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 or any of the excipients (see section 6.1). 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: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and *torsades de pointes* (see section 4.5).

Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).

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

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including *torsades de pointes* (see sections 4.4 and 4.5).

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

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.4).

Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine (see sections 4.4 and 4.5).

Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated.

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

4.4 Special Warnings and Precautions for Use

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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 to severe renal impairment (see section 4.3).

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile.* CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Colchicine

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 (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).

Cardiovascular Events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including *torsades de pointes*), clarithromycin should be used with caution in the following patients;

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Clarithromycin must not be given to patients with hypokalaemia or hypomagnesaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

<u>Pneumonia</u>

In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia.

In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

<u>Skin and soft tissue infections of mild to moderate severity</u>

These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed.

In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium*

minutissimum, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis and DRESS); clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

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

HMG-CoA Reductase Inhibitors (statins):
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathyIn situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered (see section 4.5).

Oral Hypoglycemic Agents/Insulin
The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended.

Oral Anticoagulants
There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, ~~and~~ apixaban and edoxaban, particularly to patients at high risk of bleeding (see section 4.5).

Excipients

Clarithromycin Modified Release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, ~~the Lapp~~ total lactase deficiency or glucose-galactose malabsorption should not take these medicines.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine

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).

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 fibrillation and *torsade de pointes* (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three 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.

Ergot alkaloids

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated (see section 4.3).

Oral Midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated (see section 4.3)

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

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

The use of clarithromycin is also contraindicated with ticagrelor, ivabradine and ranolazine metabolized mainly by CYP3A4 (see section 4.3).

Effects of Other Medicinal Products on Clarithromycin
Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14(R)-hydroxy-clarithromycin (14-OHclarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine
Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-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 CLCR 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see Bi-directional Drug Interactions).

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics

There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

CYP3A-based Interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)

The DOACs dabigatran and edoxaban are ~~is~~ a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil, and vardenafil

Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of

clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine

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

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other Drug Interactions

Colchicine

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 colchicine. Concomitant use of clarithromycin and colchicine is contraindicated (see sections 4.3 and 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

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 to allow for a 4-hour interval between each medication. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional Drug Interactions

Hydroxychloroquine and chloroquine

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 ml/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5).

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 frequent and common adverse reactions related to clarithromycin therapy for both adult population are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin MR.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Adverse Reactions Reported with Clarithromycin				
MedDRA System	**Very common**	**Common**	**Uncommon**	**Not Known* (cannot be**

Organ Class	≥ 1/10	≥ 1/100 to < 1/10	≥ 1/1,000 to < 1/100	estimated from the available data)
Infections and infestations			Candidiasis, vaginal infection, gastroenteritis	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia	Agranulocytosis, thrombocytopenia
Immune system disorders			Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram QT prolonged, palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders				Hemorrhage
Respiratory, thoracic and mediastinal disorder			Epistaxis	
Gastrointestinal disorders		Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Gastroesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discoloration

Hepatobiliary disorders		Liver function test abnormal	Alanine aminotransferase increased, aspartate aminotransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Pruritus, urticaria	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders			Myalgia	Rhabdomyolysis, myopathy
Renal and urinary disorders				Renal failure, nephritis interstitial
General disorders and administration site conditions			Asthenia	
Investigations				International normalised ratio increased, prothrombin time prolonged, urine color abnormal
* Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin. **In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).				

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional

gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Immunocompromised Patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

In adult patients, the most frequently reported adverse events by patients events treated with total doses of 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea rash, flatulence, headache, constipation, hearing disturbance, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) elevations. Additional low-frequency events included dyspepsia, insomnia, and dry mouth.

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. On the basis of this criteria, about 2 to 3% of these patients who received 1000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients also had elevated BUN levels.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pv.indonesia@abbott.com and/or pv-center@pom.go.id.

4.9 Overdose

Symptoms

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.

Treatment

Adverse 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

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide
ATC-Code: J01FA09

ABBOTIC® (Clarithromycin) is a semi-synthetic macrolide antibiotic obtained by substitution of a CH_3O group for the hydroxyl (OH) group at position 6 of 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.

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*. It is bactericidal to Helicobacter pylori; this activity of clarithromycin is greater at neutral pH than at acid pH. In vitro and in vivo data show this antibiotic has activity against clinically significant mycobacterial species. The in vitro data indicate Enterobacteriaceae, pseudomonas species and other non-lactose fermenting Gram-negative bacilli are not susceptible to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following micro- organisms both in vitro and in clinical infections as described in section 4.1:

Aerobic Gram-Positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae

Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella pneumophila

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

Mycobacteria
Mycobacterium leprae
Mycobacterium avium complex (MAC) consisting of: Mycobacterium avium
Mycobacterium Intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter
Helicobacter pylori
In cultures performed prior to therapy, *H. pylori* was isolated and clarithromycin MIC's were determined pre-treatment in 104 patients. Of these, four patients had resistant strains, two patients had strains with intermediate susceptibility, and 98 patients had susceptible strains. The following *in vitro* data are available, **but their clinical significance is unknown.** Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Viridans group streptococci

Aerobic Gram-negative microorganisms
Bordetella pertussis
Pasteurella multocida

Anaerobic Gram-positive microorganisms
Clostridium perfringens
Peptococcus niger

Propionibacterium acnes

Anaerobic Gram-negative microorganisms
Bacteroides melaninogenicus

Spirochetes
Borrelia burgdorferi

Campylobacter
Campylobacter jejuni

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.

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, while that of the 14-OH-clarithromycin was approximately 8.9 hours of the parent drug at the 1000 mg dose level was approximately 5.8 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%.

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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.

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. The 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 functions. 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. K elimination 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

Incompatibilities
Not applicable

Shelf life
Expiry date is indicated on the packaging

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

Nature and Contents of Container
Abbotic XL: Modified release tablet 500 mg List No. M299
Box, 1 blister @ 10 tablets
Reg. No.: DKL1700206414A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER
Prescription-Only Medicine

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

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INFORMASI UNTUK PASIEN
ABBOTIC XL TABLET 500 mg
(*Clarithromycin*)

Baca seluruh isi brosur ini secara seksama sebelum Anda mulai minum obat ini karena brosur ini berisi informasi penting bagi Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Hal ini dapat membahayakan mereka, bahkan jika gejalanya sama dengan Anda.
- Jika Anda mengalami efek samping, sampaikan kepada dokter atau apoteker Anda. Termasuk kemungkinan efek samping yang tidak tercantum di dalam brosur ini. Lihat bagian 4.

Apa yang ada di dalam brosur ini:

1. Apa yang dimaksud dengan tablet Abbotic XL dan apa kegunaannya?

Setiap butir tablet Abbotic XL mengandung 500 mg bahan aktif *Clarithromycin*. Abbotic XL termasuk dalam kelompok obat yang disebut antibiotik makrolida (*macrolide antibiotic*). Antibiotik menghentikan pertumbuhan bakteri yang menyebabkan infeksi. Tablet Abbotic XL digunakan untuk mengobati infeksi seperti:
1. Infeksi pernafasan, seperti bronkitis dan pneumonia
2. Infeksi tenggorokan dan sinus
3. Infeksi kulit dan jaringan ringan sampai sedang

Tablet Abbotic diindikasikan untuk orang dewasa.

2. Apa yang perlu Anda ketahui sebelum minum tablet Abbotic XL

Jangan minum tablet Abbotic XL 500mg jika Anda;
- mengetahui bahwa Anda **alergi** terhadap *clarithromycin*, antibiotik makrolida lainnya seperti erythromycin atau azithromycin, atau bahan lainnya di dalam tablet Abbotic.
- sedang mengonsumsi obat yang disebut tablet alkaloid ergot (misalnya *ergotamine* atau *dihydroergotamine*) atau menggunakan inhaler *ergotamine* untuk migrain.
- sedang mengonsumsi obat-obatan yang disebut *terfenadine* atau *astemizole* (banyak digunakan untuk *hay fever* atau alergi) atau *cisapride* atau *domperidone* (untuk gangguan lambung) atau *pimozide* (untuk masalah kesehatan mental) karena menggabungkan obat-obatan ini terkadang dapat menyebabkan gangguan serius pada irama jantung. Konsultasikan dengan dokter Anda untuk mendapat saran tentang obat-obatan alternatif.
- sedang mengonsumsi obat lain yang diketahui menyebabkan gangguan serius pada irama jantung.
- sedang mengonsumsi lovastatin atau simvastatin (penghambat reduktase HMG-CoA, umumnya dikenal sebagai statin, yang digunakan untuk menurunkan kadar kolesterol (sejenis lemak) dalam darah).
- sedang mengonsumsi *midazolam* oral (obat penenang).

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- sedang minum obat yang mengandung *lomitapide.*
- memiliki kadar kalium atau magnesium yang sangat rendah di dalam darah Anda (hipokalemia atau hipomagnesemia).
- memiliki penyakit hati yang **parah** dengan penyakit ginjal.
- atau seseorang di keluarga Anda memiliki riwayat gangguan irama jantung (*ventricular cardia arrhythmia*, termasuk *torsades de pointes*) atau kelainan elektrokardiogram (EKG, rekaman listrik jantung) yang disebut "sindrom long QT".
- sedang mengonsumsi obat yang disebut *ticagrelor*, *ivabradine*, atau *ranolazine* (untuk serangan jantung, nyeri dada, atau angina).
- sedang mengonsumsi *colchicine* (biasanya digunakan untuk gout/asam urat)
- sedang mengonsumsi obat jantung (untuk mengatasi aritmia, bradikardia, perpanjangan interval QT, penyakit jantung iskemik, atau gagal jantung kongestif).
- sedang mengonsumsi obat untuk gangguan elektrolit (hipokalemia atau hipomagnesemia).

Peringatan dan tindakan keselamatan
Bicarakan dengan dokter atau apoteker Anda sebelum minum tablet Abbotic XL 500mg:
- jika Anda memiliki masalah jantung (misalnya penyakit jantung, gagal jantung, detak jantung sangat lambat)
- jika Anda memiliki masalah hati atau ginjal
- jika Anda memiliki, atau rentan terhadap, infeksi jamur (misalnya sariawan)
- jika Anda hamil atau menyusui

Obat-obatan lain dan tablet Abbotic XL
Anda tidak boleh minum tablet Abbotic XL jika Anda sedang mengonsumsi salah satu obat yang tercantum di bagian “Jangan minum tablet Abbotic XL jika Anda” di atas;

Beritahu dokter atau apoteker Anda jika Anda sedang mengonsumsi, belum lama ini telah mengonsumsi, atau kemungkinan mengonsumsi obat-obatan lain karena dosis Anda mungkin perlu diubah atau mungkin Anda perlu melakukan tes rutin:
- *digoxin*, *quinidine* atau *disopyramide* (untuk masalah jantung)
- *warfarin*, atau antikoagulan lainnya, misalnya, *dabigatran*, *rivaroxaban*, *apixaban, edoxaban* (untuk pengencer darah)
- *carbamazepine, valproate, phenobarbital* atau *phenytoin* (untuk epilepsi)
- *atorvastatin, rosuvastatin* (inhibitor HMG-CoA reductase, yang umumnya dikenal sebagai *statin*, dan digunakan untuk menurunkan kadar kolesterol (sejenis lemak) di dalam darah). *Statin* dapat menyebabkan *rhabdomyolysis* (suatu kondisi yang menyebabkan kerusakan jaringan otot yang dapat mengakibatkan kerusakan ginjal) dan tanda-tanda miopati (nyeri otot atau kelemahan otot) harus dipantau.
- *nateglinide, pioglitazone, repaglinide, rosiglitazone* atau *insulin* (digunakan untuk menurunkan kadar glukosa darah)
- *gliclazide* atau *glimepiride* (sulfonilurea yang digunakan dalam pengobatan diabetes tipe II)
- *theophylline* (digunakan pada pasien dengan kesulitan bernapas, misalnya asma)
- *triazolam, alprazolam* atau *midazolam* (obat penenang) intravena ataupun oromukosa
- *cilostazol* (gangguan peredaran darah)
- *methadone* (digunakan dalam pengobatan kecanduan opioid)
- kortikosteroid (misalnya metilprednisolon), diberikan melalui mulut, melalui suntikan, atau dihirup (digunakan untuk membantu menekan sistem kekebalan tubuh - berguna dalam mengobati berbagai kondisi)
- *vinblastine* (untuk pengobatan kanker)
- *ciclosporin, sirolimus* dan *tacrolimus* (penekan kekebalan)

- *etravirine, efavirenz, nevirapine, ritonavir, zidovudine, atazanavir, saquinavir* (obat anti-virus yang digunakan dalam pengobatan HIV)
- *rifabutin, rifampicin, rifapentine, fluconazole, itraconazole* (digunakan dalam pengobatan infeksi bakteri tertentu)
- *tolterodine* (untuk kandung kemih yang terlalu aktif)
- *verapamil, amlodipine, diltiazem* (untuk tekanan darah tinggi)
- *sildenafil, vardenafil* dan *tadalafil* (untuk disfungsi ereksi pada pria dewasa atau untuk digunakan pada hipertensi arteri pulmonal (tekanan darah tinggi pada pembuluh darah paru-paru))
- *St John's Wort* (produk herbal yang digunakan untuk mengobati depresi)
- *quetiapine* atau obat antipsikotik lainnya
- obat makrolida lainnya, seperti *lincomycin* dan *clindamycin*
- *hydroxychloroquine* atau *chloroquine* (digunakan untuk mengobati kondisi-kondisi termasuk *rheumatoid arthritis*, atau untuk mengobati atau mencegah malaria). Mengonsumsi obat-obatan ini pada saat bersamaan dengan *clarithromycin* dapat meningkatkan peluang Anda mengalami efek samping yang mempengaruhi jantung Anda

Kehamilan dan menyusui
Jika Anda sedang hamil atau menyusui, merasa mungkin Anda hamil atau berencana untuk memiliki bayi, tanyakan kepada dokter atau apoteker Anda sebelum minum obat ini karena keamanan tablet Abbotic XL pada kehamilan dan menyusui belum diketahui.

Mengemudi dan Mengoperasikan Mesin:
Tablet Abbotic XL dapat membuat Anda merasa pusing atau mengantuk. Jika hal ini memengaruhi Anda, jangan mengemudi, mengoperasikan mesin, atau melakukan hal apapun yang mengharuskan Anda untuk waspada.

Tablet Abbotic XL mengandung laktosa. Obat ini mengandung laktosa, yakni sejenis gula. Jika Anda telah diberitahu bahwa Anda memiliki intoleransi terhadap gula, hubungi dokter Anda sebelum minum obat ini.

3. Cara minum tablet Abbotic XL

Selalu minum tablet Abbotic XL persis seperti yang diberitahukan oleh dokter Anda kepada Anda. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

Dosis yang dianjurkan untuk tablet Abbotic XL untuk orang dewasa adalah satu tablet 500 mg sekali sehari selama 7 sampai 14 hari.

Dokter Anda dapat meningkatkan dosis menjadi dua tablet 500 mg sehari pada infeksi berat. Tablet Abbotic XL harus diminum bersama dengan makanan dan harus ditelan utuh dan tidak boleh dikunyah.

Jika Anda minum tablet Abbotic XL lebih banyak dari yang seharusnya
Jika Anda secara tidak sengaja minum tablet Abbotic XL dalam satu hari lebih banyak daripada yang diberitahukan oleh dokter kepada Anda, atau jika seorang anak secara tidak sengaja menelan tablet ini, segera hubungi dokter Anda atau unit gawat darurat rumah sakit terdekat. Overdosis tablet Abbotic XL kemungkinan dapat menyebabkan muntah dan sakit perut.

Jika Anda lupa minum tablet Abbotic XL
Jika Anda lupa minum satu dosis tablet Abbotic XL, minumlah satu dosis segera setelah Anda ingat. Jangan minum tablet Abbotic XL dalam satu hari lebih banyak dari yang disarankan oleh dokter Anda.

Jika Anda berhenti minum tablet Abbotic XL
Jangan berhenti minum tablet Abbotic XL, meskipun Anda sudah merasa sehat. Penting untuk minum tablet ini selama yang telah diberitahukan oleh dokter kepada Anda, jika tidak maka masalahnya mungkin akan kembali. Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Kemungkinan efek samping
Seperti halnya semua obat, tablet Abbotic XL dapat menyebabkan efek samping meskipun tidak semua orang mengalaminya.

Jika Anda menderita salah satu dari hal berikut ini selama pengobatan Anda, HENTIKAN MINUM tablet Anda dan segera hubungi dokter Anda:
- diare parah atau berkepanjangan, yang mungkin disertai darah atau lendir di dalamnya. Diare dapat terjadi lebih dari dua bulan setelah pengobatan dengan *clarithromycin*, dalam hal ini Anda harus tetap menghubungi dokter Anda.
- ruam, kesulitan bernapas, pingsan atau pembengkakan pada wajah, lidah, bibir, mata dan tenggorokan. Ini adalah tanda bahwa Anda mungkin mengalami reaksi alergi.
- kulit menguning (sakit kuning/ *jaundice*), iritasi kulit, tinja berwarna pucat, urin berwarna gelap, rasa sakit pada saat penekanan daerah perut atau tidak nafsu makan. Ini adalah tanda-tanda bahwa hati Anda mungkin mengalami peradangan dan tidak berfungsi dengan baik.
- Reaksi kulit yang parah seperti melepuh yang menyakitkan pada kulit, mulut, bibir, mata, dan alat kelamin (gejala reaksi alergi yang jarang terjadi yang disebut sindrom Stevens-Johnson/nekrolisis epidermal toksik).
- ruam, memerah dan bersisik dengan benjolan di bawah kulit dan melepuh (gejala pustulosis eksantematosa). Frekuensi efek samping ini tidak diketahui (tidak dapat diperkirakan dari data yang tersedia).
- reaksi alergi kulit yang jarang yang menyebabkan penyakit parah dengan ulserasi pada mulut, bibir dan kulit yang menyebabkan sakit parah dengan ruam, demam dan radang organ dalam (DRESS).
- nyeri otot atau kelemahan otot yang dikenal sebagai *rhabdomyolysis* (suatu kondisi yang menyebabkan kerusakan jaringan otot yang dapat mengakibatkan kerusakan ginjal).

Efek samping lainnya

Efek samping yang umum (dapat mempengaruhi hingga 1 dari 10 orang) meliputi:

- sulit tidur
- perubahan indera perasa
- sakit kepala
- pelebaran pembuluh darah
- masalah perut seperti mual, muntah, sakit perut, gangguan pencernaan, diare
- keringat meningkat

Efek samping yang tidak umum (dapat meliputi hingga 1 dari 100 orang) termasuk:

- suhu tinggi
- pembengkakan, kemerahan atau gatal pada kulit
- ‘sariawan’ mulut atau vagina (infeksi jamur)
- radang lambung dan usus

- penurunan kadar trombosit darah (trombosit darah membantu menghentikan pendarahan)
- penurunan jumlah sel darah putih (leukopenia)
- penurunan neutrofil (*neutropenia*)
- kekakuan sendi
- menggigil
- peningkatan eosinofil (sel darah putih yang terlibat dalam imunitas)
- respon imun yang berlebihan terhadap zat asing
- nafsu makan kurang atau hilang
- kecemasan, kegugupan
- mengantuk, lelah, pusing atau gemetar
- gerakan otot secara tidak sadar
- *vertigo*
- telinga berdengung atau hilang pendengaran
- nyeri dada atau perubahan irama jantung seperti jantung berdebar atau detak jantung tidak teratur
- asma: penyakit paru-paru yang berhubungan dengan penyempitan saluran udara, yang membua sulit bernapas
- mimisan
- penggumpalan darah yang menyebabkan penyumbatan mendadak pada arteri paru (emboli paru)
- radang selaput kerongkongan (esofagus) dan selaput perut
- nyeri dubur
- kembung, sembelit, masuk angin, bersendawa
- mulut kering
- situasi dimana empedu (cairan yang diproduksi oleh hati dan disimpan di kantong empedu) tidak dapat mengalir dari kantong empedu ke duodenum (*cholestasis*)
- radang kulit yang ditandai dengan adanya bula (benjolan) berisi cairan, ruam gatal dan nyeri, kejang otot, nyeri otot atau hilangnya jaringan otot. Jika anak Anda menderita *myasthenia gravis* (kondisi dimana otot menjadi lemah dan mudah lelah), *clarithromycin* dapat memperburuk gejala ini.
- meningkatnya nilai dari pemeriksaan fungsi ginjal dan hati yang abnormal dan peningkatan kelainan hasil tes darah
- merasa lemah, lelah dan tidak bertenaga

Efek samping yang belum diketahui (frekuensinya tidak dapat diperkirakan dari data yang tersedia):
- radang usus besar
- infeksi bakteri pada lapisan luar kulit
- penurunan tingkat sel darah tertentu (yang dapat membuat infeksi lebih mungkin terjadi atau meningkatkan risiko memar atau pendarahan)
- kebingungan, kehilangan arah, halusinasi (melihat sesuatu), perubahan rasa realita atau panik, depresi, mimpi tidak normal atau mimpi buruk dan mania (perasaan gembira atau terlalu bersemangat)
- kejang (sawan)
- kesemutan (*paraesthesia*), yang lebih dikenal sebagai '*pins and needles*'
- kehilangan rasa atau penciuman atau ketidakmampuan untuk mencium dengan benar
- jenis gangguan irama jantung (*Torsade de pointes*, *ventricular tachycardia*)
- kehilangan darah (*haemorrhage*)
- radang pankreas
- perubahan warna pada lidah atau gigi
- jerawat

- perubahan kadar produk yang dihasilkan oleh ginjal, radang ginjal atau ketidakmampuan ginjal untuk berfungsi dengan baik (Anda mungkin merasakan kelelahan, terjadi pembengkakan atau bengkak di wajah, perut, paha atau pergelangan kaki atau masalah dengan buang air kecil)

Pelaporan efek samping
Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker Anda. Ini mencakup kemungkinan efek samping yang tidak tercantum dalam brosur ini. Anda juga dapat melaporkan efek samping secara langsung ke: pv.indonesia@abbott.com

Dengan melaporkan efek samping Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara menyimpan tablet Abbotic XL

Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.
Jangan menggunakan tablet ini setelah tanggal kedaluwarsanya (exp.) yang tercetak di kemasan blister. Simpan pada temperatur tidak melebihi 30°C dan di tempat yang kering. Simpan di dalam kemasan aslinya.

Jangan membuang obat melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang tidak Anda gunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa yang terkandung di dalam tablet Abbotic XL
Setiap tablet Abbotic XL mengandung 500 mg bahan aktif *clarithromycin*.
Bahan lainnya adalah: asam sitrat, natrium alginat, natrium kalsium alginat, laktosa, povidone, talkum, asam stearat, magnesium stearat, *hidroksimetilpropil selulosa*, polietilen glikol, titanium dioksida, asam sorbat, *quinoline yellow* (*aluminium lake* E104).

Seperti apa penampakan tablet Abbotic XL dan isi kemasan
Tablet Abbotic XL adalah tablet bersalut berwarna kuning, oval, *modified release tablets*.
Box, 1 blister @ 10 tablets
Reg. No.: DKL1700206414A1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
PT Abbott Indonesia
Jl. Raya Jakarta Bogor Km. 37
Depok, Indonesia

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