[a] n = the number of patients successfully treated; N = the number with resistance to the listed drug of the 36 evaluable patients with CAP due to MDRSP.
[b] Includes isolates tested for resistance to either tetracycline or doxycycline.

Visual Adverse Events

Table 9 provides the incidence of all treatment-emergent visual adverse events in controlled Phase III studies by age and gender. The group with the highest incidence was females under the age of 40, while males over the age of 40 had rates of visual adverse events similar to comparator-treated patients.

Table 9. Incidence of All Treatment-Emergent Visual Adverse Events in Controlled Phase III Studies

Gender/Age	Telithromycin	Comparators*
Female ≤ 40	2.1% (14/682)	0.0% (0/534)
Female > 40	1.0% (7/703)	0.35% (2/574)
Male ≤ 40	1.2% (7/563)	0.48% (2/417)
Male > 40	0.27% (2/754)	0.33% (2/614)
Total	1.1% (30/2702)	0.28% (6/2139)

* Includes all comparators combined

ANIMAL PHARMACOLOGY

Repeated dose toxicity studies of 1, 3, and 6 months' duration with telithromycin conducted in rat, dog and monkey showed that the liver was the principal target for toxicity with elevations of liver enzymes and histological evidence of damage. There was evidence of reversibility after cessation of treatment. Plasma exposures based on free fraction of drug at the no observed adverse effect levels ranged from 1 to 10 times the expected clinical exposure.

Phospholipidosis (intracellular phospholipid accumulation) affecting a number of organs and tissues (e.g., liver, kidney, lung, thymus, spleen, gall bladder, mesenteric lymph nodes, GI-tract) has been observed with the administration of telithromycin in rats at repeated doses of 900 mg/m^2/day (1.8x the human dose) or more for 1 month, and 300 mg/m^2/day (0.61x the human dose) or more for 3-6 months. Similarly, phospholipidosis has been observed in dogs with telithromycin at repeated doses of 3000 mg/m^2/day (6.1x the human dose) or more for 1 month and 1000 mg/m^2/day (2.0x the human dose) or more for 3 months. The significance of these findings for humans is unknown.

Pharmacology/toxicology studies showed an effect both in prolonging QTc interval in dogs *in vivo* and *in vitro* action potential duration (APD) in rabbit Purkinje fibers. These effects were observed at concentrations of free drug at least 8.8 (in dogs) times those circulating in clinical use. *In vitro* electrophysiological studies (hERG assays) suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism.

Rev. February 2007

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Rx only

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing: Twelfth Informational Supplement; Approved Standard, NCCLS Document M2-A8 and M7-A6, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2004.

MEDICATION GUIDE
KETEK® (*KEE tek*) Tablets
(telithromycin)

READ THE MEDICATION GUIDE THAT COMES WITH KETEK BEFORE YOU START TAKING IT. TALK TO YOUR DOCTOR IF YOU HAVE ANY QUESTIONS ABOUT KETEK. THIS MEDICATION GUIDE DOES NOT TAKE THE PLACE OF TALKING WITH YOUR DOCTOR ABOUT YOUR MEDICAL CONDITION OR TREATMENT.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT KETEK?

1. **Do not take KETEK if you have Myasthenia Gravis (a rare disease which causes muscle weakness). Worsening of myasthenia gravis symptoms including life-threatening breathing problems have happened in patients with myasthenia gravis after taking KETEK in some cases leading to death.**

KETEK can cause other serious side effects, including:

2. SEVERE LIVER DAMAGE (HEPATOXICITY). **SEVERE LIVER DAMAGE, IN SOME CASES LEADING TO A LIVER TRANSPLANT OR DEATH HAS HAPPENED IN PATIENTS TREATED WITH KETEK. SEVERE LIVER DAMAGE HAS HAPPENED DURING TREATMENT, EVEN AFTER A FEW DOSES, OR RIGHT AFTER TREATMENT WITH KETEK HAS ENDED.**

Stop KETEK and call your doctor right away if you have signs of liver problems. Do not take another dose of KETEK unless your doctor tells you to do so.

Signs of liver problems include:
- increased tiredness
- loss of appetite
- yellowing of the skin and/or eyes
- right upper belly pain
- light-colored stools
- dark urine
- itchy skin

Do not take KETEK if you have ever had side effects of the liver while taking KETEK or macrolide antibiotics. Macrolide antibiotics include erythromycin, azithromycin (Zithromax®), clarithromycin (Biaxin®) or dirithromycin (Dynabac®).

3. **Vision problems.** KETEK may cause blurred vision, trouble focusing, and double vision. You may notice vision problems if you look quickly from near objects to far objects.

4. **Fainting.** You may faint especially if you are also having nausea, vomiting, and lightheadedness.

- BE AWARE THAT VISION PROBLEMS AND FAINTING WHILE TAKING KETEK MAY AFFECT YOUR ABILITY TO DRIVE OR DO DANGEROUS ACTIVITIES. LIMIT DRIVING AND OTHER DANGEROUS ACTIVITIES.
- IF YOU HAVE VISION PROBLEMS OR FAINT WHILE TAKING KETEK
  - DO NOT DRIVE, OPERATE HEAVY MACHINES, OR DO DANGEROUS ACTIVITIES.
  - CALL YOUR DOCTOR BEFORE TAKING ANOTHER DOSE OF KETEK IF YOU HAVE VISION PROBLEMS OR FAINT.

See "What are the possible side effects of KETEK? for other side effects of KETEK.

WHAT IS KETEK?

KETEK is an antibiotic. KETEK is used to treat adults 18 years of age and older with a lung infection called "community acquired pneumonia" that is caused by certain bacteria germs.

- KETEK is not for other types of infections caused by bacteria
- KETEK, like other antibiotics, does not kill viruses.

WHO SHOULD NOT TAKE KETEK?

Do not take KETEK if you:

- have myasthenia gravis
- have had side effects on the liver while taking KETEK or macrolide antibiotics.
- have ever had an allergic reaction to KETEK or macrolide antibiotics.
- take cisapride (Propulsid®) or pimozide (Orap®).

KETEK may not be right for you. Before taking KETEK, tell your doctor about all of your medical conditions, including if you:

- have myasthenia gravis
- have liver problems
- have (or have a family history of) a heart problem called "QTc prolongation"
- have other heart problems
- are pregnant or breastfeeding

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. KETEK and other medicines may affect or interact with each other, sometimes causing serious side effects.

You should not take the following cholesterol lowering medicines while taking KETEK:

- simvastatin (Zocor®, Vytorin®)
- lovastatin (Mevacor®)
- atorvastation (Lipitor®)

Know the medicines you take. Keep a list of your medicines with you to show your doctor or pharmacist.

Do not take other medicines with KETEK without first checking with your doctor. Your doctor will tell you if you can take other medicines with KETEK.

HOW SHOULD I TAKE KETEK?

- Take KETEK exactly as your doctor tells you. Skipping doses or not taking all of an antibiotic may:
  - make the treatment not work as well
  - increase the chance that the bacteria will develop resistance to the antibiotic
- The usual dose is two 400 mg KETEK Tablets taken at the same time once a day for 7 to 10 days. If you have kidney disease, your doctor may prescribe a lower dose for you.
- Take KETEK with or without food.
- Swallow KETEK tablets whole.
- Call your doctor if you took too much KETEK.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF KETEK?

See "What is the most important information I should know about KETEK?" for worsening of myasthenia gravis symptoms, and serious liver, vision, and fainting side effects.

Other serious side effects include:

- **Pseudomembranous colitis** (an intestine infection). Pseudomembranous colitis can happen with most antibiotics, including KETEK. Call your doctor if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may also have stomach cramps and a fever. Pseudomembranous colitis can happen up to 2 months after you have finished your antibiotic.

The most common side effects of KETEK are nausea, headache, dizziness, vomiting, and diarrhea.

These are not all of the side effects of KETEK. Ask your doctor or pharmacist for more information.

HOW SHOULD I STORE KETEK?

- Store KETEK tablets at room temperature, 59° to 86°F (15° to 30°C).
- **Keep KETEK and all medicines out of the reach of children.**

GENERAL INFORMATION ABOUT KETEK

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use KETEK for a condition for which it was not prescribed.
- Do not share KETEK with other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about KETEK. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about KETEK that was written for healthcare professional. This information is also available on the KETEK website at www.KETEK.com.

What are the ingredients in KETEK?

Active Ingredient: telithromycin
Inactive Ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide

Rx Only

Medication Guide as of February 2007

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

BIAXIN® (clarithromycin) is a registered trademark of Abbott Laboratories.
ZITHROMAX® (azithromycin) is a registered trademark of Pfizer Inc.
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（様式第６）

医薬品　外国における製造等の中止、回収、廃棄等の措置　調査報告書

識別番号・報告回数	G-07000028	第2報	報告日 2007年04月24日	第一報入手日 2007年03月30日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	01：テリスロマイシン		外国における措置の公表状況	EMEAホームページ	公表国 イギリス	
販売名（企業名）	01：ケテック （サノフィ・アベンティス（株））					

外国における措置の概要

□製造・輸入の中止 □販売中止 □回収・廃棄 ■その他問題点（ケテックの適応症に関するEMEAの勧告、意識消失及び視覚障害に関する注意喚起）
ケテックの４つの適応症のうち３つについて、使用を制限するよう勧告することが3月30日付でEMEAのホームページに掲載された。
その内容は下記のとおり。
ケテックは、気管支炎および副鼻腔炎、扁桃炎/咽頭炎の治療には、その原因菌がマクロライド系もしくはβ-ラクタム系抗菌剤の耐性菌、もしくは耐性菌が疑わしい場合、あるいはこれらの抗菌剤が使用できない感染症にのみ使用すること。
もう１つの適応症である、市中肺炎の治療には上記の使用制限は勧告されていない。
EMEAの医薬品委員会（CHMP：Committee for Medicinal Products for Human Use）は、重症筋無力症患者へのケテックの使用を禁忌とすること、一過性の意識消失および視覚への影響に関する注意喚起を強めることをあわせて勧告した。
CHMPが承認した添付文書（案）の主な改訂点は下記のとおり。
・慢性気管支炎の急性増悪及び急性副鼻腔炎：原因菌がβ-ラクタムまたはマクロライドに耐性株あるいはその疑いのある場合に限定。
・扁桃炎/咽頭炎：原因菌が化膿レンサ球菌で、βラクタム系の抗菌薬での治療が不適切な場合で、「マクロライド耐性率が高い国・地域において、その耐性が特定の遺伝子（ermTRまたはmefA）によるもの」（「 」部分追加）。
・重症筋無力症患者への投与は禁忌
・視覚障害の詳細追記（視調節障害、霧視、複視）
・視覚障害及び意識消失による障害を避けるため、ケテックを睡眠時に服用することを推奨。
・視覚障害、意識消失が起こることから、自動車の運転、重機の操作及び危険を伴う機械の操作を行わないこと。また、ケテック服用中に視覚障害または意識消失が発現した場合は、このような操作を行わないこと。

使用上の注意記載状況・その他参考事項等

【効能・効果】
〈適応菌種〉
本剤に感性のブドウ球菌属，レンサ球菌属，肺炎球菌，モラクセラ（ブランハメラ）・カタラーリス，インフルエンザ菌，レジオネラ属，ペプトストレプトコッカス属，プレボテラ属，肺炎クラミジア（クラミジア・ニューモニエ），肺炎マイコプラズマ（マイコプラズマ・ニューモニエ）
〈適応症〉
咽頭・喉頭炎，扁桃炎，急性気管支炎，肺炎，慢性呼吸器病変の二次感染，副鼻腔炎，歯周組織炎，歯冠周囲炎，顎炎
【使用上の注意】
「重要な基本的注意」
重症筋無力症の患者に投与した場合、症状が悪化することが報告されている。
呼吸器感染症の治療目的で本剤を投与した場合、初回投与後、数時間以内に急性呼吸不全を起こすことがあり、致死的な例も報告されているので、他の治療がない場合を除き、本剤の使用は避けることが望ましい。
他に治療法がなく、本剤の投与が必要な場合、観察を十分に行い、異常があらわれた場合には直ちに投与を中止し、適切な処置を行うこと。
なお、当該措置は2007年4月2日にFAX報告済みである。
また、当該措置は「治験外国措置報告」においても審査部に報告済みである。

報告企業の意見

海外における適応症の制限の情報を入手したので措置報告を行う。
企業としては、禁忌に「重症筋無力症患者」を追加する方向で検討中である。その他の変更箇所については、現行の使用上の注意の記載で注意喚起できていると考える。

今後の対応

国内「使用上の注意」改訂について検討中である。なお、USPI、SmPCの改訂に対する国内の対応は、厚生労働省等と協議中である。本内容も含めて検討を行う。

7-07000028(ｱﾃﾍﾞﾝﾃｨｽ合3 500 mg)

European Medicines Agency
Press office

London, 30 March 2007
Doc. Ref. EMEA/129901/2007

PRESS RELEASE
European Medicines Agency recommends restricted use and strengthened warnings for Ketek

The European Medicines Agency (EMEA) has recommended restrictions on the use of Ketek (telithromycin) in three of its four approved indications. For the treatment of bronchitis, sinusitis and tonsillitis/pharyngitis, Ketek should only be used for infections caused by bacterial strains that are suspected or proven to be resistant to or cannot be treated with macrolide or beta-lactam antibiotics.

No such restrictions are recommended for the remaining indication, the treatment of community-acquired pneumonia.

The Agency's Committee for Medicinal Products for Human Use (CHMP) also recommended the contraindication of the use of Ketek in patients with myasthenia gravis and strengthened warnings on transient loss of consciousness and effects on vision.

The CHMP has been carrying out a comprehensive review of the safety and effectiveness of Ketek since January 2006, following reports of severe liver injuries in patients taking telithromycin. As part of this review several updates relating to the safety of Ketek were made to the Product Information during 2006. These included strengthening the warnings on serious liver reactions and contraindicating the use of the medicine in patients with a previous history of serious liver disorders. In January 2007, the Committee requested updated information from the marketing authorisation holder for Ketek, to allow a comprehensive assessment of the benefits and risks in each of the medicine's approved indications.

Finalising the review at its 19-22 March 2007 meeting, the Committee concluded that the effectiveness of Ketek has been demonstrated in the approved indications. However, its use is associated with a greater risk of certain side effects, some of which may be serious. These include a worsening of myasthenia gravis (which can be life-threatening), transient loss of consciousness, and temporary visual disturbances. Severe problems with the liver have been reported rarely, but do not occur more frequently than with other relevant antibiotic medicines.

The Committee concluded that the benefits of Ketek continue to outweigh its risks in the treatment for bronchitis, sinusitis and tonsillitis/pharyngitis, if used in accordance with the updated product information.

Prescribers are advised to consider the official guidance on the appropriate use of the antibiotics and the local prevalence of resistance.

--ENDS--

NOTES
1. More information about the recommendations for Ketek is available in a separate question and answer document.
2. The European Commission is currently conducting the procedures laid down in Community legislation with a view to issuing a decision to update the product information for Ketek.
3. The updated product information, for which the Commission decision is pending, is available here.

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4. In the European Union, telithromycin is authorised as Ketek and Levviax. The marketing authorisation holder is Aventis Pharma S.A. It is marketed only as Ketek. The European public assessment report for Ketek is published on the EMEA website and can be found here.
5. Ketek is marketed in the European Union/European Economic Area in Austria, Belgium, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom.
6. The EMEA's statement on the safety of Ketek from January 2006 can be found here.
7. This press release, together with other information about the work of the EMEA, may be found on the EMEA website: http://www.emea.europa.eu.

Media enquiries only please contact:
Martin Harvey Allchurch or Monika Benstetter
Tel. (44-20) 74 18 84 27, E-mail: press@emea.europa.eu

SUMMARY OF PRODUCT CHARACTERISTICS

This SPC was approved by the CHMP on 22 March 2007 and is pending for endorsement by the European Commission

1. NAME OF THE MEDICINAL PRODUCT

Ketek 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of telithromycin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Light orange, oblong, biconvex tablet, imprinted with H3647 on one side and 400 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

When prescribing Ketek, consideration should be given to official guidance on the appropriate use of antibacterial agents and the local prevalence of resistance (~~S~~see also sections 4.4 and 5.1).

Ketek is indicated for the treatment of the following infections:

In patients of 18 years and older:

-• Community-acquired pneumonia, mild or moderate (see section 4.4).

• When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin (see sections 4.4 and 5.1):

- Acute exacerbation of chronic bronchitis,
- Acute sinusitis

~~Tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, as an alternative when beta-lactam antibiotics are not appropriate.~~

In patients of 12 years and older~~to 18 years old~~:

•Tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, as an alternative when beta lactam antibiotics are not appropriate in countries/regions with a significant prevalence of macrolide resistant S. pyogenes, when mediated by ermTR or mefA (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The recommended dose is 800 mg once a day i.e. two 400 mg tablets once a day. The tablets should be swallowed whole with a sufficient amount of water. The tablets may be taken with or without food. Consideration may be given to taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness (see section 4.4).

In patients of 18 years and older, according to the indication, the treatment regimen will be:

- Community-acquired pneumonia: 800 mg once a day for 7 to 10 days,
- Acute exacerbation of chronic bronchitis: 800 mg once a day for 5 days,
- Acute sinusitis: 800 mg once a day for 5 days,
- Tonsillitis/pharyngitis caused by *Streptococcus pyogenes:* 800 mg once a day for 5 days.

In patients of 12 to 18 years old, the treatment regimen will be:

- Tonsillitis/pharyngitis caused by *Streptococcus pyogenes:* 800 mg once a day for 5 days.

In the elderly:
No dosage adjustment is required in elderly patients based on age alone.

In children:
Ketek is not recommended for use in children below 12 years of age due to lack of data on safety and efficacy (see section 5.2).

Impaired renal function:
No dosage adjustment is necessary in patients with mild or moderate renal impairment. Ketek is not recommended as first choice in patients with severe renal impairment (creatinine clearance <30ml/min) or patients with both severe renal impairment and –co-existing hepatic impairment, as an optimal dosage format (600 mg) is not available. If telithromycin treatment is deemed necessary, these patients may be treated with alternating daily doses of 800 mg and 400 mg, starting with the 800 mg dose.
In haemodialysed patients, the posology should be adjusted so that Ketek 800 mg is given after the dialysis session (see also section 5.2).

Impaired hepatic function:
No dosage adjustment is necessary in patients with mild, moderate, or severe hepatic impairment, unless renal function is severely impaired, however the experience in patients with impaired hepatic function is limited. Hence, Ketek should be used with caution (see also section 4.4 and 5.2).

4.3 Contraindications

Ketek is contraindicated in patients with myasthenia gravis (see section 4.4).

Hypersensitivity to the active substance, to any of the macrolide antibacterial agents, or to any of the excipients.

Ketek must not be used in patients with previous history of hepatitis and/or jaundice associated with the use of telithromycin.

Concomitant administration of Ketek and any of the following substances is contraindicated: cisapride, ergot alkaloid derivatives (such as ergotamine and dihydroergotamine), pimozide, astemizole and terfenadine -(see section 4.5).

Ketek should not be used concomitantly with simvastatin, atorvastatin and lovastastin. -Treatment with these agents should be interrupted during Ketek treatment (see section 4.5).

Ketek is contraindicated in patients with a history of congenital or a family history of long QT syndrome (if not excluded by ECG) and in patients with known acquired QT interval prolongation.

In patients with severely impaired renal and/or hepatic function, concomitant administration of Ketek and strong CYP3A4 inhibitors, such as protease inhibitors or ketoconazole, is contraindicated.

4.4 Special warnings and precautions for use

As with macrolides, due to a potential to increase QT interval, Ketek should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and or hypomagnesaemia, bradycardia (<50 bpm), or during concomitant administration of Ketek with QT interval prolonging agents or potent CYP 3A4 inhibitors such as protease inhibitors and ketoconazole.

As with nearly all antibacterial agents, diarrhoea, particularly if severe, persistent and /or bloody, during or after treatment with Ketek may be caused by *pseudomembranous colitis*. If *pseudomembranous colitis* is suspected, the treatment must be stopped immediately and patients should be treated with supportive measures and/or specific therapy.

Exacerbations of myasthenia gravis haves been reported in patients ~~with myasthenia gravis~~ treated with telithromycin and sometimes~~. This usually~~ occurred within ~~one to three~~a few hours ~~after intake~~ of the first dose ~~of telithromycin~~.
Reports have included death and life threatening acute respiratory failure with ~~a~~ rapid onset (see section 4.8)~~.in myasthenic patients treated for respiratory tract infections with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless other therapeutic alternatives are not available.~~

~~Patients with myasthenia gravis taking telithromycin should be advised to immediately seek medical attention if they experience exacerbation of their symptoms. Ketek must then be discontinued and supportive care administered as medically indicated (see section 4.8).~~

Alterations in hepatic enzymes have been commonly observed in clinical studies with telithromycin. Post-marketing cases of severe hepatitis and liver failure, including fatal cases (which have generally been associated with serious underlying diseases or concomitant medications), have been reported (see section 4.8). These hepatic reactions were observed during or immediately after treatment, and in most cases were reversible after discontinuation of telithromycin.
Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Due to limited experience, Ketek should be used with caution in patients with liver impairment (see section 5.2).

Ketek may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. (see sections 4.7 and 4.8).

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome (see sections 4.7 and 4.8).

Consideration may be given to taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness.

Ketek should not be used during and 2 weeks after treatment with CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort). Concomitant treatment with these medicinal products is likely to result in subtherapeutic levels of telithromycin and therefore encompass a risk of treatment failure (see section 4.5).

Ketek is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to telithromycin and other antibiotics.

In community acquired pneumonia, efficacy has been demonstrated in a limited number of patients with risk factors such as *pneumococcal bacteraemia* or age higher than 65 years.

Experience of treatment of infections caused by penicillin/or erythromycin resistant *S. pneumoniae* is limited, but so far, clinical efficacy and eradication rates have been similar compared with the

treatment of susceptible *S. pneumoniae*. Caution should be taken when *S. aureus* is the suspected pathogen and there is a likelihood of erythromycin resistance based on local epidemiology.

L. pneumophila is highly susceptible to telithromycin *in vitro*, however, the clinical experience of the treatment of pneumonia caused by *legionella* is limited.

As for macrolides, *H. influenzae* is classified as intermediately susceptible. This should be taken into account when treating infections caused by *H. influenzae*.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

- Effect of Ketek on other medicinal product

Telithromycin is an inhibitor of CYP3A4 and a weak inhibitor of 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 degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, Ketek should not be used during treatment with medicinal products that are CYP3A4 substrates, unless plasma concentrations of the CYP3A4 substrate, efficacy or adverse events can be closely monitored. Alternatively, interruption in the treatment with the CYP3A4 substrate should be made during treatment with Ketek.

Medicinal products with a potential to prolong QT interval
Ketek is expected to increase the plasma levels of cisapride, pimozide, astemizole and terfenadine. This could result in QT interval prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Concomitant administration of Ketek and any of these medicinal products is contraindicated (see section 4.3).

Caution is warranted when Ketek is administered to patients taking other medicinal products with the potential to prolong QT interval (see section 4.4).

Ergot alkaloid derivatives (such as ergotamine and dihydroergotamine)
By extrapolation from erythromycin A and josamycin, concomitant medication of Ketek and alkaloid derivatives could lead to severe vasoconstriction ("ergotism") with possibly necrosis of the extremities. The combination is contraindicated (see section 4.3).

Statins
When simvastatin was coadministered with Ketek, there was a 5.3 fold increase in simvastatin C_{max}, an 8.9 fold increase in simvastatin AUC, a 15-fold increase in simvastatin acid C_{max} and an 11-fold increase in simvastatine acid AUC. In vivo interaction studies with other statins have not been performed, but Ketek may produce a similar interaction with lovastatin and atorvastatin, a lesser interaction with cerivastatin and little or no interaction with pravastatin and fluvastatin. Ketek should not be used concomitantly with simvastatin, atorvastastin and lovastatin. Treatment with these agents should be interrupted during Ketek treatment. Cerivastatin should be used with caution and patients should be carefully monitored for signs and symptoms of myopathy.

Benzodiazepins
When midazolam was coadministered with Ketek, midazolam AUC was increased 2.2-fold after intravenous administration of midazolam and 6.1-fold after oral administration. The midazolam half-life was increased about 2.5-fold. Oral administration of midazolam concomitantly with Ketek should be avoided. Intravenous dosage of midazolam should be adjusted as necessary and monitoring of the patient be undertaken. The same precautions should also apply to the other benzodiazepins which are metabolized by CYP3A4, (especially triazolam but also to a lesser extent alprazolam). For those benzodiazepins which are not metabolized by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with Ketek is unlikely.

Cyclosporin, tacrolimus, sirolimus
Due to its CYP3A4 inhibitory potential, telithromycin can increase blood concentrations of these CYP34A4 substrates. Thus, when initiating telithromycin in patients already receiving any of theses immunosuppressive agents, cyclosporin, tacrolimus or sirolimus levels must be carefully monitored and their doses decreased as necessary. When telithromycin is discontinued, cyclosporin, tacrolimus or sirolimus levels must be again carefully monitored and their dose increased as necessary.

Metoprolol
When metoprolol (a CYP2D6 substrate) was coadministered with Ketek, metropolol Cmax and AUC were increased by approximately 38%, however, there was no effect on the elimination half-life of metoprolol. The increase exposure to metoprolol may be of clinical importance in patients with heart failure treated with metoprolol. In these patients, co-administration of Ketek and metoprolol, a CYP2D6 substrate, should be considered with caution.

Digoxin
Ketek has been shown to increase the plasma concentrations of digoxin. The plasma trough levels, C_{max}, AUC and renal clearance were increased by 20 %, 73 %, 37 % and 27% respectively, in healthy volunteers. There were no significant changes in ECG parameters and no signs of digoxin toxicity were observed. Nevertheless, monitoring of serum digoxin level should be considered during concomitant administration of digoxin and Ketek.

Theophylline
There is no clinically relevant pharmacokinetic interaction of Ketek and theophylline administered as extended release formulation. However, the co-administration of both medicinal products should be separated by one hour in order to avoid possible digestive side effects such as nausea and vomiting.

Oral anticoagulants
Increased anticoagulant activity has been reported in patients simultaneously treated with anticoagulants and antibiotics, including telithromycin. The mechanisms are incompletely known. Although Ketek has no clinically relevant pharmacokinetic or pharmacodynamic interaction with warfarin after single dose administration, more frequent monitoring of prothrombin time/INR (International Normalised Ratio) values should be considered during concomitant treatment.

Oral contraceptives
There is no pharmacodynamic or clinically relevant pharmacokinetic interaction with low-dose triphasic oral contraceptives in healthy subjects.

- Effect of other medicinal products on Ketek

During concomitant administration of rifampicin and telithromycin in repeated doses, C_{max} and AUC of telithromycin were on average decreased by 79% and 86% respectively. Therefore, concomitant administration of CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) is likely to result in subtherapeutic levels of telithromycin and loss of effect. The induction gradually decreases during 2 weeks after cessation of treatment with CYP3A4 inducers. Ketek should not be used during and 2 weeks after treatment with CYP3A4 inducers.

Interaction studies with itraconazole and ketoconazole, two CYP3A4 inhibitors, showed that maximum plasma concentrations of telithromycin were increased respectively by 1.22 and 1.51 fold and AUC by respectively 1.54 fold and 2.0 fold. These changes in the pharmacokinetics of telithromycin do not necessitate dosage adjustment as telithromycin exposure remains within a well tolerated range. The effect of ritonavir on telithromycin has not been studied and could lead to larger increase in telithromycin exposure. The combination should be used with caution.

Ranitidine (taken 1 hour before Ketek) and antacid containing aluminium and magnesium hydroxide has no clinically relevant influence on telithromycin pharmacokinetics.

4.6 Pregnancy and lactation

There are no adequate data from the use of Ketek in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ketek should not be used during pregnancy unless clearly necessary.

Telithromycin is excreted in the milk of lactating animals, at concentrations about 5 times those of maternal plasma. Corresponding data for humans is not available. Ketek should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Ketek may cause undesirable effects such as visual disturbances which may reduce the capacity for the completion of certain tasks. In addition, rare cases of transient loss of consciousness, which may be preceded by vagal symptoms, have been reported (see section 4.8). **Because of potential visual difficulties or loss of consciousness, patients should attempt to minimize activities such as driving a motor vehicle, operating heavy machinery or engaging in other hazardous activities during treatment with Ketek. If patients experience visual disorders or loss of consciousness while taking Ketek, patients should not drive a motor vehicle, operate heavy machinery or engage in other hazardous activities (see sections 4.4 and 4.8).**
Patients should be informed that these undesirable effects may occur as early as after the first dose of medication. Patients should be cautioned about the potential effects of these events on the ability to drive or operate machinery.

4.8 Undesirable effects

In 2461 patients treated by Ketek in phase III clinical trials, the following undesirable effects possibly or probably related to telithromycin have been reported. This is shown below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.