ABBOTIC XL
Clarithromycin

1. NAME OF THE MEDICINAL PRODUCT
Abbotic XL 500 mg, Modified-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 500 mg Clarithromycin.
Excipient: Lactose 115 mg per tablet

For the full list of excipients, see section List of excipients.

3. PHARMACEUTICAL FORM
Yellow, ovaloid film-coated tablet

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ABBOTIC® XL (Clarithromycin MR) is indicated for the treatment of mild to moderate, infections caused by susceptible strains of the designed microorganisms in the conditions listed below:

1) Upper respiratory tract infections:
   * Pharyngitis/Tonsilitis due to *Streptococcus pyogenes*.
   * Acute maxillary sinusitis due to *Streptococcus pneumoniae*.
2) Lower respiratory tract infections:
   *Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.
   * Pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.
3) Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*.
   Abscesses usually require surgical drainage.

4.2 Posology and method of administration
The usual recommended dosage is ABBOTIC® XL (Clarithromycin MR) tablets in adults is 500 mg once-daily with food. In more severe infections the dosage may be increased to 1000 mg once-daily (2 x 500 mg).

The usual duration of therapy is 7 to 14 days.

Clarithromycin modified release should not be used in patients with significant renal impairment (creatinine clearance less than 30 mL/min). Clarithromycin 500 mg immediate release tablets may be utilized in this patient population (see section 4.3).

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs. As the dose cannot be reduced from 500 mg once-daily, clarithromycin MR is contraindicated in patients with creatinine clearance less than 30 mL/min. Clarithromycin 500 mg immediate release tablets may be utilized in this patient population.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide and terfenadine and astemizole (see section 4.5).

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalemia or hypomagnesaemia, due to risk of prolongation of QT- interval).

Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Clarithromycin should not be used in pregnant woman, except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patients should be apprised of the potential hazard of the fetus.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of bacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridium difficile is a primary cause of “Antibiotic associated colitis”. After the diagnosis of pseudomembranous colitis usually respond to discontinuation the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against Clostridium difficile.

PRECAUTIONS

Clarithromycin is principally metabolized by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate renal impairment (see section 4.3).

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Prolonged or repeated use of Clarithromycin may result in an over growth of non susceptible bacteria or fungi. If superinfection occurs Clarithromycin should be discontinued and appropriate therapy instituted.

*) “Nursing mothers”: It is not known whether Clarithromycin is excreted in human milk. Caution should be excercised when Clarithromycin is administered to a nursing women. It is known that Clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk.

*) Pediatric use: Safety and effectiveness of clarithromycin in children under 6 months of age have not been established and the safety of clarithromycin has not been studied in MAC patients under the age of 20 months.

*) Geriatric use: In a steady-state study in which healthy elderly subjects (age 65 - 81 years old) were given 500 mg every 12 hours, the maximum concentrations of Clarithromycin and 14-OH Clarithromycin were increased. The AUC was also increased.These changes in pharmacokinetics parallel known age-related decreases in renal functions. In clinical trials elderly patients did not have an increased incidence of adverse events when compared to younger patients, dosage adjustment should be considered in the elderly patients with severe renal impairment.

Attention should also be paid to the possibility of cross resistance between CLARITHROMYCIN and other macrolide drugs, as well as lincomycin and clindamycin.

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q 8 hours and clarithromycin 500 mg q 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-(R)-hydroxy-clarithromycin was noted. 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} $\leq$30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

4.5 Interaction with other medicinal products and other forms of interaction

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophyline or carbamazepine levels when either of these drugs are administered concomitantly with clarithromycin.

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolized by the cytochrome P-450 system (e.g. cyclosporine, disopyramide, ergot alkaloids, lovastatin, midazolam, phenytoin, triazolam, and warfarin) may be associated with elevations in serum levels of these other drugs.

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and *torsades de pointes*. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see section 4.3).

Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increasing levels of terfenadine which has occasionally been associated with cardiac arrhytmias such as QT prolongation, ventricular tachycardia, ventricular vibrilation and torsade de pointes (see CONTRAINIDICATIONS). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 2 to 3 fold increase in the serum level of the acid metabolites of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

Lomitapide

Concomitant administration of clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

4.6 Fertility, Pregnancy and lactation

Pregnancy

The safety of clarithromycin for use in pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breastfeeding

Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin. The safety of clarithromycin use during breast-feeding of infants has not been established.

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

The most frequently reported side effects of clarithromycin in clinical studies in adults were gastrointestinal-related complaints, i.e., nausea, dyspepsia, abdominal pain, vomiting and diarrhea. Other side effects included headache, taste perversion, and transient elevations of liver enzymes.

Post Marketing Experience

Hepatic dysfunction, including increases liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is ussualy reversible. In very rare instances, hepatic failure and fatal outcome has been reported and generally has been associated with serious underlying disease and/or concomitant medications.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis, Stevens-Johnsons Syndromehave occurred with orally administered clarithromycin.

There have been reports of transients central nervous system side effects ranging from dizziness, anxiety, insomnia, hallucinations and bad dreams to confusion, hallucination and psychosis; however, a cause and effect relationship has not been established.

There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy. Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been reported.

Glossitis, stomatitis, oral monilia and tongue discoloration have been reported with clarithromycin therapy. There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning.

There have been rate reports of hypoglycemia, some of which haveoccurred in patients on concomitant oral hypoglycemic agents or insulin.

Isolated cases of thrombocytopenia have been reported. Rarely, erythromycin has been associated with ventricular arrythmias, including ventricular tachycardia, and torsade de pointes, individuals with prolonged QT intervals.

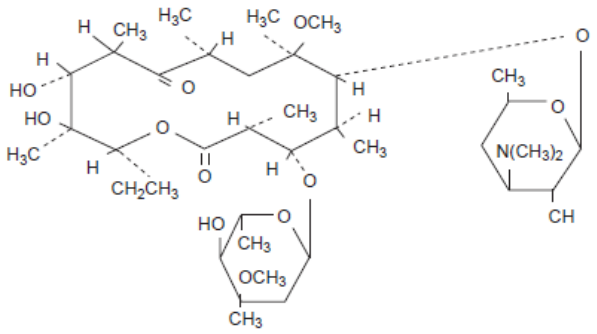
4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behavior, hypokalemia, and hypoxemia.
Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ABBOTIC® (Clarithromycin) is semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Specifically, Clarithromycin is 6-0 Methyl Erythromycin A. The white to off white antibiotic powder is practically odorless, essentially insoluble in water, and slightly soluble in ethanol, methanol, and acetonitrile. Its molecular weight is 747.96 and the structural formula is as follows:



ABBOTIC® XL is available in modified release (MR) tablets, containing 500 mg of the active antibiotic. The modified release tablet is a homogeneous matrix which provides sustained release during its transit through the gastrointestinal tract.

Microbiology

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

Clarithromycin has demonstrated in vitro activity against both standard strains of bacteria and clinical isolates. 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 one $\log_2$ dilution more potent than the MICs of erythromycin.

In vitro data also indicate clarithromycin has activity against *Legionella pneumophila* and *Mycoplasma pneumoniae*. The in vitro antibacterial spectrum of clarithromycin against respiratory tract and skin structure pathogens is as follows:

USUALLY SENSITIVE BACTERIA

Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus viridans
Streptococcus pneumoniae
Haemophilus influenzae
Haemophilusparainfluenzae
Neisseria gonorrhoeae
Legionella pneumophila
PasteureIlamultocida
Mycoplasma pneumoniae
Campylobacter jejuni
Chlamydia pneumoniae (TWAR)
Chlamydia trachomatis
MoraxeIla (Branhamella) catarrhalis
Bordetella pertussis
Borrelia burgdorferi
Staphylococcus aureus
Clostridium perfringens
Peptococcusniger
Propionibacterium acnes
Bacteroides melaninogenicus
Mycobacterium avium
Mycobacterium intracellulare

NON-SENSITIVE BACTERIA
Enterobacteriaceae
Pseudomonas species

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-OH-CLARITHROMYCIN. This metabolite is as active or 1- to 2-fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *H. influenzae* in vitro and in vivo, depending on bacterial strains.

Clarithromycin was found to be two to ten times more active than erythromycin in several experimental animal infection models. It was shown, for example, to be more effective than erythromycin in mouse systemic infection, mouse subcutaneous abscess, and mouse respiratory tract infections caused by *S. pneumoniae*, *S. aureus*, *S. pyogenes*, and *H. influenzae*. In guinea pigs with Legionella infection this effect was more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility Tests
Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 µg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for

clarithromycin. The MICs are determined by the broth or agar dilution method.The recommended test medium for susceptibility testing of *Haemophilus influenzae* according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (H.T.M.)

CLARITHROMYCIN INTERPRETIVE STANDARDS

	Inhibition Zone Diameter (mm)			MIC (mcg/mL)		
Organisms	S	I	R	S	I	R
All Organisms (except Haemophilus and staphylococci)	≥ 18	14-17	≤ 13	≤ 1	2-4	≥ 8
Staphylococci	≥ 20	.....	≤ 19	≤ 0.5	–	≥ 1
Haemophilus influenzae when tested on HTM*	≥ 13	11-12	≤10	≤ 8	16	≥ 32
*HTM = Haemophilus Test Medium S = Susceptible I = Intermediate R= Resistant						

With these procedures, a report from the laboratory of "susceptible" indicates the infecting organism is likely to respond to therapy. A report of "resistant" indicates the infective organism is not likely to respond to therapy. A report of "Intermediate Susceptibility" suggests the therapeutic effect of the drug may be equivocal or the organism would be susceptible if higher doses were used. (Intermediate susceptibility is also referred to as moderately susceptible.)

5.2 Pharmacokinetic properties

Absorption

The kinetics of orally administered clarithromycin MR has been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets. The extent of absorption was found to be equivalent when equal daily doses were administered with the MR tablets taken with food. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found, and the metabolic disposition did not change in humans following multiple dosing. Based upon the finding of equivalent extent of absorption, the following in vitro and in vivo data is applicable to the modified release formulation. Concomitant food intake increases the exposure to clarithromycin. Therefore, clarithromycin MR tablets should be taken with food.

Distribution, Biotransformation and Elimination

In vitro

In vitro studies showed the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 to 4.5 µg/ml. A decrease in binding to 41% at 45.0 µg/ml suggested the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug levels.

In vivo

Results of animal studies showed clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

Normal Subjects

In fed patients given 500 mg clarithromycin MR once-daily, the peak steady state plasma concentration of clarithromycin and 14-OH-clarithromycin were 1.3 and 0.48 µg/ml, respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 hours and 7.7 hours, respectively. When clarithromycin MR 1000 mg once-daily (2 x 500 mg) was administered, the steady state Cmax for clarithromycin and its hydroxylated metabolite averaged 2.4 µg/ml and 0.67 µg/ml, respectively. The half-life of the parent drug at the 1000 mg dose level was approximately 5.8 hours, while that of the 14-OH-clarithromycin was approximately 8.9 hours. The Tmax for both the 500 mg and 1000 mg doses was approximately six hours. At steady state the 14-OH-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behavior of clarithromycin, coupled with the overall decrease in the formation of 14- hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Urinary excretion accounts for approximately 40% of the clarithromycin dose. Fecal elimination accounts for approximately 30%.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Limited data from a small number of patients suggests clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (*i.e.*, only 1 to 2% of serum levels in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations.

CONCENTRATION		
Tissue Type	Tissue (mcg/g)	Serum (mcg/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

Hepatic Impairment

In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250 mg of clarithromycin immediate release b.i.d. for two days and

a single 250 mg dose the third day, steady state plasma levels and systemic clearing of clarithromycin were not significantly different between the two groups. In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects. These results indicate no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Renal Impairment
A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500 mg oral doses of clarithromycin immediate release in subjects with normal and decreased renal function. The plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. Kelim and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference (see sections 4.3 and 4.2).

Elderly Subjects
A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin immediate release in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and 14-OH metabolite. However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age per se.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Citric acid
Sodium alginate
Sodium calcium alginate
Lactose
Povidone
Talc
Stearic acid
Magnesium stearate

Coating Solution

Hydroxymethylpropyl cellulose
Polyethylene glycol
Titanium dioxide
Quinoline Yellow (E104 aluminium lake)
Sorbic acid

HOW SUPPLIED
Abbotic XL: Modified release tablet 500 mg List No. M299
Box, 1 blister @ 10 tablets
Reg. No.:DKL1700206414A1

Store at temperature not exceed 30°C and dry place area.
Protect from light.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
PT. Abbott Indonesia
Jl. Raya Jakarta Bogor km. 37
Depok 16415
Indonesia

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