Preparation for Use
To yield the reconstituted suspension, the concentration of clarithromycin is 250 mg per 5 mL.

When the appropriately indicated amount of water is added (see Clinical Experience in Patients with Mycobacterial Infections), an appropriately indicated amount of water is administered as 7.5, 15, or 30 mg/kg/day in two divided doses. Some statistically significant clinical improvement was observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and dilatation of bile ducts was observed. No deaths occurred and no changes in the general condition of the animals were noted.

In juvenile beagle dogs, three weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, treatments of approximately 20, 60, 180, and 540 mg/kg were administered. Clinical observations of drug-related toxicity were recorded. These treatments were carried out on the basis of the presumed maximum human clinical dose of 500 mg b.i.d. (approximately 20 mg/kg b.i.d. for a 70 kg human patient). No unique hazard to the conceptus was noted. A mortality of 30% in the 30 mg/kg group was noted. Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 2.5 to 5 times the upper range of the usual daily human dose (500 mg b.i.d.) and, at these doses, maternal toxicity was noted. These findings were attributed to maternal toxicity at very high doses of clarithromycin, but not at 35 times the upper range of the usual daily human dose (500 mg b.i.d.), suggesting that the species specificity may play a role in the development of embryonic toxicity.

In a study in pregnant monkeys at gestation day 20, this effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant beagle dogs at approximately 10 times the upper range of the usual daily human dose (500 mg b.i.d.) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 70 times the upper range of the usual daily human dose), no embryonic toxicity was noted. These findings are consistent with the lack of embryonic toxicity in humans and the Japanese population.

In a study in pregnant mice, a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human dose (500 mg b.i.d.) was noted. The results of these studies provided no evidence of mutagenic potential at drug concentrations up to 500 mg b.i.d. for non-mycobacterial infections. The usual duration of treatment is for 5 to 10 days depending on the severity of the condition. The prepared suspension can be taken with or without meals, and can be stored for 1 month at room temperature or 1 year if refrigerated, but not frozen.

Dosage Guide for Pediatric Patients

<table>
<thead>
<tr>
<th>Weight (mg)</th>
<th>1.0</th>
<th>2.5</th>
<th>5.0</th>
<th>7.5</th>
<th>12.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>12-19</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>20-29</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>30-40</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

In children with creatinine clearance less than 30 ml/min/1.73 m², the dosage of clarithromycin should be reduced by one-half, i.e., 7.5 mg/kg b.i.d. to a maximum of 500 mg b.i.d. for non-mycobacterial infections. The usual duration of treatment is for 5 to 10 days depending on the severity of the condition. The prepared suspension can be taken with or without meals, and can be stored for 1 month at room temperature or 1 year if refrigerated, but not frozen.

Manufactured by: Abbott Laboratories (Pakistan) Ltd.

Lahore, Karachi

01-226R4

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DRUG INTERACTIONS

Be considered.

Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should

other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports

HMG-CoA Reductase Inhibitors

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see

HMG-CoA Reductase Inhibitors

clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is

The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome

clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated

These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to

this medicine.

Clarithromycin Granules for Oral Suspension (Adult Sachet, Pediatric Suspension) contains sucrose. Patients with rare

risk for ventricular arrhythmias (including torsades de pointes), clarithromycin should be used with caution in the following

Prolongation of the QT Interval

intravenous or oromucosal midazolam (see

with renal or hepatic impairment (see

and clarithromycin concomitantly. Concomitant administration of clarithromycin and colchicine is contraindicated in patients

Clarithromycin should not be used concomitantly with colchicine.

Drug-dose interactions

Drugs that are inactivates CYP3A by phase 2 enzymes, such as barbiturates, phenytoin, or phenobarbital. In this group, Warfarin may reduce the anticoagulant effect of oral anticoagulants or its need for warfarin. Oral contraceptives, on the other hand, can increase the levels and actions of oral contraceptives. Oral contraceptives, on the other hand, can increase the levels and actions of oral contraceptives. However, clopidogrel and ranitidine do not appear to interfere with the metabolism of clarithromycin. Therefore, coadministration of these drugs is not expected to result in any clinically significant drug interactions.

Similarly, the concomitant use of clarithromycin with other antifungal agents (e.g., fluconazole) has been reported to cause an increase in the levels of these antifungal agents. The concomitant use of clarithromycin with rifabutin has been shown to increase the levels of rifabutin and decrease the levels of clarithromycin, resulting in a potential for drug interactions.

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 with HMG-CoA reductase inhibitors is considered in patients at increased risk for cardiovascular events.

CONTRAINDICATIONS

oral midazolam and clarithromycin is contraindicated. (see

Oral Midazolam

clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme

Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme

Clarithromycin is a substrate for human cytochrome P450 3A (CYP3A). This enzyme is involved in the metabolism of many drugs and is highly expressed in the intestinal wall and liver. Clarithromycin is metabolized through the CYP3A pathway, which involves the formation of a metabolite, 14-deoxycaritromycin. This metabolite is then further metabolized to form 14-demethoxyclarithromycin. These metabolites are then excreted in the urine.

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Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome
**Bi-directional Drug Interactions**

Increased serum levels of clarithromycin have been reported when administered concomitantly with drugs that are substrates for CYP3A4 and the P-glycoprotein (Pgp) efflux transporter.

**Digoxin**

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. There is a risk of digoxin toxicity in patients taking clarithromycin. The American College of Cardiology and American Heart Association (ACC/AHA) recommend allowing for a 4-hour interval between each medication.

**Colchicine**

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. Other macrolides also inhibit Pgp and may increase the risk of colchicine toxicity.

**Other Drug Interactions**

- Clarithromycin may increase the risk of dizziness and vertigo in patients taking other medications that cause these side effects.
- Clarithromycin may interact with other drugs that are metabolized by the cytochrome P450 (CYP) system, potentially increasing plasma concentrations of those drugs.
- Clarithromycin can increase the risk of drug interactions with other medications, especially those that are dependent on CYP3A for their metabolism.
- Clarithromycin can interact with drugs that are substrates or inhibitors of CYP3A, leading to increased or decreased plasma concentrations of the interacting drugs.

**ADVERSE REACTIONS**

The most common adverse reactions associated with clarithromycin therapy are gastrointestinal and disulfiram-like reactions. Other rare adverse reactions include liver function test abnormalities, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**Pregnancy/Infant**

Pregnancy Category B: No evidence of risk in humans. Clarithromycin is not known to cause birth defects. According to animal studies, there is no evidence of harm; no specific information is available on use in pregancy.

**Lactation**

It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman.

**Drug Interactions**

- **P-Glycoprotein (Pgp)**: Clarithromycin is a substrate for Pgp and can increase the plasma concentrations of other Pgp substrates.
- **CYP3A**: Clarithromycin is an inhibitor of CYP3A, leading to increased plasma concentrations of other CYP3A substrates.
- **Other Enzymes and Transporters**: Clarithromycin can inhibit or induce other enzymes and transporters, leading to potential drug interactions.

**Drug Administration and Dosage**

- **Adults**: 500 mg orally twice daily for 10 days, followed by 500 mg orally once daily for 21 days.
- **Children**: 12 mg/kg orally twice daily for 10 days, followed by 12 mg/kg orally once daily for 21 days.

**Pharmacokinetics**

- **Oral Absorption**: Clarithromycin is well absorbed following oral administration, with a bioavailability of about 50%.
- **Distribution**: Clarithromycin is widely distributed to tissue and fluids, achieving high concentrations in the middle ear, lungs, and saliva.
- **Metabolism**: Clarithromycin is metabolized mainly by the liver, with a small fraction excreted unchanged in the urine.
- **Elimination**: Clarithromycin is eliminated primarily by hepatic metabolism and biliary excretion, with a terminal half-life of about 30 hours.

**Table: Adverse Reactions Reported in Clinical Trials**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Embolism 1, cardiac arrest 1, atrial fibrillation 1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Gastroenteritis 2, infection 3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain 4, constipation 1, tongue discoloration, pancreatitis acute</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Acne, rash, vitiligo, pruritus</td>
</tr>
<tr>
<td>Hematological</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Central Nervous</td>
<td>Somnolence, dizziness 1, vertigo, hearing impaired, tinnitus, abnormal dreams, mania, depression, insomnia 1, mania, depersonalisation, depression, insomnia 1, mania, depersonalisation</td>
</tr>
<tr>
<td>Other</td>
<td>Hemorrhage 1, ventricular fibrillation</td>
</tr>
</tbody>
</table>

**Notes**

1. Observed in ≥ 1/100 patients
2. Observed in ≥ 1/1,000 patients
3. Observed in < 1/10,000 patients
4. Observed in < 1/100,000 patients
Albumin–globulin ratio abnormal

Staphylococcus aureus

Aerobic Gram-Positive microorganisms

vitro and in clinical infections as described in the pseudomonas species and other non-lactose fermenting Gram-negative bacilli are not susceptible to clarithromycin. show this antibiotic has activity against clinically significant mycobacterial species. The in vitro data indicate Enterobacteriaceae,

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

PHARMACOLOGIC PROPERTIES

and all other appropriate supportive measures should be instituted.

patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously

Additional low-frequency events included dyspnea, insomnia, and dry mouth.

In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1000 mg of

mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration

the granules formulation. Clarithromycin was found to be two to ten

Borrelia burgdorferi

The principal metabolite of clarithromycin in man and other primates is a microbiologically- active metabolite, 14-OH-

7