USA: Aftate; Blis-To-Sol; Dr Scholl's Athlete's Foot; Genaspor; Lamisil AF Defense; Podactin; Quinsana Plus; Tinactin; ***Venez.:*** Tinaderm; Tolnaftan.

Multi-ingredient: ***Arg.:*** Bacticort Complex; Cevaderm; Quadriderm†; ***Austral.:*** Mycil Healthy Feet; ***Braz.:*** Cremederme; Permut; Poliderms; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Tetraderm; ***Hong Kong:*** Alber T†; Dermafacte; Mycil; Quadriderm; Triditol-G; ***India:*** Fourderm; Quiss; ***Irl.:*** Mycil; Tinaderm-M; ***Israel:*** Phytoderm Compositum; ***Malaysia:*** Elan-Forte; ***Philipp.:*** Quadriderm; Quadrotopic; ***S.Afr.:*** Duoderm†; Quadriderm; ***Singapore:*** Quadriderm†; ***Spain:*** Cuatroderm; ***Switz.:*** Quadriderm; ***Thai.:*** Alber T; Ezon-T; ***UK:*** Mycil; Tinaderm-M; ***USA:*** Absorbine Athletes Foot Care; Dermasept Antifungal.

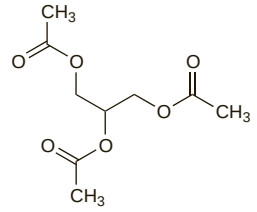
Triacetin *(rINN)*

E1518; Glicerin-triacetát; Glycerol Triacetate; Glycerolum Triacetas; Glyceryl Triacetate; Triacetina; Triacetinas; Triacétine; Triacetinum; Triacetyna; Triasetiini. 1,2,3-Propanetriol triacetate.

Триацетин

$C_9H_{14}O_6$ = 218.2.

CAS — 102-76-1.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Triacetin). A clear, colourless, slightly viscous, oily liquid. Soluble in water; miscible with dehydrated alcohol and with toluene. Store in well-filled containers.

USP 31 (Triacetin). A colourless, somewhat oily liquid with a slight, fatty odour. Soluble in water; slightly soluble in carbon disulfide; miscible with alcohol, with chloroform, and with ether. Store in airtight containers.

Profile

Triacetin is reported to possess fungistatic properties based on the liberation of acetic acid. It has been applied topically in the treatment of superficial dermatophyte infections. It has also been used as a plasticiser in oral preparations.

Triacetin may destroy rayon fabric. It should not come into contact with metals.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Micosan†; ***Hong Kong:*** Alber T†; ***Thai.:*** Alber T; Ezon-T.

Trimetrexate Glucuronate *(BANM, USAN, rINNM)*

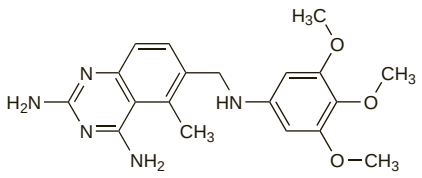
CI-898 (trimetrexate); Glucuronato de trimetrexato; JB-11 (trimetrexate); NSC-352122; NSC-249008 (trimetrexate); NSC-328564 (trimetrexate); Trimétrexate, Glucuronate de; Trimetrexati Glucuronatum. 5-Methyl-6-(3,4,5-trimethoxyanilinomethyl)quinazolin-2,4-diyldiamine mono-D-glucuronate.

Триметрексата Глюкуронат

$C_{19}H_{23}N_5O_3.C_6H_{10}O_7$ = 563.6.

CAS — 52128-35-5 (trimetrexate); 82952-64-5 (trimetrexate glucuronate).

ATC — P01AX07.



(trimetrexate)

Incompatibility. Trimetrexate is reported to be incompatible with foscarnet. Trimetrexate should not be mixed with folinic acid or chloride ions, since precipitation occurs instantly.

Adverse Effects, Treatment, and Precautions

Trimetrexate is a dihydrofolate reductase inhibitor and therefore adverse effects and precautions are similar to those of methotrexate, p.745. It must be given with folinic acid, which should be continued for 72 hours after the last dose of trimetrexate.

Interactions

Studies in *animals* suggest that cimetidine and imidazole antifungals such as clotrimazole and ketoconazole may inhibit trimetrexate metabolism, and there is a risk of possible interactions with all drugs that affect hepatic cytochrome P450 systems.

Antimicrobial Action

Trimetrexate is an inhibitor of dihydrofolate reductase and consequently prevents formation of the active coenzyme tetrahydrofolate and production of DNA and RNA precursors, leading to cell death. At therapeutic doses the selective transport of trimetrexate, but not folinic acid, into *Pneumocystis jirovecii* allows folinic acid to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting its antifungal activity. *In-vitro* trimetrexate has shown dose-related inhibition of growth of the trophozoite stage of *P. jirovecii*.

Pharmacokinetics

The pharmacokinetics of intravenous trimetrexate have been described as both biphasic and triphasic, with a terminal elimination half-life of about 16 to 18 hours. After use with folinic acid a biphasic disposition with a terminal half-life of 11 hours has also been reported. It is extensively protein bound; reports suggest that it is 95 to 98% bound at low serum concentrations, but that binding is saturable, with free fraction increasing at plasma concentrations above 1 microgram/mL. Trimetrexate is excreted mainly in the urine, as unchanged drug and metabolites, some of which may be active. The major metabolic pathway appears to be oxidative O-demethylation followed by conjugation to the sulfate or glucuronide.

Uses and Administration

Trimetrexate is a dihydrofolate reductase inhibitor with general properties similar to those of methotrexate (p.749). It is used in the management of moderate to severe pneumocystis pneumonia in immunocompromised patients, notably patients with AIDS, where other therapy has proved ineffective (see also p.521). It has also been tried as an antineoplastic in the management of various solid tumours.

Trimetrexate is given as the glucuronate but doses are stated in terms of trimetrexate. Trimetrexate glucuronate 1.53 mg is equivalent to about 1 mg of trimetrexate. It is given by intravenous infusion, over 60 to 90 minutes. The schedule in pneumocystis pneumonia is 45 mg/m^2 daily for 21 days, in association with folinic acid rescue for 24 days. The dosage of trimetrexate and folinic acid should be adjusted according to the results of blood tests, which should be performed at least twice a week during therapy. Renal and hepatic function and haemoglobin values should also be monitored. Treatment with zidovudine and other myelosuppressive drugs should be interrupted to allow full doses of trimetrexate to be given.

◊ Reviews.

1. Fulton B, *et al*. Trimetrexate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of Pneumocystis carinii pneumonia. *Drugs* 1995; **49:** 563–76.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Neutrexin†; ***Irl.:*** Neutrexin†; ***Spain:*** Neutrexin†; ***Thai.:*** Neutrexin†; ***USA:*** Neutrexin†.

Undecenoic Acid

Acide Undécylénique; Acidum undecylenicum; 10-Hendecenoic Acid; Kyselina undecylenová; Undecilénico, ácido; Undecileno rūgštis; Undecilénsav; Undecylenic Acid; Undecylensyra; Undesenoatlar; Undesilenatlar; Undesyleenihappo. Undec-10-enoic acid.

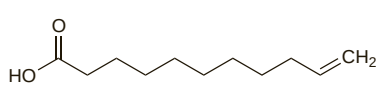
Ундеценовая Кислота

$C_{11}H_{20}O_2$ = 184.3.

CAS — 112-38-9.

ATC — D01AE04.

ATC Vet — QD01AE04.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Undecylenic Acid; Undecenoic Acid BP 2008). A colourless or pale yellow liquid or a white or very pale yellow crystalline mass. Practically insoluble in water; freely soluble in alcohol and in fatty and essential oils. Store in nonmetallic containers. Protect from light.

USP 31 (Undecylenic Acid). A clear, colourless to pale yellow liquid with a characteristic odour. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils. Store in airtight containers. Protect from light.

Calcium Undecenoate

Calcium Undecylenate *(USAN)*; Undecilenato de calcio. Calcium di(undec-10-enoate).

Ундециленат Кальция

$(C_{11}H_{19}O_2)_2Ca$ = 406.6.

ATC — D01AE04.

ATC Vet — QD01AE04.

Pharmacopoeias. In *US.*

USP 31 (Calcium Undecylenate). A fine white powder with a characteristic odour and no grit. Practically insoluble in water, in cold alcohol, in acetone, in chloroform, and in ether; slightly soluble in hot alcohol.

Zinc Undecenoate

Cinko undecilenatas; Çinko Undesilenat; Cink-undecilenát; Sinkkiundesylenaatti; Undecilenato de zinc; Undecilinato de Zinco; Undecylenan zinečnatý; Zinc Undecylenate; Zinc, undécylénate de; Zinci undecylenas; Zinkundecylenat. Zinc di(undec-10-enoate).

Ундециленат Цинка

$(C_{11}H_{19}O_2)_2Zn$ = 431.9.

CAS — 557-08-4.

ATC — D01AE04.

ATC Vet — QD01AE04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Zinc Undecylenate; Zinc Undecenoate BP 2008). A fine white or almost white powder. Practically insoluble in water and in alcohol. Protect from light.

USP 31 (Zinc Undecylenate). A fine, white powder. Practically insoluble in water and in alcohol.

Adverse Effects

Irritation may rarely occur after the topical application of undecenoic acid or its salts.

Antimicrobial Action

Undecenoic acid and its derivatives are active against some pathogenic fungi, including the dermatophytes *Epidermophyton, Trichophyton*, and *Microsporum* spp.

Uses and Administration

Undecenoic acid and its zinc salt are applied topically in the prophylaxis and treatment of superficial dermatophytoses, particularly tinea pedis (p.521). Typical concentrations are undecenoic acid 2 to 5% and zinc undecenoate 20%. They are used in creams, ointments, solutions, or powders, often with each other. Calcium undecenoate is used as a 10 or 15% powder.

Several other salts and derivatives of undecenoic acid including methyl, phenyl, and propyl undecenoate, disodium sulfosuccinated undecenoic acid monoethanolamide, and undecenoic acid monoethanolamide and diethanolamide have been used similarly.

◊ A systematic review[1] of topical treatments for fungal skin or nail infections considered undecenoates to be effective, although comparative studies with other classes of topical antifungal were largely lacking.

1. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/07/08).

Preparations

USP 31: Compound Undecylenic Acid Ointment.

Proprietary Preparations (details are given in Part 3)

Arg.: Bentophyto; Sinamida Pies; Umasam; ***Austria:*** Crino Cordes; Mayfung; Pelsana Med; ***Canad.:*** Desenex; ***Cz.:*** Mykoseptin; ***Fr.:*** Mycodecyl; ***Hung.:*** Lubex; ***Indon.:*** Decyline; Topix; Undecyl; ***Irl.:*** Caldesene; Desenex; ***Israel:*** Undecyl; ***Mex.:*** Derman; ***Pol.:*** Mykodermina; Unguentum Undecylenicum; ***Rus.:*** Mykoseptin (Микосептин); ***S.Afr.:*** Mycota; ***Switz.:*** Fungex; Lubex; Turexan Creme; Turexan Douche; ***Turk.:*** Undo-Pate; Utalk; ***UK:*** Mycota; ***USA:*** Blis-To-Sol; Caldesene; Cruex; Decylenes; Desenex; Elon Dual Defense; Protectol; Undelenic.

Multi-ingredient: ***Arg.:*** Bacteroskin†; Bentophyto; Bifena; Champuacid; Cicatrol; Clevosan; Dettonjab; Farm-X; Fungicida†; Fungocop; Hipoglos Cicatrizante; Laurinol Plus; LB Jabon con Purcelin†; Novo Miconol; Novofarma Champu; Piecidex†; Plusderm†; Tersoderm Anticaspa†; ***Austral.:*** Mycoderm†; Pedoz; Sebitar; Seborrol†; ***Austria:*** Dequafungan; Mycopol; Pelsana Med; Salvyl; ***Braz.:*** Andriodermol; Micosan†; Micotox†; Micoz†; ***Chile:*** Fittig; Hansaplast Footcare†; Lady Fittig†; NP-27; ***Cz.:*** Hexadecyl†; ***Fr.:*** Paps; ***Ger.:*** Gehwol Fungizid†; Gehwol Nagelpilz†; Skinman Soft; ***Gr.:*** Ekzegamma†; ***Hong Kong:*** Acnederm; Fungifax†; Mycoderm†; Sebitar; ***Hung.:*** Squa-med; ***Indon.:*** Decyline; Mikorex; Skintex; ***Irl.:*** Ceanel†; ***Israel:*** Fungimon; Pedisol; Pitrisan; ***Ital.:*** Balta Intimo†; Foot Zeta; Genisol; Micofoot; Propast; ***Malaysia:*** Acnederm†; Sebitar; ***Mex.:*** Micotex; ***NZ:*** Acnederm†; Egomycol†; Grans Remedy; Sebitar; Seborrol†; ***Pol.:*** Undofen; ***Port.:*** Edoltar†; Micaveen; ***S.Afr.:*** AF; Mycota†; ***Singapore:*** Sebitar; ***Switz.:*** Crimanex; Ederphyt; Fungex; Pelsano; Pruri-med; Sebo Shampooing; Trosyd†; Turexan Emulsion†; ***Turk.:*** Fungecyl; Undo-Talk; ***UK:*** Ceanel; Healthy Feet; Monphytol†; Mycota; ***USA:*** Breezee Mist Foot Powder; Dermasept Antifungal; Gordochom; Phicon-F; ***Venez.:*** Diodonato†.

Voriconazole *(BAN, USAN, rINN)*

UK-109496; Voriconazol; Voriconazolum; Vorikonazol. (2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

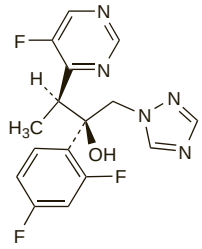
Вориконазол

$C_{16}H_{14}N_5F_3O$ = 349.3.

CAS — 137234-62-9.

ATC — J02AC03.

ATC Vet — QJ02AC03.



Adverse Effects

The most commonly reported adverse effects with voriconazole are visual disturbances, fever, rashes, nausea, vomiting, diarrhoea, abdominal pain, headache, sepsis, respiratory disorders, and peripheral oedema. There have been some serious hepatic reactions including fatalities. Skin reactions have included rare cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions may occur and are more likely during long-term treatment.

Other adverse effects reported as being common during treatment with voriconazole include: chills, flu-like syndrome, asthenia, back pain, chest pain, injection site reactions, facial oedema, hypotension, sinusitis, altered liver function tests, jaundice, cheilitis, blood disorders, hypokalaemia, hypoglycaemia, dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia, pruritus, alopecia, exfoliative dermatitis, acute renal failure, and haematuria. Hypersensitivity reactions, including anaphylaxis, have occurred rarely.

Effects on the blood. Fever and leucocytosis with eosinophilia in one patient has been attributed to voriconazole treatment.[1]

1. Vishnubhotla P, *et al.* Fever and eosinophilia associated with voriconazole. *Ann Pharmacother* 2004; **38:** 900–901.

Effects on the heart. Bradycardia with a prolonged QT interval and asymptomatic episodes of torsade de pointes occurred in a 15-year-old patient, after 3 weeks of voriconazole therapy at usual doses.[1] All drug treatment was stopped but the effects recurred on rechallenge with a small dose of voriconazole.

1. Alkan Y, *et al.* Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; **39:** e49–e52.

Effects on mental function. There have been reports[1,2] of patients experiencing hallucinations (auditory or visual) during treatment with voriconazole. In one study 18 of 415 patients (4.3%) given voriconazole had visual hallucinations compared with 2 of 422 (0.5%) given amphotericin B.[1]

1. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346:** 225–34.
2. Agrawal AK, Sherman LK. Voriconazole-induced musical hallucinations. *Infection* 2004; **32:** 293–5.

Precautions

Acute renal failure may occur with voriconazole and renal function should be monitored during treatment. Liver function should also be monitored before and during treatment with voriconazole. It should be used with caution in patients with hepatic impairment and doses may need to be adjusted (see under Uses and Administration, below). Patients should avoid sunlight during treatment as photosensitivity reactions have been reported. Visual disturbances may occur and patients affected should not drive or operate hazardous machinery. In addition, all patients, whether affected by visual disturbances or not, should not drive at night, and should have their visual function monitored if they are receiving voriconazole for more than 28 days. Voriconazole has been associated with QT interval prolongation and should therefore be given with caution to patients with potentially pro-arrhythmic conditions.

Voriconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with voriconazole.

Interactions

Voriconazole is metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Use of drugs that either inhibit or induce these isoenzymes may increase or decrease plasma concentrations of voriconazole, respectively. Rifampicin has been shown to decrease voriconazole plasma concentrations and a similar effect may be expected with carbamazepine or phenobarbital; use of voriconazole with these drugs is therefore not recommended.

Concentrations of other drugs that are metabolised by CYP2C19, CYP2C9, or CYP3A4 may be increased by voriconazole. Increased plasma concentrations of astemizole, cisapride, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. Increased plasma concentrations of sirolimus and tacrolimus have been noted; use with sirolimus is contra-indicated, although tacrolimus may be used providing its dose is reduced and concentrations monitored. Similarly, reduced dose with monitoring is recommended for ciclosporin. Likewise, monitoring and possible dose reductions of methadone are recommended during concomitant use. Concentrations of oral anticoagulants may be affected and increased prothrombin time has occurred with warfarin; monitoring should therefore be carried out. Close monitoring of blood glucose is necessary if voriconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for some statins, calcium-channel blockers, vinca alkaloids, and some benzodiazepines (such as midazolam and triazolam) if their plasma concentrations are increased.

Interactions may occur where both voriconazole and the other drug are affected. Examples are phenytoin and rifabutin (where concentrations of voriconazole are reduced but those of phenytoin or rifabutin are increased). If it is essential to give either drug with voriconazole, then an increase in the dose of voriconazole is recommended. With omeprazole, the plasma concentration of both drugs may be increased and a reduced dose of omeprazole is recommended.

Voriconazole may inhibit metabolism of non-nucleoside reverse transcriptase inhibitors and they in turn may either inhibit the metabolism of voriconazole (e.g. delavirdine and efavirenz) or induce the metabolism of voriconazole (e.g. efavirenz and nevirapine). Co-administration of voriconazole and efavirenz is contra-indicated. Similarly, voriconazole may inhibit metabolism of HIV-protease inhibitors (e.g. saquinavir, amprenavir, and nelfinavir) while they may in turn inhibit the metabolism of voriconazole. High doses of ritonavir (400 mg twice daily) significantly decrease plasma concentrations of voriconazole and co-administration is contra-indicated. Similar effects have been seen with low doses of ritonavir (100 mg twice daily) and use with voriconazole should be avoided where possible. Indinavir, however, does not appear to interact with voriconazole.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Voriconazole is a triazole antifungal that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in the impairment of ergosterol synthesis in fungal cell membranes. Voriconazole has a broad spectrum of activity against all *Candida* species, including fluconazole-resistant strains, as well as *Aspergillus* spp., *Scedosporium* spp., and *Fusarium* spp.

◊ Reports of breakthrough zygomycosis and other fungal infections in immunocompromised patients treated empirically or prophylactically with voriconazole.[1-5]

1. Marty FM, *et al.* Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; **350:** 950–2.
2. Siwek GT, *et al.* Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis* 2004; **39:** 584–7.
3. Imhof A, *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; **39:** 743–6.
4. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. *Clin Infect Dis* 2005; **40:** 770–1.
5. Vigouroux S, *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; **40:** e35-e37.

Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. It is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma protein binding of voriconazole is about 58%. Voriconazole diffuses into CSF.

Voriconazole is metabolised by hepatic cytochrome P450 isoenzyme CYP2C19; the major metabolite is the inactive *N*-oxide. Metabolism via isoenzymes CYP2C9 and CYP3A4 has also been demonstrated *in vitro*. About 80% of voriconazole is excreted in the urine.

◊ References.

1. Purkins L, *et al.* Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46:** 2546–53.
2. Johnston A. The pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 1.
3. Walsh TJ, *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; **48:** 2166–72.
4. Theuretzbacher U, *et al.* Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; **45:** 649–63.

Uses and Administration

Voriconazole is a triazole antifungal used mainly in immunocompromised patients for the treatment of invasive aspergillosis (p.517), candidaemia (p.518) in non-neutropenic patients, fluconazole-resistant serious invasive candidiasis, oesophageal candidiasis, and serious fungal infections due to *Scedosporium* and *Fusarium* spp.

Voriconazole may be given orally or intravenously.

Oral doses as film-coated tablets should be taken at least 1 hour before, or 1 hour after, a meal; oral suspensions should be taken at least 1 hour before, or 1 to 2 hours after, a meal. The oral suspension may be preferred in children.

The following ***oral loading doses*** of voriconazole are given every 12 hours for the first 24 hours:

- adults and adolescents weighing more than 40 kg: 400 mg
- under 40 kg: 200 mg
- children aged 2 to 12 years: no loading dose

Subsequent ***oral maintenance doses*** are:

- adults and adolescents over 40 kg: 200 mg twice daily, increased to 300 mg twice daily if the response is inadequate
- under 40 kg: 100 mg twice daily, increased to 150 mg twice daily if the response is inadequate
- children aged 2 to 12 years: 200 mg twice daily