KLACID®

CLARITHROMYCIN

DESCRIPTION AND COMPOSITION

KLACID 250mg tablets: yellow, ovaloid, film-coated tablet containing 250mg clarithromycin

KLACID 500mg tablets: yellow, ovaloid, film-coated tablet containing 500mg clarithromycin

KLACID XL ***(Also known as Klacid RM, Klacid MR)*** **500mg tablets:** yellow, ovaloid, film-coated tablet containing 500mg clarithromycin in a modified-release preparation.

KLACID granules 125mg/5ml: white to off - white granules for oral suspension.
After mixing each 5ml of suspension contains 125mg clarithromycin

KLACID granules 250mg/5ml: white to off - white granules for oral suspension.
After mixing each 5ml of suspension contains 250mg clarithromycin

CLINICAL PARTICULARS

Therapeutic indications

All Pharmaceutical forms:

Treatment of infections caused by susceptible organisms. Indications include:

- Upper respiratory tract infections for example, sinusitis, tonsillitis and pharyngitis.
- Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia.
- Skin and soft tissue infections of mild to moderate severity for example, impetigo, erysipelas, folliculitis, furunculosis, and infected wounds.

KLACID granules 125mg/5ml and KLACID granules 250mg/5ml:

- Treatment of acute otitis media

KLACID 500mg tablets:

- Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is indicated for the eradication of *H.pylori* in patients with duodenal ulcers.

Posology and method of administration

KLACID 250mg tablets and 500mg tablets:

Adults: The usual dose is 250mg twice daily for 7 days. This may be increased to 500mg twice daily for up to 14 days in severe infections.

Children older than 12 years: As for adults.

KLACID 500mg tablets for eradication of *H.pylori* in patients with duodenal ulcers:

Adults:

Dual Therapy (14 days):
The usual dose of Clarithromycin is 500mg three times daily for 14 days. Clarithromycin should be administered with oral omeprazole 40mg once daily. The pivotal study was conducted with omeprazole 40mg once daily for 28 days. Supportive studies have been conducted with omeprazole 40mg once daily for 14 days.

Triple Therapy (7-14 days):
Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with amoxycillin 1000mg twice daily for 7-14 days.

Triple Therapy (7 days):
Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with metronidazole 400mg twice daily for 7 days.

Triple Therapy (7 days):
Clarithromycin 500mg twice daily and omeprazole 40mg daily should be given with amoxycillin 1000mg twice daily or metronidazole 400mg twice daily for 7 days.

Triple Therapy (10 days):
Clarithromycin 500mg twice daily should be given with amoxycillin 1000mg twice daily and omeprazole 20mg daily for 10 days.

Elderly: As for adults.

Renal impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250mg once daily or 250mg twice daily in more severe infections.

KLACID maybe given without regard to meals as food does not affect the extent of bioavailability.

KLACID XL (Klacid RM, Klacid MR) Tablets:
Adults: The usual recommended dosage is one 500mg modified-release tablet daily to be taken with food. In more severe infections, the dosage can be increased to two 500mg modified-release tablets daily. The usual duration of treatment is 7 to 14 days.

Children older than 12 years: As for adults.

Renal impairment: Klacid XL should not be used in patients with renal impairment (creatinine clearance less than 30mL/min). Klacid immediate release tablets may be used in this patient population.

KLACID granules 125mg/5ml: For infants 6 months and above, the recommended daily dosage is 15mg/kg/day in two divided doses. The dose can be increased according to the severity of illness and physician's opinion

Child weight (kg)	Dosage (ml) bid
5-10	2.5ml
11-20	5ml
21-30	7.5ml

KLACID granules 250mg/5ml: The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. The recommended daily dosage of Klacid Paediatric Suspension 250mg/5ml in children is given in the following table and is based on a 7.5mg/kg twice a day dosage regimen. Doses up to 500mg twice a day have been used in the treatment of severe infections.

KLACID PAEDIATRIC SUSPENSION 250MG/5ML DOSAGE IN CHILDREN

Weight *(kg)	Approx Age(yrs)	Dosage (ml) bid
8-11	1-2	1.25
12-19	3-6	2.5
20-29	7-9	3.75
30-40	10-12	5

* Children < 8kg should be dosed on a per kg basis (approx. 7.5mg/kg twice a day)

Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs and other ingredients.

Clarithromycin and ergot derivatives should not be co-administered. Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Klacid XL: As the dose cannot be reduced from 500mg daily, Klacid XL is contraindicated in patients with creatinine clearance less than 30mL/min.

Special warnings and precautions for use

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic or renal function. Prolonged or repeated use of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted. *H.pylori* organisms may develop resistance to clarithromycin in a small number of patients. There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

Klacid XL (Klacid RM, Klacid MR) and Klacid peadiatric suspension: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interactions with other medicaments and other forms of interaction

Clarithromycin has been shown not to interact with oral contraceptives. As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (eg. Cilostazol, methylprednisolone, oral anticoagulants (eg. warfarin), quinidine, sildenafil, ergot alkaloids, alprazolam, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporine vinblastine, valproate and tacrolimus,) may be associated with elevations in serum levels of these other drugs. Rhabdomyolysis, co-incident with the coadministration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin or simvastatin has been reported. The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity. The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients. The effects of digoxin may be potentiated with concomitant administration of Clarithromycin. Monitoring of serum digoxin levels should be considered. Clarithromycin may potentiate the effects of carbamazepine due to a reduction in the rate of excretion.

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of Clarithromycin and zidovudine by 1-2 hours. To date, this interaction does not appear to occur in paediatric HIV-infected patients taking klacid paediatric suspension (Klacid 125mg/5ml granules, Klacid 250mg/5ml granules) with zidovudine or dideoxyinosine. Interaction studies have not been conducted with Klacid XL and Zidovudine. If concomitant administration of clarithromycin and zidovudine is required, then an immediate release formulation of clarithromycin should be used.

Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{cr} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{cr} <30ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be coadministered with ritonavir.

For patients with renal impairment an immediate release form of clarithromycin should be used.

There have been postmarketed reports of Torsade de Pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Levels of these medications should be monitored during clarithromycin therapy.

Post-marketing reports also indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischaemia of the extremities and other tissues including the central nervous system.

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicines. Patients should be monitored for clinical symptoms of colchicine toxicity.

Klacid 250mg Tablets & Klacid 500mg Tablets:
Although the Plasma Concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. At the dosages recommended, there is no clinically significant interation between clarithromycin and lansoprazole. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with Maalox or ranitidine. No adjustment to the dosage is necessary.

Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk. Some animal studies have suggested an embryotoxic effect, but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

Effects on ability to drive and use machines

None known.

Undesirable effects

Clarithromycin is generally well tolerated. Side effects include nausea, dyspepsia, diarrhoea, vomiting, abdominal pain and paraesthesia. Stomatitis, glossitis, oral monilia and tongue discolouration have been reported. Other side-effects include headache, arthralgia, myalgia and allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis have been reported. There have been reports of Stevens-Johnson syndrome / toxic epidermal necrolysis with orally administered clarithromycin.
Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.
There have been reports of transient central nervous system side-effects including dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucinations, psychosis and depersonalisation. There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening. There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin. There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible. Isolated cases of leukopenia and thrombocytopenia have been reported.
As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.
Cases of increased serum creatinine, interstitial nephritis, renal failure, pancreatitis and convulsions have been reported rarely.
As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.
There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

Overdosage:

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin. The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:-

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.*

Gram-negative Bacteria: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila, Bordetella pertussis, Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Mycobacterum kansasii; Mycobacterium chelonae; Mycobacterium fortuitum; Mycobacterium intracellulare.*

Anaerobes: Macrolide-susceptible *Bacteroides fragilis; Clostridium perfringens;* Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes.*

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H.pylori and Campylobacter spp. The activity of clarithromycin against H.pylori is greater at neutral pH than at acid pH.

Further information: *H.pylori* is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. *H.pylori* is also implicated as a major contribution factor in the development of gastritis and ulcer recurrence in such patients. In a well controlled study, clarithromycin 500mg tid for 14 days administered with omeprazole 40gm od for 28 days eradicated in excess of 80% of H.pylori isolates in patients with duodenal ulcer. Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include: Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone. Clinical studies using various different *H.pylori* eradication regimens have shown that eradication of *H.pylori* prevents ulcer recurrence.

Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.
When clarithromycin 500mg is given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500mg twice daily dosage. Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin penetrates into the middle ear fluid at concentrations greater than in the serum. Clarithromycin is 80% bound to plasma proteins at therapeutic levels. Clarithromycin also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

Klacid granules 125mg/5ml and Klacid granules 250mg/5ml:
Klacid Paediatric Suspension does not contain tartrazine or other azo dyes, lactose or gluten.

Klacid XL (Klacid RM, Klacid MR): The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following *in vitro* and *in vivo* data are applicable to the modified-release formulation. (A) *In vitro:* Results of in vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70 % at concentrations of 0,45 - 4,5µg/mL.
A decrease in binding to 41% at 45.0µg/mL suggested that the binding sites might become saturated, but this only occurred at concentrations in excess of therapeutic drug levels. (B) *In vivo:* Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20. The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg clarithromycin modified-release daily, the peak steady state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1,3 and 0,48µg/mL, respectively. When the dosage was increased to 1000mg daily, these steady-state values were 2.4µg/mL and 0.67µg/mL respectively. Elimination half-lives of the parent drug and its metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its 14-hydroxyl metabolite tended to be longer at higher doses. Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

PHARMACEUTICAL PARTICULARS

List of Excipients

KLACID 250mg tablets: Croscarmellose sodium, starch pregelatinised, cellulose microcrystalline, silica gel, povidone (K 29-32), stearic acid, magnesium stearate, talc, Hypromellose, hydroxypropylcellulose, propylene glycol, sorbitan monooleate, titanium dioxide (E171), sorbic acid, vanillin, quinoline yellow (E104).

KLACID 500mg tablets: Croscarmellose sodium, cellulose microcrystalline, silicon dioxide, povidone (K 29-32), stearic acid, magnesium stearate, talc, Hypromellose, hydroxypropylcellulose, propylene glycol, sorbitan monooleate, titanium dioxide (E171), sorbic acid, vanillin, quinoline yellow (E104).

KLACID XL (Also known as Klacid RM, Klacid MR) 500mg tablets: Citric acid anhydrous, sodium alginate, sodium calcium alginate, lactose, povidone (K 30), talc, stearic acid, magnesium stearate, methyl hydroxypropylcellulose, polyethylene glycol 400, macrogol 8000, titanium dioxide (E171), sorbic acid, quinoline yellow (E104).

KLACID granules 125mg/5ml: Carbopol 974p, povidone k90, hypromellose phthalate (HP-55), castor oil, silicon dioxide, sucrose, xanthan gum, flavour-fruit punch, pottasium sorbate, citric acid, titanium dioxide (E171), Maltodextrin.

KLACID granules 250mg/5ml: Carbopol 974p, povidone k90, hypromellose phthalate (HP-55), castor oil, silicon dioxide, sucrose, xanthan gum, flavour-fruit punch, pottasium sorbate, citric acid, titanium dioxide (E171). Maltodextrin.

Incompatibilities

None known.

Special precautions for storage

Klacid 250mg tablets: Store at room temperature not exceeding 30°C.
Klacid 500mg tablets: Store in a dry place below 30°C. Protect from light.
Klacid XL (Klacid RM, Klacid MR) tablets: Store between 15°C and 30°C. Protect from light.
Klacid granules 125mg/5ml: Store at room temperature not exceeding 30°C.
Klacid granules 250mg/5ml: Store at room temperature between 15°C and 30°C.
Keep cap tightly closed.

How supplied:

Klacid 250mg tablets: blister packs containing 14 tablets of 250mg each
Klacid 500mg tablets: blister packs containing 14 tablets and 20 tablets
Klacid XL (Klacid RM, Klacid MR) tablets: blister packs containing 7 tablets and 14 tablets
Klacid granules 125mg/5ml: 60ml and 100ml bottles with dispenser
Klacid granules 250mg/5ml: 100ml bottle with dispenser

Manufacturer

See outer pack

Name of Marketing Authorization Holder

Klacid 500mg tablets, Klacid XL tablets, Klacid granules 250mg/5ml:
Abbott Laboratories Ltd
Abbott house, Vanwall Road
Maidenhead Berks SL6 4XE, UK

Klacid 250mg tablets, Klacid granules 125mg/5ml, Klacid RM tablets, Klacid MR tablets:
Abbott S.R.L., Campoverde di Aprilia (Latina) Italy

DATE OF TEXT REVISION

February 2011

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health and its consumption contrary to instructions dangerous to you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDREN

Council of Arab Health Ministers
Union of Arab Pharmacists

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