry place. Protect from light.

Reconstituted Suspension: Store reconstituted suspension in a refrigerator and use within 7 days.

Nature and Specification of Container

CEFSPAN DT - 100

Strips of 10 tablets each, packed in a carton.

CEFSPAN ORAL SUSPENSION

Bottle with measuring cup in a carton.

All presentations may not be marketed in the country.

Instructions for Use / Handling

CEFSPAN DT - 100

Disperse the tablet in a spoonful (5 mL) of boiled and cooled water before administration.

CEFSPAN ORAL SUSPENSION

Direction for reconstitution: Shake the bottle well to loosen the powder. Tilt slightly and slowly add boiled and cooled water upto the mark on the bottle. Shake the bottle well to mix the medicine properly. Add more water if necessary to adjust the volume upto the mark.

For further information please contact:
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