SCIENTIFIC DISCUSSION
**PRODUCT INFORMATION**

<table>
<thead>
<tr>
<th>Tradename of the medicinal product:</th>
<th>Ketek</th>
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| **Applicant:**                    | Aventis Pharma S.A.  
20 avenue Raymond Aron  
F-92160 Antony  
France |
| **Active substance:**             | Telithromycin |
| **International Nonproprietary Name:** | Telithromycin |
| **Pharmaco-therapeutic group (ATC Code):** | Antibacterial for systemic use  
JO1 |
| **Therapeutic indications:**      | When prescribing Ketek, consideration should be given to official guidance on the appropriate use of antibacterial agents.  
Ketek is indicated for the treatment of the following infections:  

*In patients of 18 years and older:*  
- Community-acquired pneumonia, mild or moderate,  
- Acute exacerbation of chronic bronchitis,  
- Acute sinusitis,  
- Tonsillitis/pharyngitis caused by Group A *beta streptococci*, as an alternative when beta lactam antibiotics are not appropriate.  

*In patients of 12 to 18 years old:*  
Tonsillitis/pharyngitis caused by Group A *beta streptococci*, as an alternative when beta lactam antibiotics are not appropriate |
1. Introduction

Telithromycin is a novel semi-synthetic antibacterial agent belonging to a new family of antibiotics, the ketolides, closely related to the well-known macrolide antibiotics. Telithromycin (HMR 3647) is indicated for oral administration for treatment of community-acquired pneumonia (CAP), and for acute exacerbation of chronic bronchitis, acute sinusitis and tonsillitis/pharyngitis. The proposed dose is 800 mg once daily and the treatment duration is 5 days for all indications except CAP, for which a treatment duration of 7 to 10 days is suggested.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Telithromycin tablets are formulated as an immediate release tablet, with a film-coating. The product is composed of excipients commonly used in this type of product: maize starch; microcrystalline cellulose; povidone K25; croscarmellose sodium (); magnesium stearate); lactose monohydrate); and a hypromellose-based film-coating (hypromellose 6 cp, macrogol 8000, talc, titanium dioxide, red iron oxide, yellow iron oxide).

The tablets are presented in white opaque PVC/aluminium blister packs, in a variety of pack sizes: 10; 14; 20; 100 (hospital pack). Two tablets (the recommended dose) are enclosed in each blister.

Active substance

Telithromycin is a semi-synthetic antibacterial agent synthesised from erythromycin. Flow diagrams of the synthesis were provided. It is stated that none of the suppliers of the erythromycin starting material uses any genetically modified organism (GMO). The information regarding compliance of the active substance with the revised EMEA TSE Guideline was provided.

Satisfactory control specifications and associated method validations are provided for the starting materials and key intermediates and proof of structures have also been supplied for these. Satisfactory specifications have also been provided for all reagents and solvents.

Proof of the structure of telithromycin has been provided by means of elemental analysis, UV, circular dichroism, IR, NMR (H, 13C), MS and X-ray diffraction. Telithromycin is freely soluble in acidic solutions, its solubility decreasing with increasing pH.

Telithromycin is a chiral molecule possessing 13 asymmetric centres.

The HPLC method used for the determination of related substances allows for separation of all the potential impurities arising from the synthesis, including by-products from potential side reactions, and their separation from telithromycin.

The limits proposed for the related substances have been adequately justified by toxicological studies and analysis data.

Potential degradation products from stressed stability samples are presented.

The specified impurities have all been adequately characterised.

The limits for residual solvents and total impurities have been justified.

All methods in the specification have been satisfactorily described and validated.

Batch analysis data confirm both compliance with the proposed specification and consistency between batches.
It is worthy of note that although erythromycin (from which telithromycin is derived) is very sensitive to low pHs that telithromycin did not degrade when stressed in an acidic solution.

The claimed retest period () is supported.

**Other ingredients**

All excipients in the product comply with the appropriate specifications and monographs of the current PhEur except for the iron oxides, which comply with the current monographs of the Ph.Fr. (and the NF).

Regarding the TSE compliance of the excipients, the lactose originates from milk of US cows and the magnesium stearate used is of vegetable origin.

Satisfactory control specifications and certificates are provided for the packaging materials.

**Product development and finished product**

An oral dosage form was chosen based on the properties of the active substance. In order to minimise the bitter taste of the active substance the tablets were film coated.

The development work leading to the actual composition, as well as the manufacturing process, have been well described and the critical process parameters identified. In-process controls have also been defined. Three full-scale batches were manufactured and used for method validation purposes.

All methods have been satisfactorily described and validated.

Batch analyses data have been provided for the three first full-scale and pilot-scale batches and these demonstrate both compliance with the proposed specifications and consistency of manufacture.

**Stability of the product**

The conclusions from the stability data provided are that there is no significant degradation, of the telithromycin substance itself, or as part of the tablet formulation, at either the long-term or accelerated conditions studied. The data support the shelf-life claimed in the SPC, with no special storage precautions, of 2 years.

3. **Part III: Toxico-pharmacological aspects**

**Pharmacodynamics**

The pharmacological action of telithromycin involves inhibition of bacterial protein synthesis and is similar to that of macrolides, but differences on the molecular level may exist. Telithromycin interacts with the translation at the 23S ribosomal RNA level and some data also indicate that assembly of the 30S and 50S subunits may be impaired. The in vitro antibacterial profile of telithromycin has been characterised using standard strains and clinical isolates. Antibacterial activity, as indicated by MIC values against important pathogens ranged from 0.001 to 0.06 mg/l for *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* to 0.5 and 4, (8) mg/l for *Haemophilus influenzae* (parainfluenzae).

Efficacy of telithromycin has been extensively studied in animal models of local and disseminated experimental infections. These included models of infection, such as the intra-abdominal abscess in mouse induced by *B. fragilis*, that involve microorganisms not directly relevant to the applied
indications. Comparison with several macrolides showed that superior or inferior activity of telithromycin as reflected in MIC values in vitro and in vivo, by survival rates, or reduction of bacterial burden, was species and strain dependent. In mouse models of respiratory tract infection due to Haemophilus influenzae, telithromycin (50-100 mg/kg, bid) seemed more active than erythromycin, but equipotent to clarithromycin, and slightly less efficacious than azithromycin. In a guinea-pig model using Legionella pneumoniœæ, telithromycin (10-15 mg/kg, ip) seemed equipotent to erythromycin, while the rate of reduction of lung bacterial burden seemed slower than for azithromycin. In vivo studies in mouse suggested activity of telithromycin against some erythromycin and penicillin resistant strains of Streptococcus pneumoniae. In the mouse-thigh model, poor activity was evident against Staphylococcus aureus with a constitutive resistance mechanism. It is noteworthy that in some cases, and for unknown reasons, in vivo activity was not evident despite low MIC values. Data obtained in the mouse-thigh model were also taken to support AUC/MIC as the most relevant parameter for prediction of activity. Results are, however, inconclusive due to the small number of animals and infrequent sampling. The animal data support activity of telithromycin against relevant microorganisms, but are generally inconclusive with respect to prediction of active dose and appropriate dosing intervals.

Pharmacokinetics

Most of the species used in toxicology studies were characterised pharmacokinetically. Telithromycin exhibited non-linear pharmacokinetics with greater than dose-proportional increases in C max and AUC after repeated doses, particularly at high doses. Usually an increase in systemic exposure with time was also observed. Absorption was rapid and studies in rat indicated ileum as the major site of absorption and an involvement of p-glycoprotein. In mouse, maximum levels in plasma were reached at 1.5 hours, but at 0.25 hours in rat and dog, compared with 1 hour in humans. The half-life in plasma ranged from 1.2 hours in mouse to over 2 hours in dog. Protein binding ranged from 36 to 90%, depending on species and concentration. In rats, a wide distribution, except to the CNS, was evident and distribution was overall similar in the pregnant and non-pregnant rat. In the pigmented rat, high label was detected in the uveal tract, while levels were low in black skin. Telithromycin is extensively metabolised with 5 to 19 metabolites detected in plasma, urine and faeces in different species. There were differences in metabolism, but all human metabolites were represented in other species and these can be considered as valid models. The major human metabolite, RU76363 was present only at low levels in rat and dog. In rat, the major pathway involves CYP3A1/3A2 and in humans CYP3A4/3A5. The main route of excretion was faecal, with 10 to 17% excreted in urine in rats. Unchanged compound accounted for the major part.

Toxicology

The toxicity of telithromycin with respect to general, reproductive and genetic effects was investigated in mouse, rat, dog, monkey and rabbit. The studies were in compliance with relevant guidelines and toxicokinetic data was available for pivotal studies.

Similarly to macrolides, telithromycin increased ADP 90/90 values in rabbit Purkinje fibers and inhibited activity at HERG (cloned human potassium channels) and Kv1.5 (shaker channels) at concentrations of ≥10 µM (8 mg/l). Early after-polarisations were seen only with telithromycin. Inhibition of HERG channels expressed in CHO cells was overall comparable with erythromycin and clarithromycin while the major human metabolites, RU76363 and RU71094, had little effect. In rabbit Purkinje fibers, synergistic effects were noted with sotalol, supraadditive effects with quinidine and additive effects during hypokalaemic conditions. Phosphodiesterase activity was inhibited by telithromycin (IC 50 ≤10 µM). In vivo studies in dogs showed changes in the ECG and a threshold plasma level of approx. 10 mg/l was identified. Taking protein binding into account, exposure margins to expected clinical levels are approx. 10x based on a free plasma concentration of 0.6 mg/l in humans. Both preclinical and clinical studies indicate that telithromycin has cardiovascular effects comparable with those of clarithromycin. The QT effects are considered in appropriate sections of the SPC.

Effects of single doses of telithromycin on other major organ systems: renal, digestive, respiratory, and genital systems were, overall, unremarkable. In rats, gastric acid secretion was inhibited at high
doses and the compound was weakly emetic in dogs but did not cause diarrhoea. In contrast, emesis and diarrhoea were commonly seen in dogs treated with azithromycin.

Telithromycin was shown to inhibit the H₂ receptor and had some inhibitory activity at the M₁ and M₂ receptors and these interactions were suggested to be involved in the potentiation of effects in combination with yohimbine, oxotremorine, tacrine and carbachol that resulted in mortalities in mouse studies. Telithromycin is also an inhibitor of thromboxane synthetase (IC₅₀=3 µM). In vitro anti-aggregatory activity was potentiated by aspirin, but coadministration in vivo in rabbits did not indicate any anti-aggregatory interactions, possibly due to differences in metabolism. In vitro histamine release was not significantly affected by telithromycin, but histamine release was increased in dogs after intravenous infusion and observations in other in vivo studies indicated interactions with histamine. The magnitude of these effects appeared modest and the clinical relevance is likely limited.

Toxicity of telithromycin after single doses was low, with lethal oral doses over 1000 mg/kg in mouse and rat. Deaths at high doses were considered coupled to an effect on the circulatory system. Toxicity after repeated doses was primarily manifested as changes in liver enzyme activities related to histopathological changes such as single cell necrosis and hepatocellular hypertrophy. These effects were seen in rats and dogs, but not in a 1-month monkey study. Electron microscopy of livers showed that bile duct cells were primarily affected in rats, but hepatocytes in dogs, and that azithromycin caused similar changes in rats. Increased caecum weights were noted in rat studies and is an effect seen with several macrolides. Telithromycin induced phospholipidosis in lung, bile duct and lymph nodes in rat and dog, this has also been reported with macrolides. Signs of nephrotoxicity were reported in 15 and 30-day dog studies at doses of 150 mg/kg or higher. Special toxicity studies showed that single oral doses of telithromycin did not aggravate renal failure in rat induced by glycerol and furosemide. In albino rats, cataracts developed at the end of 6 months treatment. Data are consistent with this being a strain-specific effect. No ocular effects were seen in a 6-month study in pigmented rats and ERG examinations in monkey after 1 month dosing were not indicative of any significant effects on parameters monitored. In dogs given 150 mg/kg, changes occurred in the pigmentation of the tapetum lucidum, a structure not found in human. In several rat studies, decreases in APTT and PT values were noted while increases in fibrinogen were reported in rats and dogs. No statistically significant effects of oral doses of 150 mg/kg of telithromycin on Brainstem Evocated Responses Audiometry were reported in a 1-month ototoxicity study in rats with kanamycin as the “positive” control. The sensitivity of this study would have improved if erythromycin, known for its ototoxic potential, had also been included in the study.

Overall, the general toxic profile of telithromycin was qualitatively similar to that seen with macrolides. At the no-effect levels, systemic exposure in rat studies was ~1x the expected clinical exposure, approx. 4-8x in dog, and 1-2x in monkey and margins of exposure are, thus, modest.

The potential for reproduction toxicity of telithromycin was investigated in rat and rabbit. In rat, high doses were related to a slight decrease in male and female fertility indices and daily sperm production. Embryofetal development was studied in rat and in two strains of rabbit at doses up to 300 mg/kg and 180 mg/kg, respectively. In rabbit (NZW), and to some extent in rat, a pronounced decrease in systemic exposure was evident from day 6 to day 18, particularly at the high dose, and margins of exposure at the identified no effect levels are not readily apparent. In rat, 5 of 310 fetuses examined at the high dose, but none in other groups, had malformations (protruding tongue and acaudate). This was considered related to maternal toxicity, but the relationship to toxicity is not clear. Treated groups in the rabbit study (NZW) also exhibited an increased incidence of malformations (absence of tail/anus, uni/bilateral absence of kidney/ureter), while no increase in malformations was recorded in the Himalayan rabbit study. The lack of data on the disposition of telithromycin in rabbits and the contradictory results in different strains made an assessment of the potential for teratogenic effects uncertain. Supplementary data showed that the difference in teratogenic potential in the two rabbit strains was likely not directly related to differences in metabolism. Also a direct relationship to maternal toxicity was not clear. The malformations are also found in historical control data, however, taken together, studies on the potential for adverse effects on foetal development are inconclusive and results are equivocal. The sections 4.6 and 5.3 of the SPC are rephrased to reflect the data. Teratogenic effects (cleft palate) of clarithromycin have been reported in mouse, but the relevance of this finding is
unknown. Telithromycin is excreted in milk of lactating animals. In the peripostnatal study in rats, parental treatment with telithromycin caused an initial slight decrease in pup viability that subsequently was comparable with control values and physical and mental development of pups seemed unaffected.

Telithromycin was tested in the standard battery of genotoxicity tests that included some studies with monkey S9 to provide exposure to the major human metabolite, which is present only in small amounts in rat. Overall, negative results were reported. The tests using monkey S9 are equivocal in that the positive control cyclophosphamamide did not give any significant increase in mutation frequency. Separate studies with the main human metabolites RU76363 and RU71094 were, however, negative.

To conclude, the preclinical studies with telithromycin have provided an adequate characterisation of the pharmacology and toxicology of the compound.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Erythromycin A is a therapeutic alternative in respiratory tract infections especially in penicillin allergy and in infections caused by atypical agents. Newer derivatives such as clarithromycin exhibit improved bioavailability and disposition but the antibacterial activity is nevertheless reduced at a low pH, and cross-resistance between the macrolides occurs.

In ketolides, the 14-membered macrolactone ring is retained, but the α L-Cladinose sugar moiety in position 3 has been replaced by a ketone group, conferring (together with the C11-C12 carbamate side chain) new in vitro properties.

Ketolides are less affected by a low pH than the newer macrolides. Telithromycin is more active than clarithromycin against both macrolide-susceptible and most macrolide-resistant gram-positive cocci, including those harbouring an inducible type of resistance, without inducing such resistance by itself. Like macrolides in general, telithromycin inhibits protein synthesis in bacteria by acting on ribosomes, but it has a higher affinity for the 50S ribosomal subunit than erythromycin, interacts with two domains, V and II of 23S rRNA in the 50S ribosomal subunit, and blocks the protein assembly of both the 50S and 30S ribosomal subunits.

Antibacterial activity:

The antibacterial spectrum includes the main gram positive pathogens *S. pneumoniae*, *S. pyogenes* and *S. aureus* and the gram negative RTI pathogens *H. influenzae*, *H. parainfluenzae* and *M. catharralis*, which, generally, have higher MICs. Atypical organisms such as *Chlamydia* spp, *Mycoplasma* spp and *Legionella* spp are also susceptible. In addition, there is activity against anaerobic gram positive cocci and bacilli. Macrolide antibiotics are generally merely bacteriostatic, but telithromycin is reported to possess bactericidal activity, as shown in kill-kinetic studies versus *S. pneumoniae*, irrespective of antibiotic susceptibility. It is mainly bacteriostatic against *S. pyogenes*. A postantibiotic effect has been demonstrated against the major respiratory pathogens.

Under experimental conditions, ketolides lack the potential to induce resistance to erythromycin in *S. pneumoniae*, *S. aureus*, *S. pyogenes* (and *E. faecalis*), in contrast to macrolides and azithromycin. In erythromycin resistant *S. pneumoniae*, six to eight transfers in the presence of telithromycin are needed to select resistance against the ketolide. In vitro studies showed that highly erythromycin resistant *S. pyogenes* (ermB and mefA genes) also exhibited resistance to telithromycin and telithromycin is, thus, not a drug of choice in the treatment of erythromycin resistant *S. pyogenes*.

Telithromycin has been shown to be active in murine septicaemia and respiratory infection models against both erythromycin susceptible and erythromycin resistant pneumococci, as well as against *H. influenzae*. 
PK/PD relationship:

The dosage 800 mg once daily results in peak plasma concentrations of approximately 2 mg/l at steady state, with through levels of 0.07 mg/l (range 0.015 to 0.259 mg/l). The higher levels obtained at the site of infection would then exceed the MIC of the targeted respiratory pathogens, as the ratio tissue/plasma at 24 h is 1383 in granulocytes and 540 in alveolar macrophages, and 14.3 and 13.1 in epithelial lining fluid and tonsils, respectively. The applicant claims that the relationship between telithromycin plasma, tissue and WBC levels is a more accurate predictor of efficacy than classical dose comparison studies. It is, however, unclear whether all of the tissue-bound antibiotic is bioactive, and if moderately susceptible hematogenously disseminated organisms are exposed to sufficient amounts of antibiotic. MIC for the common pathogen *H. influenzae* is up to 4 mg/l, and this serum concentration is not achieved with the recommended dosing regimen. Even more susceptible strains, with a MIC of 1 mg/l, will not be exposed to telithromycin serum concentrations above 1 mg/l for more than 1/8 of the dosing interval. Therefore, the breakpoint for $S \leq 0.5$ mg/l is now suggested for *H. influenzae*, and most of the strains are, thus, considered intermediate susceptible ($\geq 1$ mg/l). The choice of dosage appears to have been influenced by preclinical studies of the PK/PD of telithromycin against *S. pneumoniae* and *S. aureus* in the mouse thigh-infection model.

In the preclinical model, the 24h AUC/MIC was found to be the best parameter determining the efficacy of telithromycin. Corresponding data are not available from human studies, and a population PK/PD analysis performed on patients from the open CAP study supplied data that could be equally interpretable of Peak/MIC as the most relevant parameter.

A reduction of the duration of treatment from the traditional 7-10 days to 5 days in most RTIs was thought to be supported by the high antibacterial activity, and the high tissue concentrations achieved. In CAP, however, the documentation was considered insufficient to support a treatment duration shorter than 7-10 days.

Pharmacokinetics

A total of 682 subjects participated in a clinical pharmacology programme of 31 studies. The pharmacokinetics of telithromycin has been well studied and the documentation was well organised. Telithromycin was studied at oral doses of 50 to 2400 mg and intravenous doses of 120 to 2000 mg. Most of the clinical pharmacokinetic studies in patients at risk, tissue penetration studies and drug interaction studies were conducted with the proposed oral dose of 800 mg telithromycin, given as 2 x 400mg tablets, once a day.

Telithromycin is fairly rapidly and almost completely absorbed. There is a substantial first pass effect and the bioavailability of a single dose of 800 mg is 57%. A mean maximum plasma concentration of about 2 mg/l is reached within 1-3 hours after dose during once daily dosing of 800 mg. Food does not affect the rate or extent of absorption.

Telithromycin displays a triexponential decay from plasma after intravenous administration with a rapid distribution half-life of 0.17 h. The volume of distribution, $V_{ss}$, is large, 2.91 ± 1.0 L/kg, and telithromycin shows good penetration into respiratory tissues and white blood cells. *In vitro* protein binding is about 70%.

Telithromycin displays non-linear pharmacokinetics with a more than proportional increase in $C_{max}$ and AUC, reduced clearance and increased elimination half-life as the dose is increased. The non-linearity seems to be due to saturation of the metabolism. At an intravenous dose of 400 mg, clearance was 57.7±5 l/h. The main elimination half-life was about 2-3 h. There is a terminal half-life of about 10 h, accounting for a small proportion of the AUC. MRT was estimated to be 3.66 h.

Telithromycin is mainly eliminated by metabolism. About 20-23% of an i.v. dose is excreted unchanged in urine and about 12% unchanged in faeces. Renal clearance seems generally to be independent of dose and is about 12 l/h. Renal excretion of telithromycin involves both filtration and active tubular secretion. After oral administration, excretion is primarily in faeces, 76%. About 17% of the dose was excreted in urine. In faeces, unchanged telithromycin represented 28.7 % of faecal excretion and 20% of the administered dose. In urine, unchanged telithromycin represented the
majority of the radioactivity (69.1% of the radioactivity excreted in urine, corresponding to 12% of the administered dose). In urine, faeces and plasma, a total of 19 metabolites were present. The plasma concentration and excretion in urine and faeces of the four main metabolites have been determined. Telithromycin is the main circulatory compound in plasma, representing 56.7% of the total AUC of radioactivity. The main metabolite identified in plasma, RU 76363, an alcohol resulting from the loss of aryl rings, represented 7.6% of the AUC of radioactivity. The other three metabolites each represented less than 2% of the AUC of radioactivity. RU 76363 is further metabolised to RU 78849, the main metabolite identified in faeces. The metabolites are not likely to contribute to the bacteriological efficacy of telithromycin. RU 76363 is not formed by human liver microsomes, is not produced by CYP or other membrane bound enzymes, but may be produced by soluble drug-metabolizing enzymes in the liver. Thus, the main metabolic pathway is not CYP dependent. CYP3A4 is the major enzyme involved in the production of other minor metabolites of telithromycin. Minor contribution by CYP1A, 2A6 and 2B6 is possible.

Concomitant medication with 3A4 inhibitors resulted in up to 2-fold increase in systemic exposure of telithromycin. The increased exposure was within a well-tolerated range. It is therefore not necessary to change the telithromycin dose during concomitant medication with CYP3A4 inhibitors. No interaction studies have been performed with CYP3A4 inducers. Concomitant administration of CYP3A4 inducers could lead to a major reduction in telithromycin exposure. The Applicant is presently conducting an interaction study with CYP3A4 inducers, but results are not yet available. Meanwhile, treatment with Ketek should be avoided during and 2 weeks after treatment with CYP3A4 inducers. Ranitidine administered 1 h before telithromycin caused a mild but not clinically relevant reduction in telithromycin C\textsubscript{max} and AUC, while Maalox (Al(OH)\textsubscript{3} and Mg(OH)\textsubscript{2}) had no effect on telithromycin pharmacokinetics. As telithromycin and its metabolites are excreted in faeces, drugs that affect the biliary excretion could possibly interact with the excretion of telithromycin and its metabolites.

In vitro data showed that telithromycin is an inhibitor of CYP3A4 and CYP2D6. In vivo studies with simvastatin, midazolam and cisapride have demonstrated a potent inhibition of intestinal CYP3A4 and a moderate inhibition of hepatic CYP3A4. The data indicate that the inhibition potential of telithromycin is similar to that of clarithromycin, and is slightly higher than that for erythromycin. The inhibition potential is, however, lower than that for itraconazole and ketokonazole. Major interaction with CYP3A4 substrates with low bioavailability is expected, while 3A4 substrates with almost complete bioavailability will be less affected. As it will be difficult to predict the extent of interaction for specific drugs, concomitant medication with drugs metabolised by CYP3A4 should be avoided during telithromycin treatment unless plasma concentrations, effect or adverse events can be closely monitored and relevant dose adjustments can be made.

An in vivo interaction study with the CYP2D6 substrate paroxetine has been performed. However, paroxetine is itself a moderate inhibitor of CYP2D6 and is not an ideal substrate to use to evaluate interaction potential with CYP2D6. These data can not be used to support a lack of interaction with CYP2D6. Also, the Ki for 3A4 inhibition (58 \textmu M) was in the same range as that for 2D6 (46 \textmu M) and telithromycin caused a 2.2-fold increase in midazolam AUC (i.v. administration). A similar inhibition of 2D6 as of hepatic 3A4 cannot be ruled out. The applicant has committed to further evaluate the interaction potential with CYP2D6.

Other in vivo interaction studies suggest that telithromycin has no effect on CYP2C9. AUC of digoxin increased by 37% and C\textsubscript{max} by 73% on conadministration with telithromycin, presumably through inhibition of gastrointestinal Eubacterium lentum. Also, renal clearance of digoxin increased by 27%. This could possibly be caused by an induction of P-gp. However, the effect on P-gp seems to be moderate (15-20%) and is probably of limited clinical relevance. Telithromycin had no clinically relevant effect on the pharmacokinetics of oral contraceptives or warfarin. According to data from in vitro studies, telithromycin has no or limited effect on CYP1A, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1.

No proper evaluation of the relationship between plasma concentration and effect in humans has been performed. In a population PK/PD analysis, the covariate influence of C\textsubscript{max}, AUC, trough concentration, Peak/MIC, AUC/MIC and time over MIC (and a number of demographic covariates) on
clinical and bacteriological outcome, respectively, was studied using a logistic model. The analysis has contributed little to the understanding of the concentration effect relationship for telithromycin. No firm conclusions can be drawn from this analysis.

The pharmacokinetics of telithromycin in subjects with CAP is comparable with that in normal subjects. In a population pharmacokinetic analysis, the results suggested that elderly subjects, subjects with decreased creatinine clearance, and subjects with severe illness at pre-dose tended to have higher telithromycin plasma concentrations, while increased body surface area (>2.1 m^2) and smoking was associated with lower telithromycin plasma concentrations. The magnitude of the covariate influence was small and considered to be of limited clinical relevance.

The pharmacokinetic parameters observed in adolescents aged 12 to 17 years were similar to those observed in healthy male volunteers aged 18 to 40 years. There was a tendency towards an increased exposure in patients of the lower weight range (< 60 kg). Moreover, there was a difference in pharmacokinetics between male and female adolescents, with females having about 50% higher AUC and more than twice as high C_{24h}. The difference persisted when the parameters were normalised to body surface area (BSA). However, all data were within the range observed in adults.

Influence of renal and hepatic impairment on telithromycin pharmacokinetics was studied after single dose administration and showed a 50% increase in AUC and increased inter-subject variability in patients with mild to severe renal impairment. Based on estimation of exposure at steady state and safety analysis of patients included in phase III studies it has been concluded that dosage adjustment is not required in renal impairment except in subjects with severe renal impairment (creatinine clearance < 30 ml/min) where the dose should be halved. AUCs were similar between patients with hepatic impairment and control subjects, C_{max} was reduced, C_{24h} increased 2-fold and main and terminal half-lives were prolonged. Thus, increased accumulation could be expected. Steady state concentrations cannot be predicted from single dose data and telithromycin should be used with caution in liver impairment.

The pharmacokinetics was similar between male and female subjects, while elderly subjects had up to twice the exposure of young subjects. The pharmacokinetics has not been studied in children below the age of 12 years. Dose adjustment is not recommended in any special population, although an increased exposure is observed in the elderly, in renal impairment and during concomitant medication with CYP3A4 inhibitors. This is acceptable, as the increase was not more than two-fold and as the increased exposure is considered to be within a tolerable range.

Overall, it can be concluded that the pharmacokinetic documentation of telithromycin is sufficient. The results from the ongoing interaction study with rifampicin should be provided when available and further evaluation of the interaction potential with CYP2D6 substrates should be performed as a postmarketing commitment.

Clinical efficacy

The phase III documentation submitted consists of 10 clinical trials (4155 subjects were randomised, and 2485 received telithromycin,) conducted by Hoechst Marion Roussel between 1997 and 1999 in the following indications:

- Four trials in community-acquired pneumonia (CAP) (Studies 3000, 3001, 3006 and 3009).
- Two studies in acute sinusitis (3002 and 3005).
- Two trials in acute bacterial exacerbation of chronic bronchitis (AECB) (3003 and 3007).
- Two trials in tonsillitis/pharyngitis caused by group A beta-hemolytic streptococci (GABHS) (3004 and 3008). The clinical trials were performed in accordance with GCP standards and agreed international medical ethics.
Dose-response studies and main clinical studies

Diagnosis criteria and analysis sets are given in tables 1-2.

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<th>Table 1</th>
<th>Diagnosis</th>
<th>Entry criteria</th>
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<td>Community acquired pneumonia (CAP)</td>
<td>At least 2 of the following: Cough, purulent sputum, positive auscultation, dyspnoea, fever (&gt;38˚ orally, &gt;38.5˚ tympanically, or &gt;39˚ rectally), WBC &gt; 10.000 or &gt;15% immature neutrophils and positive chest X-ray</td>
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<td>Acute exacerbation of chronic bronchitis (AECB)</td>
<td>Documented history of chronic bronchitis, with symptoms for &gt;2 consecutive years and most days in a consecutive 3-months period, and with a clinical diagnosis of AECB based on at least two (three) of the following clinical signs and symptoms of AECB: Increased cough/dyspnoea; increased sputum volume; increased sputum purulence (Anthonisen criteria)</td>
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<td>Acute (maxillary) sinusitis</td>
<td>At least one sign/symptom that had lasted for less than 28 days: Purulent discharge, maxillary tenderness/toothache, maxillary pain at percussion, facial pain/pressure, nasal congestion and abnormal maxillary sinus X-ray showing presence of air/fluid level and/or total sinus opacity (+amendment in controlled study: &gt; 6 mm thickening of sinus mucosa)</td>
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<td>Acute tonsillitis/pharyngitis</td>
<td>Clinical tonsillitis or pharyngitis with sore throat combined with one or more of the following: Fever, erythema or oedema of the uvula, pharynx or tonsils, exudate, cervical lymphadenopathy and positive streptococcal antigen test or a positive throat culture</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Analysis populations</th>
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<tbody>
<tr>
<td>Population</td>
<td>Definition</td>
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<tr>
<td>MITT</td>
<td>All subjects with clinical signs and symptoms of the disease who received at least one dose of study medication, as treated</td>
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<tr>
<td>BmITT</td>
<td>All mITT subjects with a causative pathogen isolated at pretherapy/entry</td>
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<tr>
<td>PPc</td>
<td>All mITT subjects excluding those with major protocol violations</td>
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<tr>
<td>PPb *</td>
<td>All PPc subjects who had a causative pathogen isolated at pretherapy/entry</td>
</tr>
<tr>
<td>Safety</td>
<td>All subjects who received at least one dose of study medication, with at least one postbaseline safety assessment, (clinical or laboratory) as treated</td>
</tr>
</tbody>
</table>

* PP in Studies 3004 and 3008 where bacteriological outcome was the primary analysis of efficacy

Subjects were included in the per-protocol population if they had no predefined major protocol violations. The mITT population was selected to avoid inclusion of subjects with clear misdiagnoses. Each study included five visits: pretherapy/entry, on-therapy, end of therapy, posttherapy/test of cure (TOC) and late posttherapy. Efficacy was analysed at the two last visits. All subjects with indeterminate response were included as failures in the mITT population and as unsatisfactory in the bmITT population.

The diagnosis of infection was clinical, with radiological confirmation in the CAP and acute sinusitis studies. Samples for bacteriological diagnosis were taken before treatment when possible in all studies, and sinus puncture cultures were performed on all subjects in Study 3002 and at selected centres in Study 3005. In the tonsillitis/pharyngitis studies, multiple throat swabs were performed. Susceptibility to telithromycin was tested at the investigator’s local laboratory and retested in a central laboratory. Overall, the susceptibility of major pathogens to telithromycin was similar for local (by disk diffusion method) and central (MIC determination) laboratories. Serologic criteria considered
diagnostic for atypical pathogens in CAP were determined for *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*.

Efficacy was evaluated in terms of both clinical and bacteriological response. Clinical efficacy was based on signs and symptoms, and also on radiological findings in CAP and acute sinusitis. The clinical response was categorised as cure or failure. Bacteriological response by pathogen and by subject was assessed. Efficacy was evaluated by the investigator as specified, and bacteriological data were compiled by computer and verified manually.

The primary analysis of efficacy was the per protocol analysis at posttherapy/TOC of clinical outcome (PPc population) in studies 3000, 3001, 3002, 3003, 3005, 3006, 3007 and 3009, and the per protocol analysis of bacteriological outcome (PP population) in studies 3004 and 3008.

Other analyses performed included per protocol analyses of clinical and bacteriological outcome at late posttherapy, and modified intent-to-treat (mITT and bmITT) analyses of clinical and bacteriological outcome at posttherapy/TOC and late posttherapy.

A two-sided 95% confidence interval (CI) was calculated for the difference in cure rate between telithromycin and comparator. A non-inferiority margin of -15% was chosen for the CAP, AECB and sinusitis studies, and -10% in the tonsillitis/pharyngitis studies. Pre-specification of non-inferiority margin, confidence level, power etc. is essential in the planning of a clinical trial. However, failure to meet the non-inferiority margin used in the sample size calculation does not necessarily invalidate a study. This must always be a matter of regulatory and clinical judgement taking internal as well as external data into account.

**Community Acquired Pneumonia (CAP)**

Four studies were performed in patients with CAP. These were mostly outpatients requiring oral therapy. Study 3000 was open and uncontrolled and enrolled hospitalised and, possibly more severely ill patients. In addition to assessment of efficacy and safety, this study used a population pharmacokinetic approach to investigate the relationship between pharmacokinetics and efficacy.

The other studies were double-blind, randomised, parallel group and active controlled. The telithromycin dose was 800 mg once daily for 10 days in Studies 3001 and 3006, and for 7 to 10 days in Studies 3000 and 3009. The comparator regimen was amoxicillin 1,000 mg three times daily for 10 days in Study 3001, clarithromycin 500 mg twice daily for 10 days in Study 3006, and trovafloxacin 200 mg once daily for 7 to 10 days in Study 3009.

A total of 1,341 patients were randomised, and 1,340 treated in the four CAP studies. The median duration of treatment was 10 days (PPc population). In the PPc population, 578 of 598 subjects received telithromycin for at least 7 days. 57 patients were treated for at least 7 but less than 10 days.

**Results**

There were considerable differences between the CAP studies as regards prognostic factors/risk factors.

In studies 3006 and 3009, only about 25% of the patients had fever >39°C at inclusion, and less than half had leukocytosis. In contrast, 3/4 of patients in study 3001 were febrile, 60% had leukocytosis, and pneumococcal bacteraemia was more common. None of the pneumococcal isolates exhibited telithromycin resistance, and the overall resistance pattern was surprisingly benign. Resistance in *H.influenzae* and *M.catarrhalis* was, however, not uncommon. The applicant does not comment on the atypical organisms detected by serology and PCR, but in practice, all respiratory mycoplasmal and chlamydial strains are regarded as susceptible.

The atypical infections diagnosed using highly specific criteria (66 telithromycin-treated and 42 comparator-treated) or less stringent criteria (346 versus 285) could explain the difference in risk factors found between study 3001 and studies 3006 and 3009. It is well known that leukocytosis and high fever are characteristic features in pneumococcal pneumonia, in contrast to atypical pneumonias, where moderate fever and absence of leukocytosis is common.
Outcome data are given in Table 3.

### Table 3. Clinical outcome (PPc) and bacteriological outcome (PPb) in CAP studies

<table>
<thead>
<tr>
<th>3000</th>
<th>3001</th>
<th>3006</th>
<th>3009</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMR 3647</td>
<td>HMR 36 47</td>
<td>AMX 47</td>
<td>HMR 36 CLA 47</td>
</tr>
<tr>
<td>Clinical outcome cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td>183/197</td>
<td>141/149</td>
<td>137/152</td>
</tr>
<tr>
<td></td>
<td>(92.9%)</td>
<td>(94.6%)</td>
<td>(90.1%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>--</td>
<td>[-2.1;11.1]</td>
<td>[-7.9;7.5]</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td>165/182</td>
<td>115/125</td>
<td>116/136</td>
</tr>
<tr>
<td></td>
<td>(90.7%)</td>
<td>(92.0%)</td>
<td>(85.3%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>--</td>
<td>[-1.7;15.1]</td>
<td>[-7.4;10.2]</td>
</tr>
<tr>
<td>Bacteriological outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>40/45</td>
<td>36/40</td>
<td>35/40</td>
</tr>
<tr>
<td></td>
<td>(88.9%)</td>
<td>(90.0%)</td>
<td>(87.5%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>43/52</td>
<td>42/48</td>
<td>39/45</td>
</tr>
<tr>
<td></td>
<td>(82.7%)</td>
<td>(87.5%)</td>
<td>(86.7%)</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>37/42</td>
<td>30/36</td>
<td>29/36</td>
</tr>
<tr>
<td></td>
<td>(88.1%)</td>
<td>(83.3%)</td>
<td>(80.6%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>41/49</td>
<td>36/44</td>
<td>34/40</td>
</tr>
<tr>
<td></td>
<td>(83.7%)</td>
<td>(81.8%)</td>
<td>(85.0%)</td>
</tr>
</tbody>
</table>

AMX = amoxicillin, CLA = clarithromycin, TVA = trovafloxacin, CI = confidence intervals
HMR 3647 = telithromycin

As can be seen, differences between treatments were within the predefined limits in all studies at posttherapy/TOC. In study 3009, 95% CI was -15.8;4.3 at late posttherapy and, consequently, not within the predefined limit at that point of time. The lower limit of the confidence interval for study 3001 and 3006, -2.1% and –7.8% respectively, is in accordance with a conclusion of non-inferiority. This conclusion is not contradicted by the outcome in the smaller and prematurely terminated study 3009, especially as trovafloxacin is no longer a relevant comparator.

The clinical cure rate – as provided by the Applicant in the original dossier - with telithromycin in the PPb population at posttherapy/TOC was 90.8% (69/76) in subjects with proven pneumococcal pneumonia, 76.5% (26/34) in H. influenzae infections, 90.0% (9/10) in H. parainfluenzae infections, and 72.7% (8/11) in M. catarrhalis infections. Using the stringent criteria for diagnosis of atypical infection, the clinical cure rate was 95.5% (63/66) for subjects with proven atypical infection (C. pneumoniae 33/35 [94.3%], M. pneumoniae 26/27 [96.3%] and L. pneumophila 4/4).

Efficacy was shown in a moderate number of patients with bacteraemic pneumococcal pneumonia, but in view of exclusion criteria to the conducted trials, it could be argued that the indication should be restricted to mild to moderate pneumonia. With additional data presented in the Applicant’s response to the CPMP questions, efficacy outcome results are available from 89 cases (82 evaluable cases) of penicillin and/or erythromycin resistant S. pneumoniae, showing that the results obtained in this subset of population were similar to those seen in the overall population with S. pneumoniae infection. This seems promising, especially as telithromycin lacks the capacity to select resistance in vitro. There are,
however, indications that cross-resistance between erythromycin and telithromycin linked by the ermB gene can appear. In vitro results have also shown that telithromycin is affected by the erythromycin ermB or mefA related mechanisms but, to a lesser extent than erythromycin. Also other mechanisms could be involved conferring telithromycin resistance. Thus, it is important to closely monitor the development of resistance to telithromycin in S. pneumoniae, especially in areas where penicillin/erythromycin resistance is as high as in the southern parts of Europe (40-50%).

The experience with treatment of erythromycin resistant pneumococci is limited and clinical failures have appeared. In areas with low incidence of penicillin and/or erythromycin resistant S. pneumoniae, telithromycin should be considered a second-hand choice. In areas with a prevalence of > 10 % of resistance against penicillin and/or erythromycin, telithromycin could be recommended for the treatment of infections caused by S. pneumoniae. Consideration should rather be given to local/regional official guidance on the appropriate use of antibacterial agents than restricting the indications under 4.1.

**Acute bacterial exacerbation of chronic bronchitis (AECB)**

Studies 3003 and 3007 were double-blind, randomised, comparative studies in subjects with AECB. Study 3003 was restricted to subjects with COPD and evidence of airway obstruction (FEV1/FVC ratio ≤ 70% in the past year). Subjects had to have 3 Anthonisen signs of acute exacerbation in Study 3003 and at least 2 in Study 3007. The dosage of telithromycin in both studies was 800 mg once daily for 5 days. Amoxicillin 500 mg/clavulanic acid 125 mg three times a day for 10 days was used as the comparator in Study 3003, and cefuroxime axetil 500 mg twice daily for 10 days in study 3007. The bacteriological evaluation in both studies was based on culture of an adequate sample (≥25 PMNs and <10 epithelial cells per high power field in direct microscopy).

**Results:**

In the bmITT population in the two studies, *H. influenzae* (102/288; 35.4%), *H. parainfluenzae* (22/288; 7.6%), *S. pneumoniae* (38/288; 13.2%) and *M. catarrhalis* (41/288; 14.2%) were the most common isolated pathogens. Among the main pathogens isolated at baseline, 1.1% (1/94) *H. influenzae*, 18.2% (4/22) *H. parainfluenzae*, 2.8% (1/36) *S. pneumoniae* and 0% (0/36) *M. catarrhalis* were resistant to telithromycin by disk diffusion method in the local laboratory. Two out of 37 (5.4%) *H. influenzae* and 2/10 (20.0%) *M. catarrhalis* isolates were resistant to amoxicillin/clavulanic acid. The median number of days of active treatment was 5 days for the telithromycin group in both studies and 10 days for both amoxicillin/clavulanic acid and cefuroxime axetil (PPc population).

The two-sided 95% confidence interval for the difference in cure rates indicated therapeutic equivalence between telithromycin and the comparator drugs (amoxicillin/clavulanic acid and cefuroxime axetil) in both studies (Table 4).
Table 4. Clinical outcome (PPc) and bacteriological outcome (PPb) in AECB studies

<table>
<thead>
<tr>
<th></th>
<th>3003</th>
<th>3007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HMR 3647 5-day</td>
<td>AMC 10-day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td>99/115 (86.1%)</td>
<td>92/112 (82.1%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[-6.4;14.3]</td>
<td>[-4.3;10.0]</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td>82/105 (78.1%)</td>
<td>81/108 (75.0%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[-9.2;15.4]</td>
<td>[-7.1;10.1]</td>
</tr>
<tr>
<td>Bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>27/39 (69.2%)</td>
<td>21/30 (70.0%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>32/42 (76.2%)</td>
<td>26/32 (81.3%)</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>19/33 (57.6%)</td>
<td>16/26 (61.5%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>21/35 (60%)</td>
<td>20/28(71.4%)</td>
</tr>
</tbody>
</table>

AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil, CI = confidence intervals

The clinical cure rates for telithromycin were slightly higher than for the comparator in both studies. Cure rates in Study 3003 were slightly lower compared to Study 3007, probably because of the severe underlying COPD in Study 3003. Cure rates at late posttherapy were lower than at posttherapy/TOC in both studies, as expected in this chronic relapsing disease.

Bacteriological responses were lower than the clinical response for both telithromycin and the comparators.

The bacteriological response by subject for telithromycin was similar to the comparator in both studies at posttherapy/TOC as well as at late posttherapy, but the eradication rate for telithromycin in Study 3003 was slightly lower than for the comparator. The by subject response and eradication rate were lower for both telithromycin and the comparator in the subjects with more severe COPD (study 3003).

The clinical cure rate in the mITT population confirmed the results of the PPc population shown in the above table.

The results indicate that 800 mg (2 x 400 mg) telithromycin given orally once daily for 5 days is as effective as 10 days therapy with the comparators in the treatment of AECB. However, persistence of pathogens, especially Gram negative such as *H. influenzae* can be seen in AECB patients despite an adequate clinical response. Since patients will be neither asymptomatic, nor bacteriologically sterile between treatments, it is difficult to assess efficacy when there is no "normal state" to return to. Objective measurements such as inflammatory parameters are not available, and the effect against a placebo comparator is unknown. Time to next exacerbation could be some kind of objective measurement, and might differ between 5 and 10 days duration of treatment. Such information is lacking. The treatment with antibiotics in AECB may sometimes be questioned, even though some of the patients treated probably will do better with antibiotics. These questions are controversial and difficult and involve not only telithromycin, but all antibiotic treatment in AECB. Positioning of telithromycin in the treatment of AECB must be guided by local/regional guidelines.

**Sinusitis**

The efficacy of telithromycin 800 mg once daily in acute sinusitis was tested in two randomised, double-blind, comparative studies (3002, 3005). X-ray confirmation of sinusitis was required in both studies. Sinus puncture was required to gain appropriate material for culture in subjects with X-ray
findings of air fluid level or total sinus opacity in study 3002. This study compared two durations of treatment (5 days vs. 10 days) with telithromycin in a blinded manner.

In Study 3005, the treatment regimens were telithromycin 800 mg once daily for either 5 days or 10 days, and amoxicillin 500 mg/clavulanic acid 125 mg three times a day for 10 days. Sinus X-ray findings of air fluid level, total opacity or mucosal thickening of ≥6 mm were required for enrolment; sinus puncture was only performed at selected centres. Equivalence was tested between the telithromycin 10-day group and amoxicillin/clavulanic acid and between the telithromycin 5-day group and amoxicillin/clavulanic acid using a closed comparison procedure. Altogether 1,132 subjects were randomized, and 1,126 treated in the two studies. The median number of days of active treatment was 5 days for the telithromycin 5-day group and 10 days for the 10-day group in both studies and 10 days for the amoxicillin/clavulanic acid group in Study 3005 (PPc population).

Results:
In the bmITT population, S. pneumoniae (81/283; 28.6%) was the most common pathogen, followed by H. influenzae (41/283; 14.5%), S. aureus (30/283; 10.6%) and M. catarrhalis (18/283; 6.4%). Among the main pathogens isolated at baseline, only 1/30 (3.3%) S. aureus and 1/6 H. parainfluenzae isolates were resistant to telithromycin by disk diffusion method in the local laboratory. Equivalence was found between the telithromycin 5-day and 10-day regimens in Study 3002, and these regimens were shown also to be equivalent to amoxicillin/clavulanic acid for 10 days in Study 3005.

Table 5. Clinical outcome (PPc) and bacteriological outcome (PPb) in acute sinusitis studies

<table>
<thead>
<tr>
<th></th>
<th>3002</th>
<th>3005</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HMR 3647 5-day</td>
<td>HMR 3647 10-day</td>
</tr>
<tr>
<td>Clinical outcome cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td>112/123 (91.1%)</td>
<td>121/133 (91.0%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[-7.7;7.9]</td>
<td>[-9.5;11.9] a</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td>96/108 (88.9%)</td>
<td>107/120 (89.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[-9.3;8.7]</td>
<td>[-12.1;11.1] a</td>
</tr>
<tr>
<td>Bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>65/70 (92.9%)</td>
<td>62/69 (89.9%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>78/86 (90.7%)</td>
<td>84/92 (91.3%)</td>
</tr>
<tr>
<td>Late posttherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>54/60 (90.0%)</td>
<td>53/61 (86.9%)</td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>63/72 (87.5%)</td>
<td>74/82 (90.2%)</td>
</tr>
</tbody>
</table>

AMC = Amoxicillin/clavulanic acid

a Pairwise comparison between 5-day HMR 3647 and AMC
b Pairwise comparison between 10-day HMR 3647 and AMC

The applicant has forwarded several explanations for the lower outcome rates in study 3005. An alternative explanation that should be considered is that all patients in study 3002 underwent a sinus
puncture. The maxillary sinuses were reportedly not rinsed, but aired. A maxillary sinus puncture may be conceived as a therapeutic intervention, and may also serve as an explanation for the continuation of the excellent clinical outcome in study 3002, in contrast to study 3005. Clinical cure was achieved in about 90% of telithromycin treated patients in the former study both at posttherapy/TOC and late posttherapy, whereas it was reduced from 75 to 70% in both telithromycin groups between posttherapy/TOC and late posttherapy in study 3005. Another plausible explanation is that in study 3005, the inclusion criteria were not as strict as in study 3002, thus allowing inclusion of patients with other diseases than acute purulent sinusitis. As *H. influenzae* is often the cause of acute sinusitis, telithromycin should only be used when other antibiotics are inappropriate, such as in allergies or in areas with high a prevalence of erythromycin resistant pneumococci.

**Tonsillitis/pharyngitis**

Telithromycin was investigated in the treatment of tonsillitis/pharyngitis due to Group A beta-hemolytic streptococci (*S. pyogenes*) in two randomised, double-blind, comparative studies. The regimen was 800 mg once a day for 5 days in both studies. In Study 3004, the comparator was penicillin V 500 mg three times daily for 10 days. In Study 3008, the comparator was clarithromycin 250 mg twice daily for 10 days.

**Results**

Of the 648 *S. pyogenes* isolates in the bmITT population, 4/631 (0.6%) were resistant to telithromycin, 13/339 (3.8%) were resistant to clarithromycin and none of the 288 isolates tested were resistant to penicillin by the disk diffusion method. The two-sided 95% confidence interval indicated equivalence between the telithromycin 5-day regimen and clarithromycin for 10 days in Study 3008. Similarly, the telithromycin 5-day regimen was shown to be equivalent to penicillin V for 10 days in Study 3004 for clinical efficacy (table 6).

**Table 6. Clinical and bacteriological outcome (PP population) in tonsillitis/pharyngitis**

<table>
<thead>
<tr>
<th></th>
<th>3004</th>
<th>3008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HMR 3647</td>
<td>PEN</td>
</tr>
<tr>
<td>Clinical outcome cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td>109/115</td>
<td>112/119 (94.1%)</td>
</tr>
<tr>
<td>(94.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-6.1;7.4]</td>
<td></td>
</tr>
<tr>
<td>Late posttherapy</td>
<td>100/108</td>
<td>100/111 (90.1%)</td>
</tr>
<tr>
<td>(92.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-5.8;10.9]</td>
<td></td>
</tr>
<tr>
<td>Bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttherapy/TOC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>97/115</td>
<td>106/119 (89.1%)</td>
</tr>
<tr>
<td>(84.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-14.3;4.8]</td>
<td></td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>98/115</td>
<td>106/119 (89.1%)</td>
</tr>
<tr>
<td>(85.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late posttherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By subject (satisfactory)</td>
<td>89/108</td>
<td>94/111 (84.7%)</td>
</tr>
<tr>
<td>(82.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-13.0;8.5]</td>
<td></td>
</tr>
<tr>
<td>By pathogen (eradicated)</td>
<td>93/108</td>
<td>96/111 (86.5%)</td>
</tr>
<tr>
<td>(86.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEN = Penicillin V, CLA = clarithromycin
The by subject bacteriological response and the eradication rate at posttherapy/TOC for telithromycin treated subjects were slightly lower than in the penicillin V group in Study 3004 and fell outside the protocol-defined non-inferiority margin of –10%. The difference was mainly due to persistence of erythromycin A resistant *S. pyogenes* in the telithromycin group. There were six isolated such strains in the telithromycin group, with clinical cure in 6/6, but eradication in only 1/6. This could be compared with cure and eradication in 8/9 cases in the PcV group. The genotyping results of the 6 erythromycin A resistant strains from telithromycin treated subjects indicated a correlation between the presence of mefA and ermB erythromycin A resistance genes and persistence of *S. pyogenes*. As the response rates for both treatment groups were lower than expected, the sample size required for the study was underestimated resulting in an increase in the width of the CI. The CPMP guideline for evaluating anti-infectives proposes that a delta of 10% can often be used. However, as mentioned in the CPMP guideline the ultimate choice will have to rely on clinical judgement and the justification available in the protocol. It is judged that the two treatments can be regarded as being equivalent.

In Study 3008, similar observations were made in telithromycin-treated patients with erythromycin A resistant strains. Clinical cure was achieved in 4/5 patients at posttherapy/TOC, but 3/5 had bacteriological persistence. Of the 4 subjects with cure at posttherapy/TOC, all were cured and had achieved eradication at late posttherapy (i.e. two patients achieved eradication secondarily). In contrast, only 2/4 in the clarithromycin group showed clinical cure, whereas 4/4 had bacteriological persistence. Both patients with cure at posttherapy/TOC had clinical cure and bacteriological persistence at late posttherapy. Also in this study, all *S. pyogenes* strains that persisted after telithromycin treatment belonged to the mefA or ermB genotypes.

Generally, five days treatment with telithromycin appears to be similarly effective as 10 days treatment with penicillin V or clarithromycin. As cross-resistance with highly erythromycin resistant (mefA, ermB resistance genes) strains has been observed, telithromycin should not be used in the treatment of acute tonsillitis caused by erythromycin resistant *S.pyogenes*. The risk/benefit of telithromycin compared with clarithromycin for the treatment of *S. pyogenes* tonsillitis could be questioned as more gastrointestinal side effects were recorded for telithromycin treated patients compared with clarithromycin. However, the side effects were not severe and would not entirely disqualify the treatment of acute tonsillitis from a positive opinion. The indication is thus modified as outlined in the SPC.

**Clinical studies in special populations**

No clinical studies have been performed with special populations as targets.

**Supportive studies**

As indicated above, the Applicant has submitted additional data on resistant *S.pneumoniae*. There are 3 ongoing studies (Two studies conducted in the US and one in Japan).

**Clinical safety**

All patients who received at least one dose of study drug and had at least one post pretherapy/entry safety evaluation were evaluated for safety. The investigators assessed the intensity and causal relationship.

**Patient exposure**

At least one adverse event irrespective of relationship to study drug was reported in 1387/2461 (56.4%) of telithromycin patients versus 48.6% of comparators. Treatment-emergent adverse events (TEAEs) were reported in 50.3% telithromycin patents and 48.6% comparators. In the controlled studies, the frequency of TEAEs was similar in the telithromycin 5-day (47.8%) and comparator
groups (48.6%) and higher in the telithromycin 10-day group (59.5%). The frequency of TEAEs was generally higher in CAP studies and in studies conducted in North America.

**Adverse events and serious adverse events/deaths**

TEAEs were most frequently reported from the digestive and nervous systems. The frequencies of events per body system were generally similar for telithromycin and comparators, but digestive system symptoms were more frequent with telithromycin (30.8%) than comparators (22.6%). Moderate and severe symptoms were essentially equally common with telithromycin (9.9% and 2.6%) as with comparator (7.7% and 1.5%). TEAEs assessed as possibly related to the study treatment were reported for 35.8% of the telithromycin patients and 28.3% of the comparator patients. Diarrhoea, nausea, dizziness, vomiting, dyspepsia, abdominal pain, flatulence and gastrointestinal pain occurred more frequently with telithromycin than with comparators, but discontinuation due to TEAEs was equally common in both groups (5.0% versus 4.4%), and the rate of discontinuation because of adverse events did not differ either (4.6% versus 4.4%).

As some 14-membered macrolides, for example erythromycin, induce contractile activity in the gastrointestinal tract, mimicking the effect of the GI peptide motilin, telithromycin’s affinity to the motilin receptor was questioned. However, it was demonstrated that the affinity of telithromycin was less than that of clarithromycin and erythromycin.

The gastrointestinal adverse effects were mostly mild and only one patient developed gastroenteritis suspected to be caused by *C. difficile* and telithromycin had a discontinuation rate due to possibly related diarrhoea similar to that of clarithromycin. The impact on the salivary and faecal microflora of telithromycin and clarithromycin showed that telithromycin caused a selective reduction of the microflora to the same extent as did clarithromycin and no *C. difficile* strains were isolated during treatment. That a motilin effect might explain the relatively high frequency of GI TEAEs is not plausible, as the affinity to the motilin receptor seems to be much weaker for telithromycin than for clarithromycin or erythromycin.

Dizziness and blurred vision have been reported more frequently in telithromycin-treated patients across all studies. The increase in dizziness is hardly significant but blurred vision, although reversible and infrequent, was reported in 15/2461 (0.6%) in the telithromycin group, versus 1/1631 (0.06%) in the comparator group. Further studies on blurred vision are planned by the applicant.

The total number of serious adverse events reported was 59 (2.4%) for telithromycin treated patients against 40 (2.5%) comparator patients. There were three serious hepatic TEAEs in telithromycin treated and one in a comparator treated patient (clarithromycin). Two telithromycin patients demonstrated a hepatocellular injury pattern (one of them with a history of alcoholic abuse), the third had an “allergic hepatitis”.

Deaths were reported in 0.1% of both telithromycin and comparator patients during the treatment-emergent period, but the events had no causal relationship to the study treatments. Three further events occurred post-treatment (one telithromycin and two comparator patients) that were likewise considered unrelated to study treatment.

**Laboratory findings**

A system of predefined changes was used in all trials. Incidences of predefined change abnormal (PCA) values and clinically noteworthy abnormal laboratory values (CNALV) were similar for telithromycin and comparator treatment patients. Abnormal findings were generally more common in CAP patients. Elevated ALT was observed in 1.1% with telithromycin 5-days and 3.3% with 7-10 days treatment, versus 1.7% in the combined comparator group. Thus, an extended duration of treatment, from 5 to 10 days, especially in association with CAP, seems to be connected with elevated transaminases. Additionally, the data from trial 3000 in CAP created concern. In this study, LFT abnormalities were reported in 28/240 (11.6%) of patients on telithromycin. However, this might be explained by the patients being more severely ill and more patients being hospitalised and that this
study was a non-controlled study. In summary, there were no clear indications that telithromycin causes more frequent or more severe hepatic adverse effects than clarithromycin.

**QTc prolongation**

Evaluation was undertaken in compliance with the CPMP points to consider document. *In vitro*, telithromycin inhibited cloned human Ikr channels to a similar extent as erythromycin and clarithromycin and increased the action potential duration in isolated rabbit purkinje cells. These effects were observed at concentrations ≥ 10x the free concentration seen in clinical use. Toxicity studies with telithromycin in dogs showed increased heart rate and QTc prolongation (16-31 msec) at concentrations of free drug approximately 8x the free concentration seen in clinical use.

In clinical pharmacology studies, multiple ECGs were recorded and alert terms were set up to detect asymptomatic corrected QT. The effect of telithromycin was studied at therapeutic and supraclinical doses, as was the potential for increased drug levels by drug interaction, such as itraconazole, ketoconazole and cisapride. At 800 mg, no clinically significant QTc changes were noted throughout the studies. Four alert terms were reported in healthy subjects, one in a young subject at 800 mg, not confirmed by the expert review, and the other three in elderly subjects (1 at 600 mg and 2 at 800 mg). No QTc prolongation >500 msec was observed and all events were asymptomatic.

In healthy volunteers given a single supra therapeutic dose of telithromycin (2400 and 3200 mg) a significant increase of QTc of 17 and 16 msec, respectively, compared with placebo was found. These doses were associated with an increased heart rate of 11 and 13 bpm and the more appropriate correction by the Fredericia formula gave a QTf of 6 and 3 msec, respectively.

In patients with hepatic impairment, 2 QTc prolongations were observed, both asymptomatic, in 2 patients who had QTc prolongation before administration of telithromycin. In patients with renal impairment, 3 QTc prolongations were declared as alert terms, none confirmed by expert reading ECG. At supraclinical doses, based on expert ECG reading, the statistical analysis showed a mean maximal increase in QTc from baseline of 28 msec at 2400 mg of telithromycin in young subjects and 19 msec at 2000 mg of telithromycin in elderly subjects. A PK/PD analysis was performed using all ECGs overread by the experts at therapeutic and supraclinical doses. In healthy subjects, an increase in telithromycin concentration led to a small concentration dependent increase in QTc interval. For each mg/L increase, there was a corresponding increase of 1.96 msec in QT, or 1.62 msec in QTf.

A study comparing the QT interval at different heart rates induced by exercise tolerance test, thereby avoiding the need for heart rate correction, showed that neither telithromycin, nor clarithromycin had significant effects on the QT interval at therapeutic doses.

In a study including 24 patients with established cardiovascular disease (presumably having an increased risk of QT prolongation and TdP), a single dose of telithromycin 1600 mg significantly prolonged QTc by 7 msec compared with placebo, but no difference was seen in the frequency of ΔQTc > 30 msec.

In the phase III studies, a modest mean increase in QTc (+1.1 (21.1) msec) and QTf (+3.1 (19.6) msec) interval was observed with telithromycin treatment. There was no clinically significant difference between telithromycin and the comparators for the change in QTc interval. Significant QT dispersion (>100 msec) was not observed either during therapy or post-treatment in any telithromycin treated patients. Subjects with prolonged QTc at baseline generally experienced a decrease of QTc during treatment with telithromycin. Data for subjects with cardiovascular disease or ECG abnormalities did not vary notably from the population as a whole. No case of cardiac arrest, torsades de pointes, other serious ventricular arrhythmias or seizures were reported during the phase III program.

It is concluded that telithromycin has a potential to induce a modest QTc prolongation, but the adequately performed study program strongly suggests that this has minor clinical relevance at therapeutic doses. The potential to induce a clinically relevant QTc prolongation is not increased in comparison with clarithromycin. This issue is considered in the relevant sections of the SPC.
Safety in special populations

Safety findings have been assessed for elderly subjects, men and women, racial origin, weight, and disease states such as cardiovascular and chronic respiratory disease, diabetes, renal and liver impairment, and in patients on treatment with drugs metabolized by CYP3A4 and CYP2D6, antiarrhythmics, theophylline, anticoagulants, cardiac glycosides, corticosteroids, CNS drugs, and with drugs known to increase QTc, and diuretics. Patients with abnormal ECG/increased QTc at baseline and with risk factors for torsade de pointes or hypokalemia have been similarly assessed. Generally, the frequencies of adverse events did not differ between telithromycin and comparators.

5. Part V: Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Thus, the physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

The preclinical documentation provides overall an adequate characterisation of the pharmacology and toxicology of telithromycin and relevant information has been included in the SPC. Preclinical studies showed the liver to be the primary target for toxic effects of telithromycin. Data from investigations on reproduction toxicology were not conclusive concerning the potential for adverse effects on fetal development and the compound should not be used during pregnancy unless clearly necessary. Telithromycin and its major human metabolites were negative in tests for genotoxic potential. As the clinical use is expected to be short-term no carcinogenicity studies were conducted.

Efficacy and Safety

Telithromycin is a new antibacterial agent, closely related to the macrolides, but with activity in vitro against most organisms that are macrolide resistant. The effect against pneumococci is bactericidal. Telithromycin was active in vitro against all penicillin-resistant pneumococci, but eradication may fail in erythromycin-resistant but telithromycin-susceptible isolates.

The performed clinical trials, in general, support similar efficacy of telithromycin and comparators in the indications investigated (CAP not clinically serious enough to warrant parenteral therapy but efficacy has been demonstrated in a limited number of patients with risk factors such as pneumococcal bacteraemia or age higher than 65 years, AECB, sinusitis, and pharyngotonsillitis caused by S. pyogenes).

In the present studies the prevalence of highly resistant S. pneumoniae was much lower than the alarming rates (>40%) reported from several countries and therefore no conclusions can be drawn as to the efficacy of telithromycin in populations dominated by highly resistant pneumococci. Clinical efficacy was, however, documented in the majority of the pneumonia or sinusitis patients infected with macrolide or penicillin resistant pneumococci studied. This seems promising, especially as telithromycin lacks the capacity to select resistance in vitro. Persistence of macrolide resistant strains and failure of therapy was, however, seen in isolated cases after telithromycin in spite of low MIC values. There are indications that cross-resistance between erythromycin and telithromycin linked by the ermB gene can appear. In vitro results have also shown that telithromycin is affected by the erythromycin ermB or mefA related mechanisms but, to a lesser extent than erythromycin. Also other mechanisms could be involved conferring telithromycin resistance. Thus, it is important to closely monitor the development of resistance to telithromycin in S. pneumoniae, especially in areas where penicillin/erythromycin resistance is as high, as in the southern parts of Europe.
Cross-resistance to highly erythromycin resistant (ermB, mefA resistance genes) *S. pyogenes* strains is a fact, and therefore telithromycin should not be used in infections caused by erythromycin resistant *S. pyogenes*.

More than half of the *H. influenzae* isolates failed to be inhibited by 1 mg/l of telithromycin, a concentration that will only be achieved during 3-4 hours of the dosing interval with the recommended dosage of 800 mg once daily. Cure rates were only around 60% in the elderly. Therefore the breakpoints for *H. influenzae* and *H. parainfluenzae* have been set to the same as for other bacteria, i.e. $S \leq 0.5$ mg/l and thus, *H. influenzae* is considered intermediately susceptible ($I \geq 1$ mg/l).

From *in vitro* data, good activity is expected against atypical organisms, and this is supported by clinical experience, although the documentation is scarce for *L. pneumophila*.

Treatment-emergent adverse events (TEAEs) are, as for macrolides, mainly reported from the digestive and nervous systems, with diarrhoea, nausea, headache and dizziness as most prevalent. TEAEs assessed as possibly related to study treatment were reported for 35.8% of the telithromycin patients, versus 28.3% of the comparators. Gastrointestinal AEs, especially diarrhoea were more common with telithromycin, however, they were mostly mild.

Serious hepatotoxicity similar to the known macrolide-associated was seen in three patients. LFT elevations occurred at similar frequencies as with comparators. Prolongation of the QTc interval, a class effect for macrolides, has been investigated. These prolongations appear to be of the same extent as for clarithromycin. Liver adverse reactions and events potentially related to QT prolongation are specifically targeted for post-marketing follow-up by the applicant.

Blurred vision, although transient, was recorded in 0.6% of patients and seemed dose-dependent. Further studies to investigate this have been planned.

Possible advantages of five days treatment vs. 10 days treatment can only be speculative, i.e., less development of resistance, better compliance etc. The applicant has not been able to show any advantages in the submitted documentation with respect to these properties.

**Benefit/risk assessment**

Telithromycin retains activity against Gram-positive cocci that are macrolide resistant by an efflux mechanism or an MLS$_B$ inducible type of resistance and is bactericidal against *S. pneumoniae*. Thus, telithromycin is considered a potentially valuable addition for the treatment of respiratory tract infections (CAP, sinusitis) caused by penicillin and/or erythromycin resistant *S. pneumoniae*. Clinical experience is still limited in the treatment of these infections but so far clinical efficacy and eradication rates have been similar compared with the treatment of susceptible *S. pneumoniae*. Telithromycin should be used with caution until further experience of emergence of resistance has been gained, especially in areas with a high prevalence of resistant pneumococci. This is further supported by data that appear to indicate that telithromycin is not unaffected by ermB and mef A resistance genes in *S. pneumoniae*.

Cross-resistance to highly macrolide resistant *S. pyogenes* seems established and there is no evidence to support preferential use of telithromycin in these infections. In pharyngotonsillitis, telithromycin could, thus, be used in the same way as macrolides, i.e. if other, more suitable agents such as beta lactam antibiotics are not appropriate.

As for macrolides, *H. influenzae* is classified as intermediately susceptible and the effect is thus less than optimal for an airway antibiotic. This should be taken into account when treating infections caused by *H. influenzae*.

Telithromycin displays a similar pattern of side effects compared with the macrolides and azithromycin, but evokes more gastrointestinal side-effects than clarithromycin. The frequency and severity of increased hepatic enzyme activity and liver disease appear similar as for clarithromycin but justify close post-marketing surveillance, as does the potential prolongation of the QT-interval.
Considering the efficacy and adverse events profiles documented, the overall risk/benefit ratio is considered favourable. There are, however, no indications that telithromycin would confer specific benefits over currently available antibiotics, except in infections caused by erythromycin resistant S. pneumoniae. Reference is made in the SPC to official guidelines that should be used to provide guidance regarding the use of telithromycin.

The Applicant has committed to perform post-marketing surveillance studies regarding emergence of resistance particularly and also addressing the effect on erythromycin resistant S. Pneumoniae.

"Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Ketek in the treatment of the following infections:

**In patients of 18 years and older:**
- Community-acquired pneumonia, mild or moderate
- Acute exacerbation of chronic bronchitis,
- Acute sinusitis
- Tonsillitis/pharyngitis caused by Group A beta streptococci, as an alternative when beta lactam antibiotics are not appropriate.

**In patients of 12 to 18 years old:**
- Tonsillitis/pharyngitis caused by Group A beta streptococci, as an alternative when beta lactam antibiotics are not appropriate.

was favourable and therefore recommended the granting of the marketing authorisation.