1. NAME OF THE MEDICINAL PRODUCT

Trademark 250 mg, Immediate-Release Tablets (IR)
Trademark 500 mg, Immediate-Release Tablets (IR)
Trademark 125 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension)
Trademark 250 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension)
Trademark 250 mg Granules for Oral Suspension (Adult Sachet)
Trademark 500 mg Granules for Oral Suspension (Adult Sachet)
Trademark 500 mg, Powder for Intravenous Solution for Injection (IV)*
Trademark 500 mg, Modified-Release Tablets (MR)
Trademark 500 mg, Extended-Release Tablets (ER)

* This product may be supplied with Water for Injection

Trademark is authorized as
Abbotic, Biaxin, Clarith, Cyllind, Biclar, Heliklar, Klacid, Klaricid, Kofron, Maclar, Mavid, Naxy, Zeclar Clacee, Makcin.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Clarithromycin 250 mg, Immediate-Release Tablet:**
One tablet contains 250 mg Clarithromycin.
Tablet sodium content: 3.4 mg per tablet

**Clarithromycin 500 mg, Immediate-Release Tablet:**
One tablet contains 500 mg Clarithromycin.
Tablet sodium content: 6.1 mg per tablet

**Clarithromycin 125 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension):**
Each 5 ml of the granules for suspension contains 125 mg of clarithromycin.
Excipient: Sucrose 550 mg/ml

**Clarithromycin 250 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension):**
Each 5 ml of the granules for suspension contains 250 mg of clarithromycin.
Excipient: Sucrose 455 mg/ml

**Clarithromycin 250 mg Granules for Oral Suspension (Adult Sachet)**
Each sachet contains 250 mg of clarithromycin.
Excipient: Sucrose: 1591 mg per sachet

**Clarithromycin 500 mg Granules for Oral Suspension (Adult Sachet)**
Each sachet contains 500 mg of clarithromycin.
Excipient: Sucrose: 3182 mg per sachet

**Clarithromycin 500 mg Powder for Intravenous Solution for Injection**
One vial contains 500 mg of clarithromycin.

**Clarithromycin 500 mg, Modified-Release Tablets:**
One tablet contains 500 mg Clarithromycin.
Excipient: Lactose 115 mg per tablet
Tablet sodium content: 15.3 mg per tablet
Clarithromycin 500 mg, Extended-Release Tablets:
One tablet contains 500 mg Clarithromycin.
Excipient: Lactose 260 mg per tablet

All formulations:
For the full list of excipients, see section 6.1.

[Note: Where local formulations deviate from those in this CCDS, the information related to the
excipients is to be adapted accordingly.]

3. PHARMACEUTICAL FORM

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Pharmaceutical Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin IR Tablets</td>
<td>Yellow, ovaloid film-coated tablet</td>
</tr>
<tr>
<td>Clarithromycin Granules for Oral Suspension</td>
<td>White to off-white granules for suspension</td>
</tr>
<tr>
<td>Clarithromycin IV</td>
<td>White to off-white caked, lyophilized powder</td>
</tr>
<tr>
<td>Clarithromycin MR Tablets</td>
<td>Yellow, ovaloid film-coated tablet</td>
</tr>
<tr>
<td>Clarithromycin ER Tablets</td>
<td>Pale yellow to yellow film-coated tablet debossed on one side with the Abbott logo and a two-letter Abbo-code designation, LC or KJ</td>
</tr>
</tbody>
</table>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin is indicated for treatment of infections due to susceptible organisms in adults and children 12 years and older [adult only formulations, e.g. tablets, IV, adult granules] / in children 6 months to 12 years [pediatric oral suspension]. Such infections include:

<table>
<thead>
<tr>
<th></th>
<th>IR</th>
<th>Granules (Adults)</th>
<th>Granules (Pediatric)</th>
<th>IV</th>
<th>MR</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infections (e.g., bronchitis, pneumonia) (see section 4.4 and 5.1 regarding Sensitivity Testing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Upper respiratory tract infections (e.g., pharyngitis, sinusitis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas) (see section 4.4 and 5.1 regarding Sensitivity Testing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disseminated or localized mycobacterial infections due to Mycobacterium avium or Mycobacterium intracellulare. Localized infections due to Mycobacterium cheloneae, Mycobacterium fortuitum, or Mycobacterium kansasii</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clarithromycin is indicated for the prevention of disseminated Mycobacterium avium complex infection in HIV-infected patients with CD4 lymphocyte counts less than or equal to 100/mm3</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Clarithromycin in the presence of acid suppression is also indicated for the eradication of H. pylori resulting in</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**COMPANY CORE DATA SHEET**

**Clarithromycin**

**Date of approval:** 25 APR 2018  
**Date of previous approval:** 10 FEB 2017

### 4.2 Posology and method of administration

**Clarithromycin IR**

**Adults**

The usual recommended dosage of clarithromycin in adults and children 12 years of age or older, is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 5 to 14 days, excluding treatment of community acquired pneumonia and sinusitis which require 6 to 14 days of therapy.

Dosage in patients with mycobacterial infections: The recommended dose for adults with mycobacterial infections is 500 mg b.i.d.

Treatment of disseminated MAC infections in AIDS patients should be continued, as long as clinical and microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Treatment of other nontuberculous mycobacterial infections should continue at the discretion of the physician.

Dosage for MAC prophylaxis: The recommended dosage of clarithromycin in adults is 500 mg twice daily.

In the treatment of odontogenic infections, the dosage of clarithromycin is one 250 mg tablet twice daily for five days.

In patients with peptic ulcer due to *H. pylori* infection, clarithromycin can be administered in a dose of 500mg twice daily in combination with other appropriate anti-microbial treatments and a proton pump inhibitor for 7-14 days in consultation with national or international guideline recommendations for *H. pylori* eradication.

**Renal Impairment**

In patients with renal impairment with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced by one-half, *i.e.*, 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

**Pediatric Population**

The use of clarithromycin IR has not been studied in children less than 12 years of age.
Clarithromycin Granules for Oral Suspension

Adult Sachet

Adults and children 12 years of age and older

Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

Patients with respiratory tract/skin and soft tissue infections

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

Eradication of \( \text{H. pylori} \) in patients with duodenal ulcers (Adults)

In patients with peptic ulcer due to \( \text{H. pylori} \) infection, clarithromycin can be administered in a dose of 500mg twice daily in combination with other appropriate anti-microbial treatments and a proton pump inhibitor for 7-14 days in consultation with national or international guideline recommendations for \( \text{H. pylori} \) eradication.

Odontogenic Infections

In the treatment of odontogenic infections, the usual dosage of clarithromycin adult sachets is 250 mg twice daily for 5 days.

Elderly Population

As for adults.

Renal impairment

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

Pediatric Suspension

Pediatric Patients under 12 years of age

Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension (granules for oral suspension).

The recommended daily dosage of Clarithromycin Pediatric Suspension (125 mg/5 ml or 250 mg/5 ml) in children is 7.5 mg/kg b.i.d. up to a maximum dose of 500 mg b.i.d. for non-mycobacterial infections. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. The prepared suspension can be taken with or without meals, and can be taken with milk.

The following table is a suggested guide for determining dosage, based on the weight of the child and the concentration of the suspension (125 mg/5 ml or 250 mg/5 ml).
COMPANY CORE DATA SHEET
Clarithromycin

Date of approval: 25 APR 2018
Date of previous approval: 10 FEB 2017

DOSAGE GUIDELINES FOR PEDIATRIC PATIENTS
Based on Body Weight

<table>
<thead>
<tr>
<th>Weight *</th>
<th>7.5 mg/kg b.i.d. dosage in ml given twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kg</td>
<td>125 mg/5 ml</td>
</tr>
<tr>
<td>8-11</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>12-19</td>
<td>5 ml</td>
</tr>
<tr>
<td>20-29</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>30-40</td>
<td>10 ml</td>
</tr>
</tbody>
</table>

* Children < 8 kg or < 18 lbs. should be dosed on a per kg or per lb. basis (approx. 7.5 mg/kg b.i.d. or 3.4 mg/lb b.i.d.)

Dosage in Patients with Mycobacterial Infections
In children with disseminated or localized mycobacterial infections (M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii), the recommended dose is 7.5 to 15 mg/kg clarithromycin b.i.d., not exceeding a maximum dose of 500 mg b.i.d.

Treatment with clarithromycin should continue as long as clinical benefit is demonstrated. The addition of other antimycobacterial agents may be of benefit.

DOSAGE GUIDELINES FOR PEDIATRIC PATIENTS WITH MYCOBACTERIAL INFECTIONS
Based on Body Weight

<table>
<thead>
<tr>
<th>Weight *</th>
<th>Dosage in ml given twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kg</td>
<td>(CLARITHROMYCIN 125 mg/5 ml)</td>
</tr>
<tr>
<td></td>
<td>7.5 mg/kg b.i.d.</td>
</tr>
<tr>
<td></td>
<td>15 mg/kg b.i.d.</td>
</tr>
<tr>
<td>8-11</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>12-19</td>
<td>5 ml</td>
</tr>
<tr>
<td>20-29</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>30-40</td>
<td>10 ml</td>
</tr>
</tbody>
</table>

* Children < 8 kg (18 lbs.) should be dosed on a per kg or per lb basis (7.5 to 15 mg/kg b.i.d or 3.4 to 6.8 mg/lb b.i.d.)

Renal Impairment
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., up to 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Preparation for Use
See section 6.6.

Clarithromycin IV

Adults
The recommended dosage of clarithromycin I.V. in adults 18 years of age or older is 1.0 g daily, divided into two equal doses, each infused after further dilution with an appropriate I.V. diluent, over a 60-minute time period. At the present time, there are no data supporting intravenous use of clarithromycin in children. Clarithromycin should not be given as a bolus or an intramuscular injection.
Dosage in Patients with Mycobacterial Infections
Although there currently is no data regarding use of clarithromycin I.V. in immunocompromised patients, data are available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localized infections (M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii), the recommended treatment, in adults, is 1000 mg/day in two divided doses.

Intravenous therapy may be limited for up to two to five days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

Renal Impairment
In patients with renal impairment who have creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Pediatric population
There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 12 years of age (see Pediatric Suspension).

In adolescents (12-18 yrs), dosing is as for adults.

Preparation for Use
See section 6.6.

Clarithromycin MR

Adults
The usual recommended dosage of clarithromycin MR tablets in adults and children 12 years of age or older 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 5 to 14 days, excluding treatment of community acquired pneumonia and sinusitis which require 6 to 14 days therapy.

Odontogenic Infections
In the treatment of odontogenic infections, the usual dosage of clarithromycin MR is one 500 mg tablet once daily for 5 days.

Do not crush or chew clarithromycin modified release tablets.

Renal Impairment
In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the usual recommended dose is 250 mg once daily. Because the modified-release tablet cannot be split, instead immediate-release tablets should be used. In more severe infections, the recommended dose is one 500 mg modified-release tablet once daily. No dose adjustment is required for patients with moderate renal impairment (creatinine clearance 30 to 60 ml/min).

Pediatric population
The use of clarithromycin MR has not been studied in children less than 12 years of age.

Clarithromycin ER

Adults
The recommended doses for clarithromycin ER in adults and children 12 years of age or older are presented in the following table.
Clarithromycin ER tablets should be taken once daily with food.

Tablets should be swallowed whole and not chewed, broken or crushed.

The doses presented in the following table were found to be efficacious in clinical studies with clarithromycin ER. Total daily doses for other indications would be equivalent to clarithromycin IR doses.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute maxillary sinusitis</td>
<td>1000 mg</td>
<td>14 days</td>
</tr>
<tr>
<td>AECB</td>
<td>500 to 1000 mg</td>
<td>5 to 7 days</td>
</tr>
<tr>
<td>CAP</td>
<td>1000 mg</td>
<td>7 days</td>
</tr>
<tr>
<td>Pharyngitis/Tonsillitis</td>
<td>500 mg</td>
<td>5 days</td>
</tr>
</tbody>
</table>

**Elderly population**

In the absence of severe renal impairment (creatinine clearance (CL\(_{CR}\)) less than 30 ml/min), use the same doses as in *Adults* section.

**Renal Impairment**

The maximum daily dose for patients with severe renal impairment (< CL\(_{CR}\) 30 ml/min) is 500 mg. No dose adjustment is required for patients with moderate renal impairment (CL\(_{CR}\) 30 to 60 ml/min).

**Hepatic Impairment**

Based on studies done with clarithromycin IR, no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

**Pediatric population**

The use of clarithromycin ER has not been studied in children less than 12 years old.

### 4.3 Contraindications

**All Formulations**

Hypersensitivity to macrolide antibiotic drugs or any of the excipients (see section 6.1).

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 hypokalemia (risk of prolongation of QT-time).

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 or ranolazine is contraindicated.

[Note: Where local formulations deviate from those in this CCDS, the information related to the excipients including any contraindications is to be adapted accordingly.]

4.4 Special warnings and precautions for use

IR and Adult Sachet

Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms.

All Formulations

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 excreted 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.

Caution is advised in patients with severe renal insufficiency.

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. *Clostridium 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
- Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (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).

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.

**Pneumonia**
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.

**Skin and soft tissue infections of mild to moderate severity**
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 myopathy. 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 (see 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.

Excipients
Clarithromycin Granules for Oral Suspension (Adult Sachet, Pediatric Suspension) contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

When prescribing to diabetic patients, the sucrose content should be taken into account.

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

Clarithromycin Modified Release tablets contain 15.3 mg sodium per tablet. If patients receive two Modified Release tablets once daily, the resulting sodium amount (in total 30.6 mg per dose) should be taken into consideration for patients on a controlled sodium diet.

[Note: Where local formulations deviate from those in this CCDS, the information related to the excipients including any warnings is to be adapted accordingly.]

4.5 Interaction with other medicinal products and other forms of interaction

All Formulations

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 increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see 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 metabolite 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**
Postmarketing 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.

**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 inhibitor 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-OH-clarithromycin), 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 (C$_{\text{min}}$) 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 C$_{\text{max}}$ increased by 31%, C$_{\text{min}}$ 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 CL$_{\text{Cr}}$ 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CL$_{\text{Cr}}$ <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.

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 hypoglycemia 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.

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), atypical antipsychotics (e.g. quetiapine), pimozone, 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.

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 ($C_{\text{max}}$, $AUC_{0-24}$, 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 dideoxynosine. 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**

**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 co-administered 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 Pregnancy and lactation**

**Pregnancy**
The safety of clarithromycin use during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

**Breastfeeding**
The safety of clarithromycin use during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

**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 and pediatric populations 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 IR, granules for oral suspension, IV, MR and ER.

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.

<table>
<thead>
<tr>
<th>Adverse Reactions Reported with Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedDRA System Organ Class</td>
</tr>
<tr>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
</tr>
<tr>
<td>Immune system disorders</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
</tr>
<tr>
<td>Cardiac disorders</td>
</tr>
</tbody>
</table>
### Adverse Reactions Reported with Clarithromycin

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Very common ≥ 1/10</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1,000 to &lt; 1/100</th>
<th>Not Known* (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>electrocardiogram QT prolonged, extrasystoles¹, palpitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tachycardia, ventricular fibrillation</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasodilation¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea, vomiting, dyspepsia, nausea, abdominal pain</td>
<td>Esophagitis¹, gastrooesophageal reflux disease², gastritis, proctalgia², stomatitis, glossitis, abdominal distension⁴, constipation, dry mouth, eructation, flatulence</td>
<td>Pancreatitis acute, tongue discoloration, tooth discoloration</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Liver function test abnormal</td>
<td>Cholestasis⁴, hepatitis⁴, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased⁴</td>
<td>Hepatic failure, jaundice hepatocellular</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash, hyperhidrosis</td>
<td>Dermatitis bullous¹, pruritus, urticaria, rash maculo-papular³</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Muscle spasms³, musculoskeletal stiffness¹, myalgia²</td>
<td></td>
<td>Rhabdomyolysis², <strong>myopathy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Blood creatinine increased¹, blood urea</td>
<td></td>
<td>Renal failure, nephritis interstitial</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Reactions Reported with Clarithromycin

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Very common ≥ 1/10</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1,000 to &lt; 1/100</th>
<th>Not Known* (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site phlebitis¹</td>
<td>Injection site pain¹, injection site inflammation¹</td>
<td>Malaise⁴, pyrexia¹, asthenia, chest pain¹, chills⁴, fatigue⁴</td>
<td>International normalised ratio increased, prothrombin time prolonged, urine color abnormal</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>Albumin globulin ratio abnormal¹, blood alkaline phosphatase increased⁴, blood lactate dehydrogenase increased⁴</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

¹ADRs reported only for the Powder for Solution for Injection formulation
²ADRs reported only for the Extended-Release Tablets formulation
³ADRs reported only for the Granules for Oral Suspension formulation
⁴ADRs reported only for the Immediate-Release Tablets formulation

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.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

**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 treated with total daily doses of 1000 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 dyspnea, 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.
4.9 Overdose

**Symptoms**
Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight 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 levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

In the case of overdosage, clarithromycin I.V. should be discontinued and all other appropriate supportive measures should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

**All Formulations**

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of a CH$_3$O group for the hydroxyl (OH) group at position 6 of the erythromycin lactonic ring. Specifically clarithromycin is 6-O-methyl erythromycin A. The white to off-white antibiotic powder is bitter, 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 excellent *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 (MIC's) of clarithromycin are generally one log$_2$ dilution more potent than the MIC's of erythromycin.

*In vitro* data also indicate clarithromycin has excellent 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
Listeria monocytogenes

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 kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
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
Streptococci (Group C,F,G)
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*

*Treponema pallidum*

**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.)

Please reference your country or region specific information regarding absolute breakpoints ranges for susceptible, resistant and intermediate susceptibility.

**Clinical Studies**

**Clarithromycin IR**

*Helicobacter pylori* is strongly associated with peptic ulcer disease. Ninety (90) to 100% of patients with duodenal ulcers are infected with this pathogen. Eradication of *H. pylori* has been shown to reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.

**Triple Therapy in Duodenal Ulcer Disease**

In a well controlled double blind study, *H. pylori* infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg b.i.d., amoxicillin 1000 mg b.i.d. and omeprazole 20 mg daily for ten days or dual therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for 14 days. *H.*...
**COMPANY CORE DATA SHEET**

**Clarithromycin**

Date of approval: 25 APR 2018

Date of previous approval: 10 FEB 2017

**pylori** was eradicated in 90% of the patients receiving clarithromycin triple therapy and in 60% of the patients receiving dual therapy.

In an independent study *H. pylori* infected patients received eradication therapy with clarithromycin 500 mg b.i.d. in conjunction with amoxicillin 1000 mg b.i.d. and omeprazole 20 mg daily (Group A) or omeprazole 20 mg b.i.d. (Group B) for seven days. In those patients not previously treated with anti-*H. pylori* therapy, *H. pylori* was eradicated in 86% (95% CI=69-95) of patients in Group A and 75% (95% CI=62-85) of patients in Group B, the difference was not statistically significant.

In an open-label study *H. pylori* infected patients with duodenal ulcer or non ulcer dyspepsia (NUD) received eradication therapy with clarithromycin 500 mg b.i.d., lansoprazole 30 mg b.i.d. plus amoxicillin 1000 mg b.i.d. for ten days. In an all-patients-treated analysis, *H. pylori* was eradicated from 91% of patients.

**Dual Therapy in Duodenal Ulcer Disease**

In well controlled, double-blind studies, *H. pylori* infected duodenal ulcer patients received eradication therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for 14 days followed by omeprazole 40 mg (study A) or omeprazole 20 mg (studies B, C and D) daily for an additional 14 days; patients in each control group received omeprazole alone for 28 days. In study A, *H. pylori* was eradicated in over 80% of patients who received clarithromycin and omeprazole and in only 1% of patients receiving omeprazole alone. In studies B, C, and D, the combined eradication rate was over 70% (clinically evaluable analysis) in patients receiving clarithromycin and omeprazole and less than 1% in patients receiving omeprazole alone. In each study, the rate of ulcer recurrence at six months was statistically lower in the clarithromycin and omeprazole treated patients when compared to patients receiving omeprazole alone.

In an investigator-blind study, *H. pylori* infected patients received eradication therapy with clarithromycin 500 mg t.i.d. in conjunction with lansoprazole 60 mg/day in single or divided doses for 14 days. The combined eradication rate was over 60%.

**Clarithromycin Granules for Oral Suspension**

**Clinical Experience in Patients with Non-Mycobacterial Infections**

In clinical studies, clarithromycin at a dose of 7.5 mg/kg b.i.d. was demonstrated to be safe and effective in the treatment of pediatric patients with infections requiring oral antibiotic treatment. It has been evaluated in over 1200 children, ages six months to 12 years, with otitis media, pharyngitis, skin infections and lower respiratory tract infections.

In these studies, clarithromycin at a dose of 7.5 mg/kg b.i.d. showed comparable clinical and bacteriological efficacy to the reference agents which included penicillin V, amoxicillin, amoxicillin/clavulanate, erythromycin ethylsuccinate, cefaclor and cefadroxil.

**Clinical Experience in Patients with Mycobacterial Infections**

A preliminary study in pediatric patients (some were HIV positive) with mycobacterial infections demonstrated that clarithromycin was a safe and effective treatment when given alone and in combination with zidovudine or dideoxyinosine. Clarithromycin Pediatric Suspension was administered as 7.5, 15 or 30 mg/kg/day in two divided doses.

Some statistically significant effects on pharmacokinetic parameters were observed when clarithromycin was administered with antiretroviral compounds; however, these changes were minor and not likely to be of clinical significance. Clarithromycin at doses of up to 30 mg/kg/day was well-tolerated.
Clarithromycin was effective in the treatment of disseminated \textit{M. avium} complex infections in pediatric patients with AIDS, with some patients demonstrating continued efficacy after more than one year of therapy.

\textbf{Clarithromycin ER}

Safety and efficacy of clarithromycin ER were evaluated in seven clinical studies in patients with community-acquired pneumonia (2 studies), acute exacerbation of chronic bronchitis (3 studies), streptococcal pharyngitis/tonsillitis (1 study), and maxillary sinusitis (1 study). The clinical studies are summarized in the table shown below. These clinical studies confirmed that clarithromycin ER has similar clinical and bacteriological responses as that of established therapies in respiratory tract indications.

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Location(s)</th>
<th>Clarithromycin ER Dosing</th>
<th>n</th>
<th>Comparator Dosing</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M99-077</td>
<td>U.S., Canada</td>
<td>1000 mg qd, 7 days</td>
<td>128</td>
<td>Levofloxacin – 500 mg qd, 7 days</td>
<td>124</td>
</tr>
<tr>
<td>M98-927</td>
<td>U.S.</td>
<td>1000 mg qd, 7 days</td>
<td>85</td>
<td>Trovafloxacin – 200 mg qd, 7 days</td>
<td>66</td>
</tr>
<tr>
<td>AECB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W00-349</td>
<td>Europe, S. America, S. Africa</td>
<td>500 mg qd, 5 days</td>
<td>307</td>
<td>clarithromycin IR – 250 mg bid, 5 days</td>
<td>307</td>
</tr>
<tr>
<td>M97-756</td>
<td>U.S., Canada</td>
<td>1000 mg qd, 7 days</td>
<td>261</td>
<td>clarithromycin IR – 500 mg bid, 7 days</td>
<td>259</td>
</tr>
<tr>
<td>M99-066</td>
<td>U.S.</td>
<td>1000 mg qd, 7 days</td>
<td>137</td>
<td>Augmentin – 875 mg bid, 10 days</td>
<td>133</td>
</tr>
<tr>
<td>Streptococcal pharyngitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W00-348</td>
<td>Europe, Uruguay, S. Africa</td>
<td>500 mg qd, 5 days</td>
<td>192</td>
<td>Penicillin V – 500 mg tid, 10 days</td>
<td>168</td>
</tr>
<tr>
<td>Acute maxillary sinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M97-667</td>
<td>U.S., Canada</td>
<td>1000 mg qd, 14 days</td>
<td>121</td>
<td>clarithromycin IR – 500 mg bid, 14 days</td>
<td>121</td>
</tr>
</tbody>
</table>

\(n = \text{number of clinically evaluable patients}\)

The clinical results, in combination with the pharmacokinetic and pharmacodynamic parameters, support the extrapolation of the clinical efficacy of clarithromycin to other infections including:

- Skin and soft tissue infections
- Disseminated or localized mycobacterial infections
- \textit{Mycobacterium avium} complex (MAC) disease prophylaxis
- Odontogenic infections

\textbf{5.2 Pharmacokinetic properties}

\textbf{Clarithromycin IR}
Absorption
The kinetics of orally administered clarithromycin has been studied extensively in a number of animal species and adult humans. These studies have shown clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Food intake immediately before dosing increases clarithromycin bioavailability by a mean of 25%. Overall, this increase is minor and should be of little clinical significance with the recommended dosing regimens. Clarithromycin may thus be administered in either the presence or absence of 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
With b.i.d. dosing at 250 mg, the peak steady state plasma concentration was attained in two to three days and averaged about 1 µg/ml for clarithromycin and 0.6 µg/ml for 14-OH-clarithromycin, while the elimination half-lives of the parent drug and metabolite were three to four hours and five to six hours, respectively. With b.i.d. dosing at 500 mg, the steady state C\text{max} for clarithromycin and its hydroxylated metabolite was achieved by the fifth dose. After the fifth and seventh doses, the steady state C\text{max} for clarithromycin averaged 2.7 and 2.9 µg/ml; its hydroxylated metabolite averaged 0.88 and 0.83 µg/ml, respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 to 4.8 hours, while that of the 14-OH-clarithromycin was 6.9 to 8.7 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.

In human adults given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Fecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

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. Examples from tissue and serum concentrations are presented below.
COMPANY CORE DATA SHEET
Clarithromycin

Date of approval: 25 APR 2018
Date of previous approval: 10 FEB 2017

### CONCENTRATION
(after 250 mg q12 h)

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue (µg/g)</th>
<th>Serum (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**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 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 in subjects with normal and decreased renal function. The plasma levels, half-life, $C_{\text{max}}$ and $C_{\text{min}}$ for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. $K_{\text{elim}}$ 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 section 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 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.

**Mycobacterium avium Infections**
Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat *Mycobacterium avium* infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 1000 and 2000 mg/day in two divided doses, steady-state clarithromycin $C_{\text{max}}$ values ranged from 2 to 4 µg/ml and 5 to 10 µg/ml, respectively. Elimination half-lives appeared to be lengthened at these higher doses as compared to that seen with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

**Concomitant Omeprazole Administration**
A pharmacokinetic study was conducted with clarithromycin 500 mg t.i.d. and omeprazole 40 mg once daily. When clarithromycin was given alone at 500 mg every eight hours, the mean steady-state $C_{\text{max}}$ value was approximately 3.8 µg/ml and the mean $C_{\text{min}}$ value was approximately 1.8 µg/ml. The mean

This information is confidential
AUC_{0-8} for clarithromycin was 22.9 µg/hr/ml. The T_{max} and half-life were 2.1 hr and 5.3 hr, respectively, when clarithromycin was dosed at 500 mg t.i.d.

In the same study when clarithromycin 500 mg t.i.d. was administered with omeprazole 40 mg once-daily, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole T_{1/2} was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min}, and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

At steady state, clarithromycin gastric mucous concentrations six hours post-dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with the clarithromycin alone group. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

**Clarithromycin Granules for Oral Suspension**

**Absorption**

Initial pharmacokinetic data were obtained with clarithromycin tablet formulations. These data indicated the drug is rapidly absorbed from the gastrointestinal tract and the absolute bioavailability of a clarithromycin 250 mg tablet was approximately 50%. Both the onset of absorption and the formation of the antimicrobially-active metabolite, 14-OH-clarithromycin, were slightly delayed by food, but the extent of bioavailability was not affected by administration of drug in the nonfasting state.

**Distribution, Biotransformation and Elimination**

*In vitro*

*In vitro* studies showed that protein binding of clarithromycin in human plasma averaged about 70% at clinically-relevant concentrations of 0.45 to 4.5 µg/ml.

**Normal Subjects**

The bioavailability and pharmacokinetics of Clarithromycin Pediatric Suspension were investigated in adult subjects and in pediatric patients. A single-dose study in adult subjects found the overall bioavailability of the pediatric formulation to be equivalent to or slightly greater than that of the tablet (dosage with each was 250 mg). As with the tablet, administration of the pediatric formulation with food leads to a slight delay in the onset of absorption, but does not affect the overall bioavailability of clarithromycin. The comparative clarithromycin C_{max}, AUC, and T_{1/2} for the pediatric formulation (non fasted state) were 0.95 µg/ml, 6.5 µg hr/ml, and 3.7 hours, respectively, and for the 250 mg tablet (fasted state) were 1.10 µg/ml, 6.3 µg hr/ml, and 3.3 hours, respectively.

In a multiple dose study in which adult subjects were administered 250 mg of the Clarithromycin Pediatric Suspension every 12 hours, steady state blood levels were nearly reached by time of the fifth dose. Pharmacokinetic parameters after the fifth dose for Clarithromycin Pediatric Suspension were: C_{max} 1.98 µg/ml, AUC 11.5 µg hr/ml, T_{max} 2.8 hours and T_{1/2} 3.2 hours for clarithromycin, and 0.67, 5.33, 2.9 and 4.9, respectively, for 14-OH-clarithromycin.

In fasting healthy human subjects, peak serum concentrations were attained within two hours after oral dosing. With b.i.d. dosing using a 250 mg tablet every 12 hours, steady-state peak serum concentrations of clarithromycin were attained in two to three days and were approximately 1 µg/ml.
Corresponding peak serum concentrations were 2 to 3 µg/ml with a 500 mg dose administered every 12 hours.

The elimination half-life of clarithromycin was about three to four hours with a 250 mg tablet administered every 12 hours but increased to five to seven hours with 500 mg administered every 12 hours. The principal metabolite, 14-OH-clarithromycin, attains a peak steady state concentration of about 0.6 µg/ml and has an elimination half-life of five to six hours after a dose of 250 mg every 12 hours. With a dose of 500 mg every 12 hours, the peak steady-state concentrations of 14-OH-clarithromycin are slightly higher (up to 1 µg/ml), and its elimination half-life is about seven hours. With either dose, the steady-state concentration of this metabolite is generally attained within two to three days.

Approximately 20% of a 250 mg oral dose given every 12 hours is excreted in the urine as unchanged clarithromycin. After a dose of 500 mg every 12 hours, urinary excretion of unchanged parent drug is approximately 30%. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin which accounts for an additional 10% to 15% of either a 250 mg or 500 mg dose administered every 12 hours.

Patients
Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below:

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue (µg/g)</th>
<th>Serum (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

In pediatric patients requiring oral antibiotic treatment, clarithromycin demonstrated good bioavailability with a pharmacokinetic profile consistent with previous results from adult subjects using the same suspension formulation. The results indicated rapid and extensive drug absorption in children and, except for a slight delay in onset of absorption, food seemed to have no significant effect on drug bioavailability or pharmacokinetic profiles. Steady-state pharmacokinetic parameters obtained after the ninth dose on treatment day five were as follows for the parent drug: C\textsubscript{max} 4.60 µg/ml, AUC 15.7 µg/hr/ml and T\textsubscript{max} 2.8 hr; the corresponding values for the 14-OH metabolite were: 1.64 µg/ml, 6.69 µg/hr/ml, and 2.7 hr, respectively. Elimination half-life was estimated to be approximately 2.2 hr for the parent compound and metabolite, respectively.

In another study, information was obtained regarding the penetration of clarithromycin in middle ear fluid in patients with otitis media. Approximately 2.5 hours after receiving the fifth dose (dosage was 7.5 mg/kg b.i.d.), the mean concentration of clarithromycin was 2.53 µg/g fluid in the middle ear and for the 14-OH metabolite was 1.27 µg/g. The concentrations of parent drug and 14-OH metabolite were generally twice as high as the corresponding concentrations in serum.

Hepatic Impairment
The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those of normal subjects; however, the 14-OH-clarithromycin concentrations were lower in the hepatically-impaired subjects. The decreased formation of 14-OH-clarithromycin was at least
partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

**Renal Impairment**
The pharmacokinetics of clarithromycin were also altered in subjects with impaired renal function who received multiple 500 mg oral doses. The plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in subjects with renal impairment than in normal subjects. 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 section 4.2).

**Elderly Subjects**
In a comparative study of healthy, young adults and healthy, elderly subjects given multiple 500 mg oral doses of clarithromycin, the circulating plasma levels were higher and elimination was slower in the elderly group compared to the younger group. However, there was no difference between the two groups when renal clearance of clarithromycin was correlated with creatinine clearance. It was concluded from these results that any effect on the handling of clarithromycin is related to renal function and not to subject age.

**Patients with Mycobacterial Infections**
Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of usual doses to patients with HIV infections (tablets for adults; granular suspension for children) were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at usual doses.

In children with HIV infection taking 15 to 30 mg/kg/day of clarithromycin in two divided doses, steady-state C\text{max} values generally ranged from 8 to 20 µg/ml. However, C\text{max} values as high as 23 µg/ml have been observed in HIV-infected pediatric patients taking 30 mg/kg/day in two divided doses as Clarithromycin Pediatric Suspension. Elimination half-lives appeared to be lengthened at these higher doses as compared to that observed with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

**Clarithromycin IV**

**Distribution, Biotransformation and Elimination**

**Normal Subjects**
In a single-dose clinical study in volunteers, clarithromycin I.V. was administered at 75, 125, 250, or 500 mg doses in 100 ml volume infused over 30 minutes, and 500, 750, or 1,000 mg doses in 250 ml volume infused over a 60-minute period. The mean peak concentration (C\text{max}) of parent drug ranged from 5.16 µg/mL after the 500 mg dose to 9.40 µg/ml after the 1000 mg dose (60 minute infusion). The mean peak concentration (C\text{max}) of the 14-hydroxy metabolite ranged from 0.66 µg/ml after the 500 mg dose to 1.06 µg/ml after the 1000 mg dose (60 minute infusion).

The mean terminal phase plasma half-life of parent drug was dose-dependent and ranged from 3.8 hours after the 500 mg dose to 4.5 hours after the 1000 mg dose (60 minute infusion). The mean estimated half-life for the 14-hydroxy metabolite showed some dose-dependent increases at higher doses and ranged from 7.3 hours after the 500 mg dose to 9.3 hours after the 1000 mg dose (60 minute infusion). The mean area under the concentration vs. time curve (AUC) showed a nonlinear dose-dependent increase for parent drug of 22.29 h•µg/ml after the 500 mg dose to 53.26 h•µg /ml after the 1000 mg dose. The mean area under the concentration vs. time curve (AUC) for the 14-
hydroxy metabolite ranged from 8.16 h•µg /ml after the 500 mg dose to 14.76 h•µg /ml after the 1000 mg dose (60 minute infusion).

In a seven-day multiple dose clinical study subjects were infused with 125 and 250 mg clarithromycin I.V. in 100 ml final volume over a 30 minute period or 500 and 750 mg of the formulation in final volumes of 250 ml over a 60-minute period; dosing was given at 12-hour intervals.

In this study, the observed mean steady-state peak clarithromycin (C_{max}) concentration increased from 5.5 µg/ml with the 500 mg dose to 8.6 µg/ml with the 750 mg dose. The mean apparent terminal half-life was 5.3 hours after infusion of the 500 mg dose over a 60-minute period and 4.8 hours after a 60 minute infusion of 750 mg.

The observed mean steady-state C_{max} for the 14-hydroxy metabolite increased from 1.02 µg/ml with the 500 mg dose to 1.37 µg/ml with the 750 mg dose. The mean terminal phase half-lives for this metabolite were 7.9 and 5.4 hours for the 500 and 750 mg dose groups, respectively. No dose-related trend was evident.

With b.i.d. oral dosing at 250 mg, the peak steady state plasma concentrations were attained in two to three days and averaged about 1 µg/mL for clarithromycin and 0.6 µg/ml for 14-OH-clarithromycin, while the elimination half-lives of the parent drug and metabolite were three to four hours and five to six hours, respectively. With b.i.d. oral dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite was achieved by the fifth dose. After the fifth and seventh doses, the steady state C_{max} for clarithromycin averaged 2.7 and 2.9 µg/ml; its hydroxylated metabolite averaged 0.88 and 0.83 µg/ml, respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 to 4.8 hours, while that of the 14-OH-clarithromycin was 6.9 to 8.7 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 that metabolism of clarithromycin approaches saturation at high doses.

The major metabolite in human plasma was 14-OH-clarithromycin, with peak levels of 0.5 µg/ml and 1.2 µg/ml after oral doses of 250 mg and 1200 mg, respectively. In humans given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Fecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

**Patients**

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Examples from tissue and serum concentrations in humans are presented below:

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue (µg/g)</th>
<th>Serum (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Patients with Mycobacterial Infections**

Although summarized data are not currently available for the use of clarithromycin I.V. in mycobacterial infections, there are pharmacokinetic data from the use of clarithromycin tablets in
these infections. Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of usual clarithromycin doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at usual doses. Elimination half-lives appeared to be lengthened at these higher doses, as compared to that seen with usual doses in normal subjects. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

**Clarithromycin MR**

**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. 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.

**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*
*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 $C_{max}$ 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 $T_{max}$ 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.

**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.

**Clarithromycin ER**

**Absorption**
Clarithromycin ER tablets allow absorption of clarithromycin from the gastrointestinal tract over 12 to 14 hours after oral administration. Relative to an equal total dose of clarithromycin IR tablets, clarithromycin ER tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour exposures for both clarithromycin and 14-OH-clarithromycin. The area under the plasma concentration-time curve (AUC) values from time zero (pre-dose) to three hours after dosing (AUC_0-3) were higher for clarithromycin IR administered b.i.d than for an equal total daily dose of clarithromycin ER, indicating that there was no dose dumping with the clarithromycin ER formulation.

The pharmacokinetics of orally administered clarithromycin IR have been studied extensively in a number of animal species and adult humans. These studies have shown clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing.

Bioequivalence studies comparing clarithromycin ER and IR formulations have shown relative bioavailability of approximately 0.96 for clarithromycin and 1.0 for 14-OH-clarithromycin. These findings support that administration of clarithromycin ER tablets to a patient population normally treated with clarithromycin IR tablets would result in similar efficacy.
While the extent of formation of 14-OH-clarithromycin following administration of clarithromycin ER tablets (1000 mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, clarithromycin ER tablets should be taken with food.

The following table presents the pharmacokinetic data by dose.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (µg/ml)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg•h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin ER 1000 mg daily*</td>
<td>2.59 ± 0.71</td>
<td>7.8 ± 4.0</td>
<td>0.76 ± 0.37</td>
<td>42.1 ± 13.2</td>
</tr>
<tr>
<td>14-OH-Clarithromycin</td>
<td>0.79 ± 0.17</td>
<td>8.7 ± 5.2</td>
<td>0.42 ± 0.13</td>
<td>15.1 ± 3.2</td>
</tr>
<tr>
<td>Clarithromycin ER 500 mg daily†</td>
<td>1.45 ± 0.43</td>
<td>5.6 ± 2.1</td>
<td>0.31 ± 0.23</td>
<td>20.4 ± 8.7</td>
</tr>
<tr>
<td>14-OH-Clarithromycin</td>
<td>0.58 ± 0.17</td>
<td>6.0 ± 2.3</td>
<td>0.23 ± 0.13</td>
<td>9.5 ± 3.5</td>
</tr>
</tbody>
</table>

Notes: C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time of C<sub>max</sub>; and C<sub>min</sub> = minimum observed plasma concentration.
* Results from Study M97-734
† Results from Study M98-976

The lower C<sub>max</sub> and the later T<sub>max</sub> values for clarithromycin, as illustrated in Figure 1, support the extended-release characteristics of the clarithromycin ER formulation.

![Figure 1. Steady-State Clarithromycin Plasma Concentration-Time Profile](image)

Distribution

Abbott
Confidential information

This information is confidential
Clarithromycin and the 14-OH-clarithromycin metabolite distribute readily into body tissues and fluids. A tissue penetration study with clarithromycin ER confirmed that therapeutic levels of clarithromycin and its active metabolite are present at tissue sites important for lower respiratory tract infections up to at least 24 hours after 1000 mg once daily dosing.

Clarithromycin ER dosed at 1000 mg once daily achieved higher steady state clarithromycin concentrations in epithelial lining fluid (4 to 25X) and alveolar macrophages (150 to 250X) as compared to simultaneous plasma concentrations throughout the 24-hour period after drug administration. Additionally, 14-OH-clarithromycin achieved higher steady-state concentrations in alveolar macrophages (40 to 80X) compared to plasma concentrations.

Concentrations of clarithromycin for the ER formulation, dosed as 500 mg or 1000 mg daily, resulted in both plasma and lung tissue concentrations that exceeded the MIC values of most common respiratory and skin and soft tissue pathogens and these concentrations were similar to the values obtained with clarithromycin IR formulations.

In vitro studies with clarithromycin 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.

**Biotransformation**
Data available to date indicate clarithromycin is metabolized primarily by the hepatic cytochrome P450 3A (CYP3A) isoform subfamily.

**Elimination**
Clarithromycin is eliminated by the liver and kidney. In human adults given single oral doses of 250 mg or 1200 mg clarithromycin IR, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Fecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

**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 IR 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 IR in subjects with normal and decreased renal function. The plasma levels, half-life, $C_{\text{max}}$ and $C_{\text{min}}$ for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. $K_{\text{elim}}$ 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 section 4.2).

**Elderly population**
A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin IR 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.

5.3 Preclinical safety data

Clarithromycin IR, MR, ER

Acute, Subchronic, and Chronic Toxicity

Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for six consecutive months.

In acute mouse and rat studies, one rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose, therefore, was greater than 5 g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for one month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for one month, to 35 mg/kg/day for three months, or to 8 mg/kg/day for six months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for one and three months, and 4 mg/kg/day for six months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of ten monkeys receiving 400 mg/kg/day died on treatment day eight; yellow discolored feces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the drug generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or edema.

Fertility, Reproduction, and Teratogenicity

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual
daily human clinical dose (500 mg b.i.d.), but not at 35 times the maximal daily human clinical dose, suggesting maternal and fetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately ten times the upper range of the usual daily human dose (500 mg b.i.d.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

**Mutagenicity**

Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/Petri plate or less. At a concentration of 50 µg the drug was toxic for all strains tested.

**Clarithromycin Granules for Oral Suspension**

*Acute and Subchronic Oral Toxicity Studies*

The acute oral LD$_{50}$ values for a clarithromycin suspension administered to three-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD$_{50}$ values in three-day old rats were 1330 mg/kg for males and 1270 mg/kg for females. For comparison, the LD$_{50}$ for orally-administered clarithromycin is about 2700 mg/kg for adult mice and about 3000 mg/kg for adult rats. These results are consistent with other antibiotics of the penicillin group, cephalosporin group and macrolide group in that the LD$_{50}$ is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behavior and spontaneous movements were depressed for the first few days following drug administration. Necropsy of animals that died disclosed dark-reddish lungs in mice and about 25% of the rats; rats treated with 2197 mg/kg or more of a clarithromycin suspension were also noted to have a reddish-black substance in the intestines, probably because of bleeding. Deaths of these animals were considered due to debilitation resulting from the depressed suckling behavior or bleeding from the intestines.

Pre-weaning rats (five days old) were administered a clarithromycin suspension formulation for two weeks at doses of 0, 15, 55, and 200 mg/kg/day. Animals from the 200 mg/kg/day group had decreased body-weight gains, decreased mean hemoglobin and hematocrit values, and increased mean relative kidney weights compared to animals from the control group. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were also observed in animals from this treatment group. The "no-toxic effect" dosage for this study was 55 mg/kg/day.

An oral toxicity study was conducted in which immature rats were administered a clarithromycin suspension for six weeks at daily dosages of 0, 15, 50, and 150 mg base/kg/day. No deaths occurred and the only clinical sign observed was excessive salivation for some of the animals at the highest dosage from one to two hours after administration during the last three weeks of treatment. Rats from the 150 mg/kg dose group had lower mean body weights during the first three weeks, and were
observed to have decreased mean serum albumin values and increased mean relative liver weight compared to the controls.

No treatment-related gross or microscopic histopathological changes were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats and the "no effect dosage" was considered to be 50 mg/kg/day.

Juvenile beagle dogs, three weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a four-week recovery period. No deaths occurred and no changes in the general condition of the animals were observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas were observed by light microscopy, and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg dose group. The toxic dose in juvenile beagle dogs was considered to be greater than 300 mg/kg and the "no effect dose" 100 mg/kg.

**Fertility, Reproduction, and Teratogenicity**

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, one study in New Zealand white rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg, b.i.d.), but not at 35 times the maximal daily human clinical dose, suggesting maternal and fetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately ten times the upper range of the usual daily human dose (500 mg b.i.d.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage of 500 mg b.i.d. produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose of 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 35 times the maximal daily human clinical dose of 500 mg b.i.d.) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

**Mutagenicity**

Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/Petri plate or less. At a concentration of 50 µg the drug was toxic for all strains tested.

**Clarithromycin IV**

**Acute Toxicity**

The intravenous LD$_{50}$ of clarithromycin I.V. in mice was found to be 184 mg/kg and 227 mg/kg in two separate studies. This was several times higher than the LD$_{50}$ in rats (64 mg base/kg). These values were lower than those obtained following administration to mice by other routes. Signs of toxicity in both species were decreased activity, ataxia, jerks, tremors, dyspnea and convulsions.
Autopsy and histopathological examinations of survivors from the mouse study from which the LD$_{50}$ of 184 mg/kg was obtained showed no changes associated with clarithromycin I.V. administration. However, in the other mouse and rat studies there were gross findings suggestive of pulmonary edema together with patchy to diffuse dark-red discoloration of lung lobes in some animals that died acutely. Although administration of the drug produced similar effects in both mice and rats, it was much more toxic to rats than mice. The exact mode of toxicity could not be determined. Although the acute toxicity signs suggested central nervous system effect, the gross necropsies revealed pulmonary changes in some of the mice and rats.

The acute intravenous toxicities of several metabolites were evaluated in mice and are summarized below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent compound</td>
<td>184 and 227</td>
</tr>
<tr>
<td>$M^1$ metabolite (desmethyl)</td>
<td>200</td>
</tr>
<tr>
<td>$M^4$ metabolite (descladinosyl)</td>
<td>256</td>
</tr>
<tr>
<td>$M^5$ metabolite (isohydroxy)</td>
<td>337</td>
</tr>
</tbody>
</table>

Signs of toxicity included inhibition of movement, respiratory distress, and clonic convulsions. It is apparent that the toxicities of these metabolites are comparable to that of clarithromycin in both quality and degree.

**Acute Vein Irritation**
Solutions of clarithromycin I.V. were evaluated for potential to cause vein irritation in the marginal ear vein of rabbits. This study demonstrated that administration of single doses at very high concentrations (7.5 to 30 mg/base/ml) were mildly irritating.

**Subacute Toxicity**
Subacute intravenous toxicity studies were performed over one month at dosage levels of 15, 50 and 160 mg/kg/day in rats and 5, 15, and 40 mg base/kg/day in monkeys. The top doses used in range-finding studies in rats (range 20 to 640 mg/kg/day) and monkeys (range 5 to 80 mg/kg/day) were found to be systemically toxic to the liver, biliary system and kidney. These are the same as the target organs found with studies in which clarithromycin was administered by the oral route.

The occurrence of severe vein irritation in the one-month studies in the rat and monkey at 160 mg/kg and 40 mg/kg, respectively, precluded the use of doses high enough to clearly demonstrate target organ toxicity. This occurred despite efforts to maximize dosing by increasing infusion volume and slowing the rate of infusion.

The no-effect-dosages in rats and monkeys determined by the one-month subacute studies were 50- and 15 mg/kg/day, respectively, and this was due to vein irritation at higher doses.

**Embryotoxicity in Rats**
Rats were administered 15, 50 and 160 mg base/kg/day of clarithromycin I.V. via tail vein. Significant signs of maternal toxicity were elicited at 160 mg/kg/day (reduced weight gain and reduced food consumption) and 50 mg/kg/day (reduced food consumption). Local effects of the test agent included swollen, bruised, necrotic and ultimate loss of a portion of the tail among high-dose animals. No
effects on mean incidences of implantation sites or resorptions were noted. No visceral or skeletal abnormalities due to drug administration were noted, except for from the dose-related trend in the proportion of male fetuses with an undescended testis. Thus, despite significant maternal toxicity, manifested as vein irritation and reduced food consumption and reduced weight gain, there was no evidence of embryotoxicity, embryolethality or teratogenicity at any doses.

**Embryotoxicity in Rabbits**
Groups of mated rabbits were given clarithromycin I.V. at doses of 3, 10 and 30 mg base/kg/day. One dam treated at 3 mg/kg/day died on gestational day 29. Vein irritation was seen in control and all treatment groups. The incidence and severity of irritation were directly related to the concentration of the drug in the formulation. Signs of maternal toxicity were elicited at 30 mg/kg/day (reduced weight gain and reduced food consumption). The incidence of abortion in the 30 mg/kg/day treatment group was significantly higher than that of the control group, but all aborted fetuses were found to be grossly normal. The no-effect levels for maternal and fetal toxicity were 10 and 30 mg/kg/day, respectively.

**Embryotoxicity in Monkeys**
Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately ten times the usual upper range (500 mg b.i.d.) daily human oral dose, starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the usual maximal intended daily dosage (500 mg b.i.d.) produced no unique hazard to the conceptus.

**Mutagenicity**
Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/Petri plate or less. At a concentration of 50 µg the drug was toxic for all strains tested.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Also consult your approved International Manufacturing Formula.

Clarithromycin 250 mg, Immediate-Release Tablet (IR)
Tablet Core
Sodium croscarmellose  
Pregelatinized starch  
Microcrystalline cellulose  
Quinoline Yellow (E104 aluminium lake)  
Silicon dioxide  
Povidone  
Stearic acid  
Magnesium stearate  
Talc

Tablet Coating, Colour and Gloss Coating
Hypromellose  
Sorbitan monooleate  
Propylene glycol  
Titanium dioxide  
Vanillin
Quinoline Yellow (E104 aluminium lake)  
Sorbic acid

**Clarithromycin 500 mg, Immediate-Release Tablet (IR)**

**Tablet Core**
- Sodium croscarmellose
- Microcrystalline cellulose
- Silicon dioxide
- Povidone
- Stearic acid
- Magnesium stearate
- Talc

**Tablet Coating, Colour and Gloss Coating**
- Hypromellose
- Sorbitan monooleate
- Propylene glycol
- Titanium dioxide
- Vanillin
- Quinoline Yellow (E104 aluminium lake)
- Sorbic acid

**Clarithromycin 125 mg/5 ml Granules for Oral Suspension (Pediatric Suspension)**

**Clarithromycin 250 mg/5 ml Granules for Oral Suspension (Pediatric Suspension)**

**Granule Component and Coating**
- Carbopol carbomers
- Povidone
- Hypromellose
- Castor oil

**Other ingredients**
- Sucrose
- Xanthan gum
- Silicon dioxide
- Potassium sorbate
- Citric acid
- Maltodextrin
- Titanium dioxide
- Fruit punch flavor

**Clarithromycin 250 mg Granules for Oral Suspension: Adult Sachet**

**Clarithromycin 500 mg Granules for Oral Suspension: Adult Sachet**

**Granule Component and Coating**
- Carbopol carbomers
- Povidone
- Hypromellose
- Castor oil

**Other ingredients**
- Sucrose
- Xanthan gum
COMPANY CORE DATA SHEET
Clarithromycin

Date of approval: 25 APR 2018
Date of previous approval: 10 FEB 2017

Clarithromycin

Silicon dioxide
Potassium sorbate
Citric acid
Maltodextrin
Titanium dioxide
Fruit punch flavor

Clarithromycin 500 mg Powder for Intravenous Solution for Injection (IV)
Lactobionic acid
Sodium hydroxide

Clarithromycin 500 mg, Modified-Release Tablets (MR)
Tablet Core
Citric acid
Sodium alginate
Sodium calcium alginate
Lactose
Povidone
Talc
Stearic acid
Magnesium stearate

Coating Solution
Hypromellose
Polyethylene glycol
Titanium dioxide
Quinoline Yellow (E104 aluminium lake)
Sorbic acid

Clarithromycin 500 mg, Extended-Release Tablets (ER)
Tablet Core
Hypermellose
Lactose monohydrate
Magnesium stearate
Talc

Coating Solution
Propylene glycol
Hypermellose
Sorbitan monooleate
Titanium dioxide
Vanillin
Quinoline Yellow (E104 aluminium lake)

[Note: Where local formulations deviate from those in this CCDS, the information related to the excipients including any warnings is to be adapted accordingly.]

6.2 Incompatibilities

Powder for Intravenous Solution for Injection (IV)
Use only Sterile Water for Injection to prepare the initial solution, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. No drug or chemical agent should be added to a clarithromycin I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

6.3 Shelf life
In accordance with local registration files.

6.4 Special precautions for storage
In accordance with local registration files.

6.5 Nature and contents of container
In accordance with local registration files.

6.6 Special precautions for disposal and other handling

**Pediatric Suspension**

**Preparation for Use**
An appropriate amount of water, consult your approved International Manufacturing Formula, should be added to the granules in the bottle and shaken until all of the particles are suspended. Avoid vigorous and/or lengthy shaking. Shake prior to each subsequent use to ensure resuspension. The concentration of clarithromycin in the reconstituted suspension is either 125 mg/5 ml or 250 mg/5 ml.

**Administration**
Several devices can be used to dose and administer Clarithromycin Pediatric Suspension.

**Conservation**
After reconstitution, store at room temperature (15° to 30°C) and use within 14 days. Do not refrigerate.

**Powder for Intravenous Solution for Injection (IV)**

**Preparation for Use**
The final solution for infusion is prepared as follows:

1. Prepare the initial solution of clarithromycin I.V. by adding 10 ml of Sterile Water for Injection to the 500 mg vial. Use only Sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Note: When the product is reconstituted as directed above, the resulting solution contains an effective antimicrobial preservative; each ml contains 50 mg of clarithromycin I.V.

2. Chemical and physical in-use stability has been demonstrated for 48 hours at 5 °C and for 24 hours at 25 °C. From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

3. The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a minimum of 250 ml of one of the following diluents before administration: 5% dextrose in Lactated Ringer's Solution, 5% dextrose, Lactated Ringer's, 5% dextrose in 0.3% sodium chloride, Normosol-M in 5% dextrose, Normosol-R in 5% dextrose, 5% dextrose in 0.45% sodium chloride, and 0.9% sodium chloride.

4. Chemical and physical in-use stability has been demonstrated for 48 hours at 5 °C and for six hours at 25 °C. From a microbiological point of view, the final diluted product should be used
immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

No drug or chemical agent should be added to a clarithromycin I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.