SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Valdocef 250 mg/5 ml granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml oral suspension contains 250 mg cefadroxil, corresponding to 262.50 mg cefadroxil monohydrate.
1 ml oral suspension contains 50 mg cefadroxil, corresponding to 52.50 mg cefadroxil monohydrate.

Excipients with known effect:
Sucrose 2780.00 mg/5 ml
Sodium approximately 12.7 mg/5 ml
Sodium benzoate (E 22) 5.00 mg/5 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Granules for oral suspension.
Light yellow granules, with visible dark yellow granules and pleasant orange odour.
The reconstituted suspension is a light lemon yellow viscous liquid with pleasant-orange odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of following infections caused by cefadroxil-susceptible organisms (see section 5.1), when an oral therapy is indicated:
- Streptococcal pharyngitis and tonsillitis
- Uncomplicated urinary tract infections
- Uncomplicated skin and soft tissue infections

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

4.2 Posology and method of administration

Posology

The dosage depends on the susceptibility of the pathogens, the severity of the disease and on the clinical status of the patient (renal and hepatic function).

Indication	**Adults and adolescents > 40 kg with normal renal function**
Streptococcal pharyngitis and tonsillitis	1000 mg once a day over at least 10 days
Uncomplicated urinary tract infections	1000 mg twice a day
Uncomplicated skin and soft tissue infections	1000 mg twice a day

For adults and adolescents > 40 kg with normal renal function who require treatment with cefadroxil, Valdocef 500 mg capsules are available.

Chronic urinary tract infection may require a prolonged and intensive treatment with continued testing of susceptibility and clinical monitoring.

- Renal impairment:

The dosage should be adjusted according to creatinine clearance rates to prevent accumulation of cefadroxil. In patients with creatinine clearance of 50 ml/min or less, the following reduced dosage schedule is recommended as a guideline for adults:

Creatinine clearance (ml/ min/ 1.73 m^2)	Serum Creatinine (mg/100ml)	Initial dose	Following dose	Dosage interval
50 - 25	1.4 - 2.5	1000 mg	500 mg - 1000 mg	every 12 hours
25 - 10	2.5 - 5.6	1000 mg	500 mg - 1000 mg	every 24 hours
10 - 0	> 5.6	1000 mg	500 mg - 1000 mg	every 36 hours

- Dosage for haemodialysis patients:

Haemodialysis eliminates 63% of 1000 mg of cephalosporin after 6 to 8 hours of haemodialysis. Elimination half-time of cephalosporin is about 3 hours during dialysis.
Patients with haemodialysis receive one additional dose of 500 mg - 1000 mg at the end of the haemodialysis.

- Hepatic impairment:

No adjustment of posology is necessary.

Paediatric population

Indication	**Children (< 40 kg) with normal renal function**
Streptococcal pharyngitis and tonsillitis	30 mg/kg/day once a day over at least 10 days
Uncomplicated urinary tract infections	30-50 mg/kg/day divided into two daily doses

Uncomplicated skin and soft tissue infections	30-50 mg/kg/day divided into two daily doses

Body weight (kg)	**General dosing recommendations based on 30-50 mg/kg/day administered twice daily**	**General dosing recommendations for pharyngitis and tonsillitis based on 30 mg/kg/day administered once daily**
5-6	2.5 to 3.75 ml twice daily	3.75 ml once daily
7-8	2.5 to 5 ml twice daily	5 ml once daily
9-10	3.75 to 5 ml twice daily	6.25 ml once daily
11-12	3.75 to 6.25 ml twice daily	7.5 ml once daily
13-14	5 to 7.5 ml twice daily	8.75 ml once daily
15-16	5 to 8.75 ml twice daily	10 ml once daily
17-18	6.25 to 10 ml twice daily	11.25 ml once daily
19-20	6.25 to 10 ml twice daily	12.5 ml once daily
21-22	7.5 to 11.25 ml twice daily	13.75 ml once daily
23-25	7.5 to 12.5 ml twice daily	15 ml once daily
26-27	8.75 to 13.75 ml twice daily	16.25 ml once daily
28-29	8.75 to 15 ml twice daily	17.5 ml once daily
30-31	10 to 16.25 ml twice daily	18.75 ml once daily
32-33	10 to 17.5 ml twice daily	20 ml once daily
34-35	11.25 to 17.5 ml twice daily	20 ml once daily*
36-37	11.25 to 18.75 ml twice daily	20 ml once daily*
38-40	12.5 to 20 ml twice daily	20 ml once daily*

*The single dose should not exceed 1000 mg.

- Children (< 40 kg) with renal impairment

Cefadroxil is not indicated in children suffering from renal insufficiency and children requiring haemodialysis.

- Elderly

As cefadroxil is excreted by renal route, the dosage should be adjusted if necessary as described under *renal impairment*.

Method of administration

Oral

Bioavailability is not affected by food and cefadroxil may be taken with meals or on an empty stomach. In case of gastro-intestinal disturbances, it may be administered with food.

Preparation of the suspension:

For instructions on reconstitution of the medicinal product before administration, see section 6.6.
The suspension should be shaken well before use.
Take the prepared suspension with plenty of liquid.

Duration of therapy:

Treatment should be applied for 2 to 3 further days after regression of the acute clinical symptoms or evidence of bacterial eradication has been obtained. In infections caused by Streptococcus pyogenes up to 10 days treatment may be considered.

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the cephalosporin or to any of the excipients listed in section 6.1.
- History of severe reactions to penicillins or to any other beta-lactam drugs.

4.4 Special warnings and precautions for use

General considerations
- Penicillin is the first drug of choice for the treatment of the Streptococcus pyogenes and for the prevention of rheumatic fever. Data for cefadroxil are not sufficiently substantial for prophylaxis therapy.
- Forced diuresis leads to a decrease of cefadroxil blood levels.
- As experience in premature infants and neonates is limited, the use of cefadroxil in these patients should only be undertaken with caution.

Hypersensitivity reactions
- Special caution should be exercised in patients with history of severe allergies or asthma.
- In patients with a history of non-severe hypersensitity to penicillins, or other non-cephalosporin beta - lactam drugs, cefadroxil should be used with special caution as cross allergies occur (incidence 5-10%).
- Treatment must be discontinued at once if allergic reactions occur (urticaria, exanthema, pruritus, fall of blood pressure and increased heart rate, respiratory disturbances, collapse, etc.) and suitable countermeasures should be taken (sympathomimetics, corticosteroids and/or antihistaminics).

Renal impairment
Caution is necessary in patients with renal impairment; the dosage must be adjusted according to the grade of renal impairment (see section 4.2).

History of gastro-intestinal disturbances
Cefadroxil should be used with caution in patients with a history of gastro-intestinal disturbances, particularly colitis.

Prolonged use
During prolonged use frequent checks on the blood count and regular hepatic and renal function tests are advisable.

Overgrowth of non-susceptible microorganisms
As with other antibiotics, use of cefadroxil may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).
Antibacterial agent–associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefadroxil and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefadroxil (see section 4.8). Discontinuation of therapy with cefadroxil and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given (see section 4.8).

Interference with diagnostic tests

The result of the Coombs' test can be transiently positive during or after treatment with cefadroxil. This also applies to Coombs' tests carried out in newborns whose mothers received treatment with cephalosporins before delivery.
A false positive reaction may be obtained in urine tests for glucose which use the copper-reduction method (Benedict's solution, Fehling's solution, Clinitest). It is recommended that the glucose oxidase method is used.

Important information about excipients
Valdocef 250 mg/5 ml granules for oral suspension contains 2.78 g of sucrose per 5 ml.
This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Valdocef 250 mg/5 ml granules for oral suspension contains approximately 12.7 mg sodium per 5 ml reconstituted suspension, equivalent to 0.64 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Valdocef 250 mg/5 ml granules for oral suspension contains 5 mg sodium benzoate (E 211) per 5 ml reconstituted suspension. Sodium benzoate (E 211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use
- Cefadroxil should not be combined with bacteriostatic antibiotics (e.g. tetracycline, erythromycin, sulfonamides, chloramphenicol) since an antagonistic effect is possible.
- Treatment with Cefadroxil in combination with aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics should be avoided since such combinations can potentiate nephrotoxic effects.

Concomitant use not recommended
- Frequent checks on coagulation parameters are necessary during concomitant long term use of anticoagulants or thrombocyte aggregation inhibitors to avoid haemorrhagic complications.

Precautions
- The concomitant administration of probenicide can produce higher and sustained concentrations of cefadroxil in the serum and in the bile.
- Cefadroxil binds to cholestyramine which may lead to reduced bioavailability of cefadroxil.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although animal studies and clinical experience have not shown any evidence of teratogenicity, the safe use of cefadroxil during pregnancy has not been established.

Breastfeeding
Cefadroxil is present in low concentrations in breast milk; sensitization, diarrhoea or colonization of the infants' mucosa with fungi are possible.
The use of cefadroxil during pregnancy and in lactating mothers should therefore be handled very strictly.

Fertility

Reproduction studies have been performed in mice and rats and have revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

Cefadroxil may cause headache, dizziness, nervousness, sleeplessness and fatigue, therefore the ability to drive and use machines may be influenced (see section 4.8).

4.8 Undesirable effects

The adverse events are ranked under headings of frequency, using the following convention: 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 form the available data).

Adverse drug reactions occur in about 6% to 7%* of treated patients.

System Organ Class	**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**
Infections and infestations		Clinical pictures due to a growth of opportunistic organisms (fungi), such as vaginal mycoses, thrush (see section 4.4).		
Blood and lymphatic system disorders			Eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis: rare cases during prolonged used, which subside upon discontinuation of therapy.	Haemolytic anemia of immunologic origin.
Immune system disorders			Serum sickness-like reactions.	Immediate allergic reaction (anaphylactic shock) (see section 4.4).
Nervous system disorders				Headache, sleeplessness, dizziness, nervousness.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain,			Pseudomenbranous colitis has been reported (may range in severity from mild to life

	glossitis (see section 4.4).			threatening) (see section 4.4).
Hepatobiliary disorders			Cholestase and idiosyncratic hepatic failure have been reported. Minor elevation of serum transaminases (ASAT, ALAT) and alkaline phosphatases.	
Skin and subcutaneous tissue disorders	Pruritus, rash, allergic exanthema, urticaria.		Angioneurotic edema.	Stevens Johnson syndrome and erythema multiforme have been reported.
Musculoskeletal and connective tissue disorders			Arthralgia.	
Renal and urinary disorders			Interstitial nephritis (see section 4.4).	
General disorders and administration site conditions			Drug fever.	Fatigue.
Investigations				Direct and indirect positive Coombs tests (see section 4.4).

*incidence of suspected adverse reactions in an observational post-marketing study in 904 patients.

4.9 Overdose

No clinical reports are as yet available on cefadroxil in this respect. However in view of experience gained with other cephalosporins the following symptoms are possible: nausea, hallucinations, hyperreflexia, extrapyramidal symptoms, clouded consciousness, or even coma and renal functional impairment. First aid after intake of toxic doses: induce vomiting at once or gastric lavage, if necessary haemodialysis. Monitor and if necessary correct the water and electrolyte balance, monitor renal function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials, First-generation cephalosporins
ATC code: J01DB05

Mechanism of action
Cefadroxil is a cephalosporin for oral administration which inhibits bacterial wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins. The result is formation of a defective cell wall that is osmotically unstable, and bacterial cell lysis.

Resistance
Cefadroxil may be active against organisms producing some types of beta-lactamase, for example TEM-1, in low to moderate quantities. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes.
Cefadroxil cannot be expected to be active against bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam drugs. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.
In vitro, oral first generation cephalosporins are less active than penicillins G and V on Gram-positive microorganisms and are less active than aminopenicillins on H. influenzae.

Breakpoints
The following breakpoint recommendations for cefadroxil according to the European Committee on Antimicrobial Susceptibly Testing (EUCAST) have been defined
(Breakpoint tables for interpretation of MICs and zone diameters, Version 3.1, February 2013):

Cefadroxil (EUCAST Clinical Breakpoint Table)	**MIC breakpoints**	
	S ≤	R>
Enterobacteriaceae (only uncomplicated urinary tract infections)	16	16
Staphylococcus spp.	Note 1	Note 1
Streptococcus groups A, B, C and G	Note 2	Note 2
Non-species related breakpoints	IE	IE

Note 1: Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for ceftazidime, cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections. Some methicillin-resistant *S. aureus* are susceptible to ceftaroline.

Note 2: The beta-lactam susceptibility of beta-hemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

IE: there is insufficient evidence that the species in question is a good target for the therapy with the drug.
PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) for individual target species (i.e. %T>MIC).

Susceptibility
The prevalence of 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
Gram-positive aerobes
Streptococci Group B, C and G
*Streptococcus pyogenes**

Species for which acquired resistance may be a problem
Gram-positive aerobes
Staphylococcus aureus (methicillin-susceptible)*
Staphylococcus epidermidis
Streptococcus pneumoniae$
Gram-negative aerobes
Citrobacter diversus$
E. coli$
K. pneumoniae$
K. oxytoca $
*P. mirabilis**$

Inherently resistant organisms
Gram-positive aerobes
Enterococci
Staphylococcus aureus (Methicillin-resistant)
Staphylococcus epidermidis (Methicillin-resistant)
Streptococcus pneumoniae (Penicillin-intermediate and -resistant)
Gram-negative aerobes
Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Morganella morganii
P. vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens
H. influenzae
Moraxella catarrhalis
Other species
Chlamydia spp
Mykoplasma spp
Legionella spp
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Organisms with natural intermediate susceptibility

5.2 Pharmacokinetic properties

Absorption
After oral administration cefadroxil is practically completely absorbed. Simultaneous intake of food has practically no effect on absorption (AUC).

Distribution
After oral doses of 500 mg (1000 mg) peak plasma concentrations of about 16 (30) µg/ml are obtained after 1-1.3 hours. Between 18 and 20% of cefadroxil is bound to plasma proteins. Cephalosporins do not penetrate in the CSF and should not be used for treatment of meningitis (see section 4.1)

Biotransformation
Cefadroxil is not metabolised.

Elimination
Cefadroxil is eliminated far more slowly than comparable oral cephalosporins (half life: about 1.4 h to 2.6 h) so that intervals between doses can be prolonged to 12-24 hours. Roughly 90% of the substance is eliminated in unchanged form through the kidneys within 24 hours. Cefadroxil may be eliminated from the organism through haemodialysis.

Renal impairment
Elimination is retarded, so that interval between doses must be prolonged (see section 4.2).

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, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Carmellose sodium
Sucrose
Xanthan gum E415
Sodium benzoate E211
Citric acid anhydrous
Sodium citrate
Polysorbate 80
Orange flavour containing:
- Flavouring ingredients
- Maltodextrin
- Sugar
- Modified corn starch
- Acacia gum
- Citric acid esters of mono- and di-glycerides of fatty acids
- Silicon dioxide E551

Colour Quinoline yellow al.lake E104

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unreconstituted product: 2 (two) years.
Reconstituted suspension: The product may be stored for 7 days below 30ºC or 21 days in a refrigerator (5ºC ± 3ºC).

6.4 Special precautions for storage

Unreconstituted product should be stored below 25ºC.
For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

The granules for oral suspension is immediate packed in a 150 ml brown neutral glass bottle, supplied with an aluminium cap with a polyethylene sealing.
Cardboard box contains one (1) bottle, one plastic graduated oral syringe for dosing and an instruction leaflet. Each bottle contains 65 g granules for preparation of 100 ml oral suspension. The 5 ml plastic oral syringe is graduated on 1.25 ml, 2.5 ml, 3.75 ml and 5 ml for measuring of the doses.

6.6 Special precautions for disposal and other handling

Preparation of the suspension

Directions for reconstituting suspension
1. Shake the bottle to loosen the granules;
2. Add 60 ml purified water to the bottle;
3. Shake well to obtain a uniform suspension. The reconstituted suspension is a light lemon yellow viscous liquid with pleasant orange odour.
4. The reconstituted suspension may be stored for 7 days below 30ºC or 21 days in a refrigerator (5ºC ± 3ºC).

Directions for using the dosing syringe
1. Shake the bottle well before use and remove the bottle cap.
2. Remove the cap from the syringe and insert the syringe into the bottle.
3. Slowly pull back the plunger of the syringe up to the graduation mark on the syringe corresponding to the quantity in milliliters (ml) prescribed by the doctor.
4. Remove the syringe from the bottle.
5. With the patient seated in an upright position, place the tip of the syringe just inside the patient's mouth, pointing towards the inside of the cheek.
6. Press the plunger of the syringe in slowly to expel the medicine without causing choking. Do NOT squirt the medicine out in a jet.
7. Repeat steps 2-6 in the same way until the whole dose has been given.
8. After giving the dose replace the bottle cap. Dismantle the syringe and wash it thoroughly in fresh drinking water. Allow the plunger and the barrel to dry naturally.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT