MYCIFOR XL 500MG PROLONGED RELEASE TABLETS

Clarithromycin citrate

PL 15894/0005

UKPAR

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MYCIFOR XL 500MG PROLONGED RELEASE TABLETS

Clarithromycin citrate

PL 15894/0005

LAY SUMMARY

On the 8th May 2012, the MHRA granted Quantum Generics a Marketing Authorisation (licence) for the medicinal product Mycifor XL 500mg Prolonged Release Tablets. This medicine is only available on prescription from your doctor.

Mycifor XL 500mg prolonged release tablets contain the active ingredient clarithromycin citrate. This medicine is an antibiotic belonging to a group called the macrolides. Antibiotics stop the growth of bacteria (bugs) which cause infections.

Mycifor XL tablets are used to treat bacterial infections such as:
- Community acquired pneumonia (infection of the lungs developed outside of hospitals or extended-care facilities)
- Short –term worsening of chronic bronchitis
- Sinusitis (infection of the sinuses)
- Pharyngitis and tonsillitis (infection of the throat or tonsils)
- Skin and soft tissue infections that are mild to moderate in severity

Mycifor XL tablets are prolonged release tablets which means that the active ingredient is released slowly from the tablet so that you only have to take them once a day.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Mycifor XL 500mg Prolonged Release Tablets outweigh the risks. Hence, a Marketing Authorisation has been granted.
MYCIFOR XL 500MG PROLONGED RELEASE TABLETS

Clarithromycin citrate

PL 15894/0005

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Mycifor XL 500mg Prolonged Release Tablets (PL 15894/0005) on the 8th May 2012. This is a prescription only medicine (POM) used in the treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, bacterial pharyngitis and tonsillitis and skin and soft tissue infections (mild to moderate severity).

This is a national abridged application for Mycifor XL 500mg Prolonged Release Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. This product cross-refers to Klaricid XL 500mg modified release tablets (PL 00037/0275), authorised on 10th December 1996 to Abbott Laboratories Limited.

Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

A pharmacovigilance system has been provided with this application and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Clarithromycin citrate
Chemical Names: 
(2R, 3S, 4S, 5R, 6R, 8R, 10R, 11S, 12S, 13R)-3-(2,6-Dideoxy-3-C, 3-O-dimethyl-a-L-ribo-hexopyranosyl-oxy-11,12-dihydroxy-6-methoxy-2, 4, 6, 8, 10, 12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-d-xylo-hexopyranosyloxy)-pentadecan-13-olide citrate.

Structure:

Molecular Formula: C_{44}H_{77}NO_{20}.
Molecular Weight: 940.08
Appearance: White to off-white hygroscopic powder.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with
the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period for the drug substance stored in the packaging proposed.

**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, hypromellose, hypromellose phthalate, magnesium stearate, talc, making up the tablet core; and Opadry II 31G52300 (lactose monohydrate, hypromellose, titanium dioxide E171, macrogol 4000, macrogol 400, talc and Quinoline Yellow Aluminium Lake E104b) making up the film-coat.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry II 31G52300 which complies with an in-house specification and EEC Directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin except for lactose monohydrate, for which the applicant provided a statement from the manufacturer stating that all conditions are met under which lactose is not considered a TSE-risk material. The applicant has confirmed that the magnesium stearate used is a vegetable origin.

**Pharmaceutical development**
Suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the originator product.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale and has shown satisfactory results. A process validation studies on the first three consecutive full-scale commercial batches has been conducted.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.
Container Closure System
The tablets are packed in polyvinylchloride/polyvinylidene chloride/aluminium blister. Each blister strip contains 7 tablets. The blister strips are packaged in a cardboard carton of 7 and 14 (2x7) tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with no special storage conditions is set. This is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.
NON-ClinICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of clarithromycin citrate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

To support the application, three bioequivalence studies have been submitted in order to establish ‘essential similarity’ with the innovator product (Klaricid XL tablets).

**Study number: 1207/031**

This study was a randomized, single dose, two treatment, two sequence, two period, two-way crossover comparative bioavailability study of Clarithromycin extended release 500mg Tablet (test) and KLARICID XL 500mg Tablet (reference) in healthy, adult male subjects under fed conditions.

The wash-out period was 7 days. Serial blood samples were drawn before dosing and post-dose after administration of each product.

The plasma concentration of Clarithromycin and 14-OH Clarithromycin (active metabolite) was determined using a validated LC-MS/MS bio-analytical method.

**Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Geo LSM</th>
<th>Ref Geo LSM</th>
<th>Ratio (T/R) *100</th>
<th>90 % CI (%)</th>
<th>Intra CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1419.410</td>
<td>1330.655</td>
<td>105.67</td>
<td>1.00-1.14</td>
<td>18.37</td>
<td>0.9999</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr X ng/mL)</td>
<td>15260.808</td>
<td>15072.681</td>
<td>101.25</td>
<td>0.96-1.07</td>
<td>14.99</td>
<td>1.0000</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr X ng/mL)</td>
<td>15355.108</td>
<td>15392.347</td>
<td>101.12</td>
<td>0.97-1.06</td>
<td>13.06</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

**Statistical Summary of Ln-transformed Pharmacokinetic Parameters of 14-OH Clarithromycin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Geo LSM</th>
<th>Ref Geo LSM</th>
<th>Ratio (T/R) *100</th>
<th>90 % CI (%)</th>
<th>Intra CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>542.377</td>
<td>480.403</td>
<td>112.94</td>
<td>1.07-1.19</td>
<td>15.37</td>
<td>1.0000</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr X ng/mL)</td>
<td>8103.063</td>
<td>7746.606</td>
<td>104.60</td>
<td>0.99-1.11</td>
<td>16.87</td>
<td>1.0000</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr X ng/mL)</td>
<td>8387.955</td>
<td>8119.720</td>
<td>103.30</td>
<td>0.98-1.09</td>
<td>15.36</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Bioequivalence between Clarithromycin 500mg prolonged release tablets and Klaricid XL 500mg under fed condition after a single dose administration was demonstrated.

**Study number: 1207/030**

A randomized, two-treatment, two-period, two-sequence, multiple-dose, two-way crossover comparative bioavailability study of Clarithromycin Extended Release 500mg Tablet (test) with a modified release formulation, KLARICID XL 500mg Tablet (reference) in healthy adult male subjects under fed condition.
The wash-out period was 7 days. Serial blood samples were drawn before dosing and post-dose after administration of each product.

Results

### Statistical Summary of Ln-transformed Pharmacokinetic Parameters of Clarithromycin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Geo LSM</th>
<th>Ref Geo LSM</th>
<th>Ratio (T/R)*100</th>
<th>90% CI</th>
<th>Intra CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnCmax (ng/mL)</td>
<td>1778.99</td>
<td>1664.92</td>
<td>106.85</td>
<td>0.99-1.16</td>
<td>18.71</td>
<td>0.9980</td>
</tr>
<tr>
<td>LnCmin (ng/mL)</td>
<td>193.33</td>
<td>205.46</td>
<td>94.34</td>
<td>0.81-1.09</td>
<td>34.99</td>
<td>0.8081</td>
</tr>
<tr>
<td>LnAUC0-t (hr X ng/mL)</td>
<td>18816.19</td>
<td>17994.61</td>
<td>104.58</td>
<td>0.95-1.16</td>
<td>24.10</td>
<td>0.9759</td>
</tr>
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</table>

### Statistical Summary of Ln-transformed Pharmacokinetic Parameters of 14-OH Clarithromycin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Geo LSM</th>
<th>Ref Geo LSM</th>
<th>Ratio (T/R)*100</th>
<th>90% CI</th>
<th>Intra CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnCmax (ng/mL)</td>
<td>456.26</td>
<td>417.30</td>
<td>109.34</td>
<td>1.02-1.18</td>
<td>17.53</td>
<td>0.9991</td>
</tr>
<tr>
<td>LnCmin (ng/mL)</td>
<td>119.18</td>
<td>116.31</td>
<td>102.46</td>
<td>0.90-1.17</td>
<td>31.35</td>
<td>0.8740</td>
</tr>
<tr>
<td>LnAUC0-t (hr X ng/mL)</td>
<td>6503.33</td>
<td>5967.73</td>
<td>108.97</td>
<td>0.99-1.20</td>
<td>22.99</td>
<td>0.9835</td>
</tr>
</tbody>
</table>

Bioequivalence between Clarithromycin 500mg prolonged release tablets and Klaricid XL 500mg under fed condition after multiple dose administration was demonstrated.

**Study number: 0108/001**

A randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover comparative bioavailability study of Clarithromycin Extended Release 500mg Tablets with a modified release formulation, Klaricid XL 500mg Tablet in a healthy adult male subjects under fasting conditions.

The wash-out period was 7 days. Serial blood samples were drawn before dosing and post-dose after administration of each product.

Results

### Statistical Summary of Ln-transformed Pharmacokinetic Parameters of Clarithromycin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Geo LSM</th>
<th>Ref Geo LSM</th>
<th>Ratio (T/R)*100</th>
<th>90% CI</th>
<th>Intra CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnCmax (ng/mL)</td>
<td>751.574</td>
<td>652.208</td>
<td>115.24</td>
<td>1.06-1.25</td>
<td>31.16</td>
<td>0.9969</td>
</tr>
<tr>
<td>LnAUC0-t (hr X ng/mL)</td>
<td>9314.455</td>
<td>8364.226</td>
<td>111.36</td>
<td>1.00-1.24</td>
<td>41.35</td>
<td>0.9535</td>
</tr>
<tr>
<td>LnAUC0-t (hr X ng/mL)</td>
<td>9798.711</td>
<td>8815.399</td>
<td>111.15</td>
<td>1.00-1.24</td>
<td>40.54</td>
<td>0.9590</td>
</tr>
</tbody>
</table>
For Clarithromycin, the 90% confidence interval for $C_{\text{max}}$ is contained on the upper bound of the 80 to 125% range. Point estimate: 1.15 and (90% CI 1.06 – 1.25%). This can be acceptable. For the metabolite 14 OH Clarithromycin, the 90% confidence interval for $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ lie outside of 80 - 125% range. This is considered acceptable in this instance in accordance to the guideline on the investigation of bioequivalence, because the 90% CI for the parent compound (Clarithromycin) has been demonstrated to fall within the bioequivalence acceptance range.

**EFFICACY**
No new efficacy data have been submitted and none are required for this application.

**SAFETY**
No new safety data have been submitted and none are required for this application.

**EXPERT REPORT**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**SUMMARY OF PRODUCT CHARACTERISTICS**
This is satisfactory.

**PATIENT INFORMATION LEAFLET**
This is satisfactory.

**LABELLING**
This is satisfactory

**MAA FORMS**
This is satisfactory.

**CONCLUSIONS**
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Mycifor XL 500mg Prolonged Release Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for applications of this type.

Bioequivalence have been demonstrated between the applicant’s Clarithromycin 500mg Tablets and Klaricid XL 500 mg Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has also been submitted.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with clarithromycin citrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
MYCIFOR XL 500MG PROLONGED RELEASE TABLETS

Clarithromycin citrate

PL 15894/0005

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 24\textsuperscript{th} August 2010</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 14\textsuperscript{th} September 2010</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 23\textsuperscript{rd} December 2010, 26\textsuperscript{th} July 2011, 7\textsuperscript{th} December 2011 and on the clinical section 24\textsuperscript{th} March 2011</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 24\textsuperscript{th} March 2011, 20\textsuperscript{th} October 2011 and 6\textsuperscript{th} March 2012 and on the clinical section on 15\textsuperscript{th} April 2011</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 8\textsuperscript{th} May 2012</td>
</tr>
</tbody>
</table>
1 **NAME OF THE MEDICINAL PRODUCT**
Mycifor XL 500mg Prolonged Release Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated prolonged release tablet contains 500mg clarithromycin as clarithromycin citrate.
Each tablet contains 293mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Prolonged release tablet
Yellow, oblong-shaped, biconvex film-coated tablet

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Mycifor XL 500mg Prolonged Release Tablets are indicated for treatment of
- Community acquired pneumonia
- Acute exacerbation of chronic bronchitis
- Acute bacterial sinusitis (adequately diagnosed)
- Bacterial pharyngitis and tonsillitis
- Skin and soft tissue infections (mild to moderate severity)
Consideration should be given to official guidance on appropriate use of antibacterial agents.

4.2 **Posology and method of administration**
Adults: The usual recommended dosage is one 500mg prolonged release tablet daily to be taken with food.
In more severe infections, the dosage can be increased to two 500mg prolonged release tablets taken as one dose daily.
The usual duration of treatment is 7 to 14 days.
Children older than 12 years: as for adults.
Children younger than 12 years: Mycifor XL is not suitable for children younger than 12 years. An alternative formulation of clarithromycin suitable for children should be used in this patient population.
Mycifor XL 500mg Prolonged Release Tablets should not be used in patients with renal impairment (creatinine clearance less than 30 ml/min). Clarithromycin immediate release tablets should be used in this patient population. (See 4.3 Contra-indications).

4.3 **Contraindications**
Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.
Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine (see section 4.5).
As the dose cannot be reduced from 500mg daily, Mycifor XL 500mg Prolonged Release Tablets are contraindicated in patients with creatinine clearance less than 30 mL/min.

4.4 **Special warnings and precautions for use**
Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic function and moderate to severe renal impairment (see also section 4.3).
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
Prolonged or repeated use of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

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). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects: cisapride, pimozide and terfenadine. Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in increased risk of ventricular rhythm disorders, especially Torsades de Pointes. Concomitant administration of clarithromycin and any of these medicinal products is contraindicated (see section 4.3).

Ergotamine/dihydroergotamine

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

Effect of other medicinal products on clarithromycin

Clarithromycin is metabolised via enzyme CYP3A4. Therefore, strong inhibitors of this enzyme may inhibit clarithromycin metabolism, this results in increased plasma concentrations of clarithromycin.

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

Fluconazole

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

Ritonavir

Co-administration of clarithromycin and ritonavir increases the area under the curve (AUC), maximum concentration (Cmax) and the minimum concentration (Cmin) of clarithromycin. 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, such as clarithromycin immediate release tablets, or clarithromycin sachet, or clarithromycin paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors (see section 4.2).

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 section below, bidirectional pharmacokinetic interactions).

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)- hydroxyclarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14(R)-hydroxy-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Antiarrhythmics
There have been post-marketing reports of torsade 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 concentrations of these medications should also be monitored.

**Carbamazepine**

During therapy with clarithromycin, the metabolism of carbamazepine may be inhibited. Consequently the serum concentrations of carbamazepine may be increased, and dose reduction may need to be considered.

**HMG-CoA Reductase Inhibitors (e.g., lovastatin, simvastatin)**

Clarithromycin inhibits the metabolism of a number of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors. This may result in elevated plasma levels of these drugs. In rare cases, the occurrence of rhabdomyolysis was reported with concomitant administration of clarithromycin and HMG-CoA reductase inhibitors (statins), such as lovastatin or simvastatin. Patients should be monitored for signs and symptoms of myopathy. Adjustment of the statin dosage or use of a statin that is less dependent on CYP3A metabolism, e.g., pravastatin, should be considered. Clarithromycin may cause similar interactions with atorvastatin.

**Oral anticoagulants (e.g., warfarin, acenocoumarol)**

In isolated cases, patients receiving combination therapy with clarithromycin and oral anticoagulants may experience increased pharmacologic effects and even toxic effects of these drugs. International normalized ratio (INR) or Prothrombin times should be carefully monitored while patients are simultaneously receiving clarithromycin and oral anticoagulants.

**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 coadministered with clarithromycin.

**Theophylline**

During therapy with clarithromycin, the metabolism of theophylline may be inhibited. Consequently the serum concentrations of theophylline may be increased, and dose reduction may need to be considered.

**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.

**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 and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not metabolised by CYP3A (temazepam, nitrazepam, lorazepam) an 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.

**Omeprazole**

The AUC of omeprazole is increased by 89% when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when...
they are co-administered with clarithromycin. Eletriptan should not be co-administered with CYP3A inhibitors such as clarithromycin.

Ciclosporin, tacrolimus and sirolimus
Concomitant administration of the oral form of clarithromycin with ciclosporin or tacrolimus results in a more than two-fold increase of Cmin plasma concentrations of ciclosporin and tacrolimus. Similar effects can also be expected with sirolimus. Plasma levels of ciclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with clarithromycin in patients on any of the abovementioned immunosuppressants, and their doses should be decreased, if necessary. Clarithromycin discontinuation in those patients also requires a thorough monitoring of ciclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with ciclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.

**Other 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. Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

**Digoxin**
Digoxin is 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**
Due to reduced gastrointestinal absorption of zidovudine in the presence of clarithromycin, reduced serum levels of zidovudine were observed in adults during concomitant therapy with clarithromycin and zidovudine. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, patients should observe a 4-hour interval between taking these two drugs. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

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

**Bidirectional pharmacokinetic interactions**

**Atazanavir**
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(R)-hydroxy-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, such as clarithromycin immediate release tablets, or clarithromycin sachet, or clarithromycin paediatric suspensions (not all presentations may be marketed). Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors (see also section 4.2).
Atazanavir is co-administered with ritonavir in the EU, therefore the comments for this medicinal product should also be taken into account.

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 bidirectional 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 area under the curve (AUC) and maximum concentration (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 done with unboosted saquinavir 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 above, effect of other medicinal products on clarithromycin).

4.6 Pregnancy and lactation
Pregnancy
The safety of clarithromycin during pregnancy and breast-feeding of infants has not been established. Clarithromycin should not be used during pregnancy or lactation unless the benefit outweighs the risk.
Data on the use of Clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects or adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.
Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should not be given to pregnant women unless it is clearly needed.

Lactation
Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be born in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on ability to drive and use machines
There are no data on the effect of this product on the driving ability. When driving or using machines, one should take into account that dizziness may occur.

4.8 Undesirable effects
The most frequently reported events in adults taking clarithromycin were gastro-intestinal disorders (diarrhoea, nausea, abnormal taste, dyspepsia, abdominal pain/discomfort), and headache.
In this section undesirable effects are defined as follows:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.

Infections and infestations
Common: oral monilia
Uncommon: gastrointestinal, vaginal candidiasis, vaginal infection
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.
Very rare: uveitis, mainly in patients treated with concomitant rifabutin.

Blood and the lymphatic system disorders
Uncommon: leukopenia, anaemia, eosinophilia, hypochromic anaemia, thrombocythaemia
Very rare: thrombocytopenia

Immune system disorders
Uncommon: allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis

Psychiatric disorders
Uncommon: depression, insomnia, nervousness, somnolence
Very rare: anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion

Metabolism and nutrition disorders
Uncommon: anorexia, hyperchloraemia, hyperuricaemia, hypocalcaemia, increased appetite

Eye disorders
Uncommon: conjunctivitis, visual disturbance

Vascular disorders
Uncommon: vasodilatation

Respiratory, thoracic and mediastinal disorders
Uncommon: asthma, dyspnoea

Reproductive system and breast disorders
Uncommon: genital discharge

General disorders and administration site conditions
Uncommon: asthenia, chest pain, face oedema, malaise, pain, thirst

Nervous system disorders
Common: headache, smell alteration
Uncommon: tremor, dizziness
Very rare: paraesthesia, convulsions

Ear and labyrinth disorders
Rare: tinnitus, vertigo
Very rare: Reversible hearing loss

Not known: irreversible loss of hearing

Cardiac disorders
Very rare: QT prolongation, ventricular tachycardia and torsade de pointes

Gastrointestinal disorders
Common: nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste
Uncommon: constipation, dry mouth, eructation, flatulence, gastrointestinal haemorrhage
Very rare: pancreatitis; pseudomembranous colitis has been reported very rarely with clarithromycin, and may range in severity from mild to life threatening.

Hepato-biliary disorders
Uncommon: hepatic dysfunction, which is usually transient and reversible, hepatitis and cholestasis with or without jaundice
Very rare: fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic drugs

Skin and subcutaneous tissue disorders
Uncommon: dry skin, eczema, hyperhidrosis, pruritus, rash, rash maculopapular, rash pustular
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders
Uncommon: arthralgia, myalgia, back pain

Renal and urinary disorders
Uncommon: albuminuria, haematuria, pyuria
Very rare: Interstitial nephritis, renal failure

Investigations
Common: elevated blood urea nitrogen
Uncommon: prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels), alanine aminotransferase increased, alkaline
phosphate increased, aspartate aminotransferase increased, blood lactate dehydrogenase increased, prothrombin decreased
Very rare: hypoglycaemia has been observed especially after concomitant administration with antidiabetic drugs and insulin

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological-therapeutical group: Macrolides
ATC Code: J01FA09

Mode of Action
Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.
Clarithromycin has relevant bactericidal activity against several bacterial strains. The organisms include *H. influenzae*, *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *M. catarrhalis*, *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*, *M. avium*, and *M. intracellulare*. The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a strain-dependent additive or synergistic effect both *in vitro* and *in vivo*.

PK/PD relationship
Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations. Clarithromycin concentrations in tonsil and whole lung tissue are 2- to 6-fold higher than those observed in the serum. Tissue and serum concentrations observed in Abbott studies with immediate-release (IR) tablets are presented below.

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

The pharmacokinetics of orally administered modified-release (MR) clarithromycin tablets have been studied in adult humans (refer to section 5.2) and compared with clarithromycin 250 mg and 500 mg IR tablets. The extent of absorption – area under curve (AUC) – was found to be equivalent when equal total daily doses were administered. The equivalent AUCs would be expected to drive tissue levels equivalent to those observed for clarithromycin IR tablets.

Mechanism of resistance
Acquired macrolide resistance in *S. pneumoniae*, *S. pyogenes*, and *S. aureus* is mediated primarily by the presence of one of two mechanisms (i.e. *erm* and *mef* or *msr*). Ribosomal binding of the antimicrobial is prevented through methylation of the ribosome by an enzyme (*erm*). Alternatively an efflux mechanism (*mef* or *msr*) can prevent the antimicrobial from reaching its ribosomal target by pumping the antimicrobial out of the cell.
No acquired resistance mechanisms have been identified in Moraxella or Haemophilus spp. Macrolide resistance mechanisms are equally effective against 14- and 15-membered macrolides including erythromycin, clarithromycin, roxithromycin, and azithromycin. The mechanisms for penicillin resistance and macrolide resistance are unrelated. Attention should be paid to the erm-mediated cross-resistance between macrolides such as clarithromycin and lincosamides such as lincomycin and clindamycin. Clarithromycin antagonises the bacterial effects of beta-lactam antibiotics. Also the effects of lincomycin and clindamycin are antagonised, at least in vitro.

Breakpoints
The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

<table>
<thead>
<tr>
<th>Breakpoints (MIC, µg/ml)</th>
<th>Microorganism</th>
<th>Susceptible (≤)</th>
<th>Resistant (&gt; =)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus spp.</td>
<td>0.25 µg/ml</td>
<td>0.5 µg/ml</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>1 µg/ml</td>
<td>2 µg/ml</td>
<td></td>
</tr>
<tr>
<td>Haemophilus spp. *</td>
<td>1 µg/ml</td>
<td>32 µg/ml</td>
<td></td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>0.25 µg/ml</td>
<td>0.5 µg/ml</td>
<td></td>
</tr>
</tbody>
</table>

Clarithromycin is used for the eradication of *H. pylori*; minimum inhibitory concentration (MIC) ≤0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

* The correlation between *H. influenzae* macrolides MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate. The activity of 14(R)-hydroxy-clarithromycin is greater than that of clarithromycin against *Haemophilus influenzae*. Studies done in vitro have suggested an additive activity of the 14(R) hydroxyclarithromycin and the parent molecule against *H. influenzae*.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

**Commonly susceptible species**

**Aerobic Gram-positive micro-organisms**
- Streptococcus group F

**Aerobic Gram-negative micro-organisms**
- Legionella pneumophila
- Moraxella catarrhalis
- Legionella spp

**Anaerobic micro-organisms**
- Clostridium perfringens

**“Other”**
- Chlamydia pneumoniae
- Chlamydia trachomatis
- Mycoplasma pneumoniae

**Species for which acquired resistance may be a problem**

**Aerobic Gram-positive micro-organisms**
- Staphylococcus aureus (resistant or susceptible* to methicillin)+
- Staphylococcus coagulase negative +
- Streptococcus group B, C, G
- Streptococcus pneumoniae* +
- Streptococcus pyogenes*
### 5.2 Pharmacokinetic properties

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following in vitro and in vivo data are applicable to the modified-release formulation.

#### In vitro

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

#### In vivo

Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20. The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg clarithromycin modified-release daily, the peak steady-state plasma concentration of clarithromycin and 14-hydroxy clarithromycin were 1.3 and 0.48μg/mL, respectively. When the dosage was increased to 1000mg daily, these steady-state values were 2.4μg/mL and 0.67μg/mL respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses. Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

### 5.3 Preclinical safety data

In acute toxicity studies in mouse and rat, the median lethal dose was greater than the highest feasible dose for administration (5g/kg). In repeated dose studies, clarithromycin toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic dose included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys.

At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.
Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core:
- Lactose Monohydrate
- Hypromellose
- Hypromellose phthalate
- Magnesium stearate
- Talc
Film-coat:
- Lactose monohydrate
- Hypromellose
- Titanium dioxide E171
- Macrogol 4000
- Macrogol 400
- Talc
- Quinoline Yellow Aluminium Lake E104b

6.2 Incompatibilities
None known

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The blisters are constructed of a rigid colourless 250µm PVC film, coated with PVDC and are heat sealed with 25µ aluminium foil. Each blister strip contains 7 tablets. The blister strips are packaged in a cardboard carton of 7 and 14 (2x7) tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
There are no special requirements for disposal. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Quantum Generics
57-65 Station Road
Redhill
Surrey
RH1 1DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15894/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/05/2012
DATE OF REVISION OF THE TEXT
08/05/2012
UKPAR Mycifor XL 500mg Prolonged Release Tablets PL 15894/0005

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
MYCIFOR XL
500mg PROLONGED RELEASE TABLETS
( Clarithromycin )

Please read this leaflet carefully before you start to take
this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your
pharmacist.
- This medicine has been prescribed for you. Do not pass it on to
others. It may harm them, even if their symptoms are the same as
yours.
- If any of the side effects gets serious, or if you notice any side
effects not listed in this leaflet, please tell your doctor or
pharmacist.

In this leaflet:
1. What Mycifor XL tablets are and what they are used for
2. Before you take Mycifor XL tablets
3. How to take Mycifor XL tablets
4. Possible side effects
5. How to store Mycifor XL tablets
6. Further information

1. WHAT MYCIFOR XL TABLETS ARE AND WHAT THEY ARE USED FOR

Mycifor XL 500mg prolonged release tablets, referred to as Mycifor
XL tablets throughout this leaflet, contain the active ingredient
clarithromycin. This medicine is an antibiotic belonging to a group called
the macrolides. Antibiotics stop the growth of bacteria (bugs) which
cause infections.

Mycifor XL tablets are used to treat bacterial infections such as:
- Community-acquired pneumonia (infection of the lungs developed
outside of hospitals or extended-care facilities)
- Short-term worsening of chronic bronchitis
- Sinusitis (infection of the nose)
- Pharyngitis and tonsillitis (infection of the throat or tonsils)
- Skin and soft tissue infections that are mild to moderate in severity
Mycifor XL tablets are prolonged-release tablets which means that the
active ingredient is released slowly from the tablet so that you only have
to take them once a day.

2. BEFORE YOU TAKE MYCIFOR XL TABLETS

Do not take Mycifor XL tablets
Tell your doctor before taking Mycifor XL tablets if you think any of these
apply to you:
- If you are allergic (hypersensitive) to clarithromycin or any other
macrolide antibiotics such as erythromycin or azithromycin or any of
the other ingredients in Mycifor XL tablets (see section 4).
- If you are taking the following medicines. Consult your doctor
for advice on alternative medicines or ask if you are not sure:
- Ergotamine or dihydroergotamine tablets or use
ergotamine inhalers (medicines used to treat migraine).
Combining these with Mycifor XL tablets may cause your blood vessels
to narrow. This will lead to a decrease of blood supply to tissues.
- Chlorpropamide (to treat stomach disorders), propranolol (to treat some
mental illness), terfenadine or astemizole (to treat hay fever or allergy).
Combining these medicines with Mycifor XL tablets can cause
serious changes in your heart rhythm.
- If you have severe kidney disease. You may have to take a lower dose.

Take special care with Mycifor XL tablets
Tell your doctor or pharmacist if you:
- Have any kidney problems (other than severe – see above)
- Have liver problems
- If your potassium levels are low (hypokalaemia)
- If you take or have recently taken colchicine (a medicine to treat gout).
This can cause very serious side effects.

3. HOW TO TAKE MYCIFOR XL TABLETS

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently
taken any other medicines, including medicines obtained without
prescription or if you are taking herbal remedies.
You should not take Mycifor XL tablets if you are taking any of the
following medicines (see Do not take Mycifor XL tablets):
- Chlorpropamide (to treat stomach disorders)
- Propranolol (to treat mental illness)
- Terfenadine or astemizole (to treat hay fever or allergy)
- Ergotamine or dihydroergotamine (to treat migraines)
Tell your doctor if you are taking any of the following medicines, because
of the possibility of reactions your doctor will decide if you can still take
Mycifor XL tablets:
- Colchicine (usually taken for gout). This may increase your risk of
side effects and lead to potential toxicity.
- Digoxin (to treat heart failure). It may cause irregular heart beat and
may also increase your risk of side effects.
- Quinidine or disopyramide (to treat abnormal heart rhythm). This
may cause you to experience seriously irregular heart beat.
- Warfarin or acenocumarol (to thin the blood). These medicines
may change the rate at which your blood clots. This might result in
side effects:
- Triazolam, alprazolam or midazolam (sedatives). These
medicines may cause sleepiness and confusion.
- Simvastatin, lovastatin, atorvastatin (to treat high cholesterol).
These medicines may lead to pain or weakness in muscles, or abnormal
muscle breakdown. This can lead to kidney problems.
- Zidovudine (anti-HIV agent). This may change the effectiveness of
zidovudine.
- Rifabutin, rifampicin, rifapentiam (to treat skin infections). These
medicines may change the effectiveness of Mycifor XL tablets.
- Efavirenz, nevirapine (HIV treatment). These medicines may
change the effectiveness of Mycifor XL tablets.
Taking the following medicines with Mycifor XL tablets may increase
your risk of side effects. Tell your doctor if you are taking any of the following:
- Carbamazepine, valproate or phenytoin (to treat epilepsy)
- Glimepiride (to treat hypoglycaemia)
- Methylprednisolone (to treat inflammation)
- Sildenafil, tadalafil, vardenafl (to treat erectile problems)
- Vinblastine (to treat cancer)
- Tolterodine (to treat urinary frequency)
- Etoricoxib (to treat migraines)
- Aprepitant (to prevent nausea and vomiting after chemotherapy)
- Haloperidol (to treat nausea)
- Omeprazole (to treat indigestion)
- Ziprasidone (to treat schizophrenia)
- Cyclosporin, tacrolimus, sirolimus (to help prevent rejection
after a transplant)
- Theophylline (to treat asthma)
- Itraconazole or fluconazole (to treat fungal infections)
- Ritonavir, atazanavir, saquinavir (anti-retroviral and anti-HIV
medicines).

Taking Mycifor XL tablets with food and drink
Mycifor XL tablets should be taken with food.

Pregnancy and breast-feeding
Do not take Mycifor XL tablets if you are pregnant without consulting
your doctor first. Your doctor will determine if the benefits to you
outweigh the risk to the baby.
Do not take Mycifor XL tablets if you are breast-feeding without
consulting your doctor first. This is because small amounts of this
medicine can pass into breast milk.
Ask your doctor or pharmacist for advice before taking any medicine if
you are pregnant, intend to become pregnant or are breast-feeding.
UKPAR Mycifor XL 500mg Prolonged Release Tablets
PL 15894/0005

Drinking and using machines
Mycifor XL tablets may cause dizziness or a feeling of being drunk as a possible side effect. If you experience these effects you should not drive or operate machines.

Important information about some of the ingredients of Mycifor XL tablets
Mycifor XL tablets contain lactose (a kind of sugar). If you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE MYCIFOR XL TABLETS
Always take Mycifor XL tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

How to take
Mycifor XL tablets should be taken with food and must be swallowed whole and not chewed.

Dosage
The usual dose of Mycifor XL for adults and children over 12 years of age is 500mg once daily for 7 to 14 days. Your doctor may increase the dose to 200mg tablets daily to treat severe infections.

Use in children
This medicine is not suitable for children under 12 years of age. Your doctor can advise you of other medicines which may be more suitable for younger children.

If you take more Mycifor XL than you should
If you accidentally take more than two Mycifor XL tablets in one day, or if a child accidentally swallows some tablets, seek medical advice immediately. An overdose of Mycifor XL is likely to cause vomiting and stomach pain and there is a possibility of allergic reactions.

If you forget to take Mycifor XL
If you forget to take a Mycifor XL tablet, take one as soon as you remember. Do not take more tablets in one day than your doctor has told you to.

If you stop taking Mycifor XL
Do not stop taking Mycifor XL because you feel better. It is important to take the tablets for as long as your doctor has told you to, otherwise the infection might come back.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Mycifor XL tablets can have side effects, although not everyone gets them.

Stopping Mycifor XL tablets and contact your doctor immediately if any of the following side effects occur:
- Allergic reactions such as:
  - swelling of the face, lips, throat or tongue
  - difficulty breathing or swallowing
  - skin flushing or rash or swelling
You may need emergency treatment.
- Severe or prolonged diarrhoea, which may have blood or mucus in it (pseudo-membranous colitis)
- Blotching of the skin, mouth, eyes or genitals (Steven Johnson syndrome)

These side effects listed above are rare but serious.

Tell your doctor if any of the following side effects occur:
Common (affect 1 to 10 users in 100):
- increased levels of urea in the blood (detected in laboratory tests)
- change in taste
- abdominal pain, diarrhoea, indigestion, feeling sick, vomiting, bloating, inflammation or ulceration of the mouth such as mouth ulcers and cold sores, inflammation of the tongue, reversible discolouration of tongue and teeth, taste disorder
- rash (very rare)

Uncommon (affect 1 to 10 users in 1,000):
- presence of protein, blood or white blood cells in the urine, changes in liver or kidney function tests or blood tests, prothrombin time prolongation (increased blood clotting time)
- leucopenia (reduction in the number of white blood cells, which may make you feel tired and more likely to catch infection)
- neutropenia (increase in red blood cells, which may make you feel more tired and more likely to catch infection)
- eosinophilia (increase in white blood cells in the blood, which may cause the skin to feel itchy and red and more likely to catch infection)
- thrombocytopenia (increase in blood platelets, which increases the risk of bleeding or clotting)
- dizziness, tremor (shaking)
- nausea (feeling sick)
- anxiety (dizziness, vertigo (spinning sensation)
- constipation, dry mouth, belching, flatulence (wind), bleeding from stomach and intestine
- redness of skin, swelling, itching, rash, rash with raised bumps, rash with pus, dry skin or eczema, increased sweating
- bad, joint or muscle pain
- glaucoma (inflammation of the eye), rhinitis (inflammation of the nose), conjunctivitis (inflammation of the eye)
- tinnitus (hearing ringing or buzzing in the ears), deafness
- headaches
- blurred vision
- increased intraocular pressure (in the eye)
- other eye problems
- blurred vision
- photophobia (sensitivity to light)
- myopia (loss of vision)
- painful sensations
- insomnia (difficulty sleeping)
- urination
- frequent urination
- pyuria (pus in the urine)
- dry eyes
- impaired vision
- fever
- sore throat
- flu symptoms
- chest pain
- nausea
- vomiting
- breathing difficulties
- bleeding or bruising
- convulsions (fits)

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If you stop taking Mycifor XL
Do not stop taking Mycifor XL because you feel better. It is important to take the tablets for as long as your doctor has told you to, otherwise the infection might come back.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

5. HOW TO STORE MYCIFOR XL TABLETS
Keep out of the reach and sight of children.
Keep Mycifor XL tablets in the original packaging. Do not use Mycifor XL tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These medicines will help to protect the environment.

6. FURTHER INFORMATION
What Mycifor XL contains
- The active ingredient is clindamycin. Each tablet contains 500mg of clindamycin.
- The other ingredients are: lactose monohydrate, hypromellose, hypromellose phthalate, magnesium stearate, talc, macrogol 4000, titanium dioxide (E171) and quinoline yellow (E143).

What Mycifor XL tablets look like and the contents of the pack
Mycifor XL tablets are yellow, oblong-shaped, biconvex tablets. They are available in blister packs containing 7 (1x7) or 14 (2x7) tablets.

Marketing Authorisation Holder
Quintessence Remedies, 57-65 Station Road, Redhill, Surrey, RH1 1DL, UK

Manufacturers/Importer
Forum Products Ltd, 37-45 Station Road, Redhill, Surrey, RH1 1DL, UK

Distributor
Kent Pharmaceuticals Ltd, Repton Road, Moordown, DC 7 7DT

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