SUMMARY OF PRODUCT CHARACTHERICTICS

1. NAME OF THE MEDICINAL PRODUCT

Spectracef ® 200 mg film-coated tablets

Spectracef ® 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spectracef 200 mg film-coated tablets
Each film-coated tablet contains 200 mg of cefditoren equivalent to 245.1 mg of cefditoren pivoxil.

Spectracef 400 mg film-coated tablets
Each film-coated tablet contains 400 mg of cefditoren equivalent to 490.2 mg of cefditoren pivoxil.
Excipient with known effect: 26.2 mg sodium per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Elliptical white tablet printed on one side with the “TMF” logo in blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spectracef is indicated in adults and adolescents (12 years of age or older) for the treatment of the following infections caused by susceptible microorganisms: (see section 5.1 Pharmacodynamic Properties):

- Acute pharyngo-tonsillitis
- Acute maxillary sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia, mild to moderate
- Uncomplicated skin and skin structure infections, such as cellulitis, infected wounds, abscesses, folliculitis, impetigo and boils.

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

4.2 Posology and method of administration

The recommended dosage depends on the severity of the infection, the basal condition of the patient and the potential micro-organisms involved.

Posology

Adults and adolescents (over 12 years)

- Acute pharyngo-tonsillitis: 200 mg cefditoren every 12 hours for 10 days.

- Acute maxillary sinusitis: 200 mg cefditoren every 12 hours for 10 days.
- Acute exacerbations of chronic bronchitis: 200 mg cefditoren every 12 hours for 5 days.
- Community-acquired pneumonia:
  - In mild cases: 200 mg cefditoren every 12 hours for 14 days.
  - In moderate cases: 400 mg cefditoren every 12 hours for 14 days.
- Uncomplicated skin and skin structure infections: 200 mg cefditoren every 12 hours for 10 days.

Elderly
No dose adjustments are necessary for elderly patients, except in the case of severe renal and/or hepatic function impairment.

Renal insufficiency

No dose adjustment is necessary for patients with mild renal impairment. In patients with moderate renal insufficiency (creatinine clearance 30-50 ml/min), the total daily dose should not exceed 200 mg cefditoren every 12 hours. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), it is recommended a single dose of 200 mg cefditoren once a day. The recommended dose has not been determined in patients undergoing dialysis (see sections 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties).

Hepatic insufficiency

No dose adjustments are necessary for patients with mild hepatic insufficiency (Child-Pugh A) to moderate hepatic insufficiency (Child-Pugh B). In the case of severe insufficiency (Child-Pugh C), there are no data available that would allow a recommended dose to be established (see section 5.2 Pharmacokinetic Properties).

Paediatric population
Spectracef is not indicated for children and adolescents under 12 years old.

Method of administration

Tablets should be swallowed whole with a sufficient quantity of water. Tablets should be taken with meals.

4.3 Contraindications

- Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients listed in section 6.1. For patients who are hypersensitive to casein, it should be noted that the medicinal product contains sodium caseinate.
- Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam active substance.
- As with other pivalate-producing compounds, cefditoren pivoxil is contraindicated in cases of primary carnitine deficiency.

4.4 Special warnings and precautions for use

Before therapy with cefditoren is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to cefditoren, cephalosporins, penicillins, or other beta-lactam active substances.

Cefditoren should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam active substance.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of cefditoren. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Cefditoren should be discontinued if severe, and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Cefditoren should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

In patients with moderate to severe renal impairment the rate and extent of exposure to cefditoren is increased (see section 5.2). For this reason, the total daily dosage should be reduced when cefditoren is administered to patients with acute or chronic moderate to severe renal insufficiency in order to avoid potential clinical consequences, such as seizures (see section 4.2).

Cephalosporin antibiotics should be given with caution to patients receiving concurrent treatment with nephrotoxic active substances such as aminoglycoside antibiotics or potent diuretics (such as furosemide) as these combinations may have undesirable effects on renal function and have been associated with ototoxicity.

Prolonged use of cefditoren may result in the overgrowth of non-susceptible organisms, such as *enterococci* and *Candida* spp.

During treatment with cephalosporins, a decrease in prothrombin activity may occur. Therefore, the prothrombin time should be monitored in patients at risk, such as patients with renal or hepatic insufficiency or patients being treated with anticoagulant therapy.

Administration of pivalate prodrugs has been associated with decreases in plasma carnitine concentrations. However, clinical studies concluded that no clinical effects of carnitine decrease were associated with the administration of cefditoren pivoxil.

Spectracef 200 mg film-coated tablets contain less than 23 mg sodium (1 mmol) per tablet, that is to say, essentially “sodium-free”.

Spectracef 400 mg film coated tablets contains 1.14 mmol (about 26.2 mg) sodium per dose**.** This must be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

Co-administration of antacids containing magnesium and aluminium hydroxide and cefditoren pivoxil together with food produced a decrease in C_{max} and AUC cefditoren of 14% and 11%, respectively. It is recommended that a period of 2 hours should lapse between the administration of antacids and cefditoren pivoxil.

H2-receptor antagonists

Concomitant administration of intravenous famotidine and oral cefditoren pivoxil produced a decrease in C_{max} and AUC cefditoren of 27% and 22%, respectively. Therefore, the concomitant use of cefditoren pivoxil with H_2-receptor antagonists is not recommended.

Probenecid

Co-administration of probenecid with cefditoren pivoxil reduces the renal excretion of cefditoren, resulting in a 49% increase in C_{max}, a 122% increase in AUC, and a 53% increase in the elimination half-life.

Oral contraceptives

Administration of cefditoren pivoxil did not alter the pharmacokinetic properties of the oral contraceptive ethinyl estradiol. Cefditoren pivoxil may be taken concomitantly with combination oral contraceptives containing ethinyl estradiol.

Medicinal Products/Laboratory Test Interactions

- Cephalosporins can induce a false positive in the direct Coombs' test, which may interfere with cross matching of blood.
- False positive results for glucose in urine may occur with copper reduction tests but not with enzyme-based tests.
- As a false-negative result may occur in the ferricyanide test for glucose determination in plasma or blood, it is recommended that either the glucose oxidase or hexokinase methods be used to determine blood/plasma glucose levels in patients receiving cefditoren pivoxil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). There are no adequate data from the use of cefditoren pivoxil in pregnant women.

Breastfeeding

There is insufficient evidence available on whether cefditoren is present in human milk. Therefore, the administration of Spectracef is not recommended during lactation.

4.7 Effects on ability to drive and use machines

Spectracef has minor or moderate influence on the ability to drive and use machines. Cefditoren pivoxil may cause dizziness and somnolence (see section 4.8).

4.8 Undesirable effects

Approximately 6000 patients received cefditoren at either 200 mg or 400 mg twice daily for up to 14 days in clinical trials. About 24% of patients reported at least one adverse reaction. Treatment discontinuation as a consequence of adverse reactions occurred in 2.6% of the patients.

The most commonly occurring adverse reactions were gastrointestinal events. In most studies, diarrhoea occurred in more than 10% of all patients and was more common with 400 mg than with 200 mg twice daily. The observed adverse reactions, reported either during clinical trials or post-marketing experience, are described below:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Very common Adverse Reactions (≥1/10)	Common Adverse Reactions (≥1/100, <1/10)	Uncommon Adverse Reactions (≥1/1,000, <1/100)	Rare Adverse Reactions (≥1/10,000, <1/1,000)	Not known (cannot be estimated from the available data)
Investigations			Leukopenia, increased ALT	Prolonged coagulation time, increased AST, increased alkaline phosphatase, albuminuria, thromboplastin time decrease, increased LDH, and increased creatinine	Serum carnitine decreased
Cardiac disorders				Atrial fibrillation, heart failure, syncope, tachycardia, ventricular extrasystole	
Blood and the lymphatic system disorders			Thrombocytosis, leukopenia	Eosinophilia, neutropenia trombocytopenia, haemolytic anaemia, lymphadenopathy	Agranulocytosis
Nervous system disorders		Headache	Nervousness, dizziness, insomnia, somnolence, sleep disorders	Amnesia, discoordination, hypertonia, meningitis, tremor	
Eye disorders				Amblyopia, eye disorder, eye pain, blepharitis	
Ear and labyrinth disorders				Tinnitus	
Respiratory, thoracic and mediastinal disorders			Pharyngitis, rhinitis, sinusitis	Asthma	Eosinophilic pneumonia, interstitial pneumonia
Gastrointestinal disorders	Diarrhoea	Nausea, abdominal pain, dyspepsia	Constipation, flatulence, vomiting, oral candidiasis, eructation, dry mouth, dysgeusia	Stomatitis, mouth ulcers, haemorrhagic colitis, ulcerative colitis, gastrointestinal haemorrhage, glossitis, hiccup, discoloured tongue	
Renal and urinary disorders				Dysuria, pain in the renal cavity, nephritis, nycturia, polyuria, incontinence, albuminuria	Acute renal failure
Skin and subcutaneous tissue disorders			Rash, pruritus, urticaria	Acne, alopecia, eczema, exfoliative dermatitis, herpes simplex, photosensitivity reaction	Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrolysis
Musculoskeletal, connective tissue disorders				Myalgia	

System Organ Class	Very common Adverse Reactions (≥1/10)	Common Adverse Reactions (≥1/100, <1/10)	Uncommon Adverse Reactions (≥1/1,000, <1/100)	Rare Adverse Reactions (≥1/10,000, <1/1,000)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			Anorexia	Dehydration, hyperglycemia, hypokalemia, hypoproteinemia	
Infections and infestations		Vaginal candidiasis	Fungal infection	Urinary tract infection, *Clostridium difficile* diarrhoea	
Vascular disorders				Postural hypotension	
General disorders and administration site conditions			Fever, asthenia, pain, sweating	Body odour, chills	
Immune system disorders					Anaphylactic shock, serum sickness disease
Hepato-biliary disorders			Hepatic function abnormal	Bilirubinemia	Liver injury, Hepatitis
Reproductive systems and breast disorders			Vaginitis, leukorrhea	Mastalgia, menstrual disorders, metrorrhagia, erectile dysfunction	
Psychiatric disorders				Dementia, depersonalisation, emotional weakness, euphoria, hallucinations, thinking disorders, increased libido	

The following adverse reactions could appear since they have been observed with other cephalosporins: cholestasis and aplastic anaemia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

No case of overdose has been reported.
Symptoms of overdose reported for other cephalosporin antibiotics are cerebral irritancy leading to convulsions. In case of overdose, gastric lavage should be performed. The patient should be closely monitored and given the proper symptomatic and support treatment.
Cefditoren pivoxil can be partially eliminated through haemodyalisis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporins, ATC code: J01DD16.

Mechanism of action
Cefditoren exerts its antibacterial action by inhibiting bacterial cell wall synthesis due to its affinity for penicillin-binding proteins (PBPs).

Mechanisms of resistance
Bacterial resistance to cefditoren may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Cefditoren may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) beta lactamases that may be induced or stably derepressed in certain aerobic gram-negative bacterial species
- reduced affinity of penicillin-binding proteins for cefditoren
- outer membrane impermeability, which restricts access of cefditoren to penicillin binding proteins in gram-negative organisms
- active substance efflux pumps.

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and/or antibacterial active substances of other families.
Gram-negative micro-organisms containing inducible chromosomally encoded beta-lactamases, like *Enterobacter spp*., *Serratia spp*., *Citrobacter spp*., and *Providentia spp*., should be regarded as resistant for cefditoren pivoxil in spite of apparent in vitro susceptibility.

Breakpoints
The recommended MIC breakpoints for cefditoren, which allow susceptible micro-organisms to be distinguished from intermediately susceptible micro-organisms, and intermediately susceptible organisms from resistant micro-organisms are: Susceptible ≤ 0.5 μg/ml, Resistant ≥ 2 μg/ml (or > 1 μg/ml according to recent criteria).
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive bacteria: Groups C and G *streptococci* *Staphylococcus aureus* methicillin - susceptible * *Streptococcus agalactiae* *Streptococcus pneumoniae** [$] *Streptococcus pyogenes**
Aerobic Gram-negative bacteria: *Haemophilus influenzae** *Moraxella catarrhalis**
Anaerobic bacteria: *Clostridium perfringes* *Peptostreptococcus* spp.
Inherently resistant organisms
Aerobic Gram-positive bacteria: *Enterococcus* spp.

Staphylococcus aureus methicillin - resistant (MRSA)+
Aerobic Gram-negative bacteria: *Acinetobacter baumanii* *Pseudomonas aeruginosa*
Anaerobic bacteria: *Bacteroides fragilis group* *Clostridium difficile*
Other: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

+ MRSA have acquired resistance to cephalosporins but are included here for convenience.

*Clinical efficacy has been demonstrated for the susceptible micro-organisms in the approved clinical indications.

$ Some strains that show high level resistance to penicillin may show a decreased susceptibility to cefditoren. Cefotaxime and ceftriaxone resistant strains should not be considered susceptible.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, cefditoren pivoxil is absorbed in the gastrointestinal tract and is hydrolysed to cefditoren by the action of esterases. The absolute bioavailability of orally administered cefditoren is approximately 15-20%.

The presence of food in the gastrointestinal tract increases the absorption of cefditoren pivoxil, with the C_{max} and the AUC approximately 50% and 70% higher compared to fasting values.

A 200 mg dose administered with food gives a mean C_{max} of 2.6 μg/ml after approximately 2.5 hours, while a 400 mg dose gives a mean C_{max} value of 4.1 μg/ml in approximately the same time period.

Distribution

Plasma protein binding to cefditoren is 88%.

The volume of distribution at steady state is not significantly different from that calculated after a single dose administration and is relatively independent of the administered dose (40-65 litres).

After a single dose administration of 400 mg, penetration in bronchial mucosa and in bronchial secretion was 60% and 20% respectively of the plasma concentration. After the same dose, cefditoren concentrations in skin blister fluid reached 40% and 56% of plasma AUC after 8 and 12 hours, respectively.

Biotransformation / Elimination

Following multiple dose administration, pharmacokinetic parameters were similar to those obtained after single dose administration, with no accumulation detected.
Up to 18% of the administered dose of cefditoren is recovered by excretion in urine without being metabolised.
The plasma elimination half-life of cefditoren is between 1 and 1.5 hours. Total clearance adjusted by bioavailability is approximately 25-30 l/h, while renal clearance is approximately 80-90 ml/min. Studies with labelled cefditoren in healthy volunteers suggest that the non-absorbed fraction is eliminated in faeces, where the majority of the administered cefditoren appears as inactive metabolites. Cefditoren pivoxil is not detected in faecal extracts or in urine. The pivalate portion is eliminated through renal excretion as the conjugated pivaloylcarnitine.

Special populations

Gender

Pharmacokinetics of cefditoren pivoxil do not show clinically relevant differences between males and females.

Elderly

Plasma levels of cefditoren in elderly subjects (over 65 years) show C_{max} and AUC that are approximately 26% and 33% higher than in younger adults. However, no dose adjustment is required except in cases of advanced hepatic and/or renal insufficiency.

Renal insufficiency

After multiple dose of cefditoren pivoxil 400 mg to patients with moderate to severe renal impairment Cmax was 2-fold and AUC between 2.5 and 3-fold than those observed in normal healthy volunteers (see section 4.2 Posology and Method of Administration). There are no data available for patients undergoing dialysis.

Hepatic insufficiency

In mild hepatic insufficiency (Child-Pugh A) to moderate hepatic insufficiency (Child-Pugh B), multiple doses of 400 mg cefditoren pivoxil gave a slight increase in pharmacokinetic parameters compared to normal subjects. No data are available in patients with severe insufficiency (Child-Pugh C) (See section 4.2 Posology and Method of Administration).

Pharmacokinetic/Pharmacodynamic relationship

With a dosage of 200 mg twice daily, plasma concentrations exceed the minimum inhibitory concentrations (MIC_{90}) for *Moraxella catarrhalis*, *Haemophilus influenzae*, *Streptococcus pyogenes* and penicillin-susceptible *Streptococcus pneumoniae* strains for at least 50% of the dose interval. The dosage of 400 mg twice daily, also provides a time above the minimum inhibitory concentrations which is enough to exceed the MIC_{90} of *Streptococcus pneumonia* resistant to penicillin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.
Studies to evaluate the carcinogenic potential of cefditoren pivoxil have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Croscarmellose sodium
Sodium caseinate
Mannitol
Magnesium stearate
Sodium tripolyphosphate

Tablet coating:
Opadry Y-1-7000 containing:
- Hypromellose
- Titanium dioxide
- Macrogol 400

Carnauba wax

Printing Ink OPACODE S-1-20986 blue including

Shellac glaze
n-butyl alcohol
Brilliant blue lacquer
isopropyl alcohol
Titanium dioxide
Propylene glycol
Ammonia solution concentrated

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date is indicated on the packaging materials.

6.4 Special precautions for storage
Do no store above 25°C. Store in the original package.

6.5 Nature and contents of container
Aluminium/ polyvinyl chloride (PVC) backing and PVC/ aluminium/ PA laminate.
Spectracef 200 mg cardboard box contains 20 film-coated tablets.
Spectracef 400 mg cardboard box contains 10 film-coated tablets.

6.6 Special precautions for disposal
No special requirements.

7. MANUFACTURER
Meiji Pharma Spain, S.A., Avda. De Madrid, 94. 28802, Alcalá de Henares, Madrid, Spain

8. MARKETING AUTHORISATION HOLDER
Taro International, 14 Hakitor St., Haifa Bay 2624761

9. MARKETING AUTHORISATION NUMBER
Spectracef 200 mg 166-36-36015
Spectracef 400 mg 166-37-36016

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