

IMPORTANT INFORMATION REGARDING RESTRICTED INDICATIONS, CONTRAINDICATIONS AND SAFETY MEASURES.

Direct Healthcare Professional Communication on the association of telithromycin (Ketek 400 mg film coated tablets) with exacerbation of myasthenia gravis, visual disorders, loss of consciousness, as well as revised therapeutic indications.

Sanofi-aventis would like to inform you about important revised prescribing and safety information for Ketek (telithromycin) 400 mg film-coated tablet.

- **Summary**

Since January 2006, the CHMP has been carrying out a comprehensive review of the safety and effectiveness of Ketek. 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 warning on serious liver reactions and contraindicating the use of Ketek in patients with a previous history of liver disorders.

In January 2007, at the request from CHMP sanofi-aventis provided updated information to allow a comprehensive assessment of the benefits and risks in each of Ketek's approved indications. Following this evaluation the EMEA concluded that Ketek use is associated with a greater risk of certain side effects, some of which may be serious. These include a worsening of myasthenia gravis, transient loss of consciousness, and temporary visual disturbances. Furthermore, severe problems with the liver have also been reported rarely.

- **New recommendations**

Further to the assessment of the recently submitted data, indications of Ketek have been restricted and SmPC has been amended as follows:

- For the indications acute exacerbation of chronic bronchitis and acute sinusitis, Ketek is indicated **only** for use 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. For the indication tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, Ketek is indicated only for use as an alternative when beta lactam antibiotics are not appropriate in **only** countries/regions with a significant prevalence of macrolide resistant *S. pyogenes*, when mediated by *ermTR* or *mefA*

- Myasthenia gravis has been upgraded from a "Special Warning and Precaution for Use" to a "Contraindication".

- Safety information regarding visual disturbances and loss of consciousness has been revised to strengthen the recommendations regarding driving and operating heavy machinery, and to add a new recommendation for bedtime administration.

- **Further information**

The SmPC has been revised as follows (changes are underlined):

Section 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 (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

In patients of 12 years and older:

In patients of 12 years and older:

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).”

Section 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).”

Section 4.3. Contraindications

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

Section 4.4. Special Warnings and Precautions for Use

“Exacerbation of myasthenia gravis has been reported in patients treated with telithromycin and sometimes occurred within a few hours of first dose. Reports have included death and life threatening acute respiratory failure with a rapid onset (see section 4.8)”

“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.”

Section 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.”

The information provided in this letter has been reviewed and endorsed by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)

- **Call for reporting**

Patient safety is the highest priority for sanofi-aventis and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe KETEK appropriately. Please review carefully the revised enclosed SmPC and contact sanofi-aventis if you have any additional questions. Any adverse events experienced by your patients should be reported to the National Reporting System according to the National Regulation.

- **Communication information**

If you have any further enquiries, please contact us as shown:

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- **Annexes:**

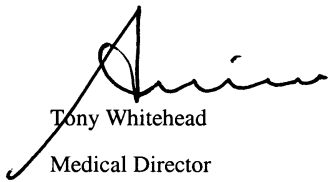
Text of the revised SmPC (with changes made visible)

- **Current Supply Status:**

Sanofi-aventis UK have been unable to supply this product until final agreed text for the safety update had been agreed with the CHMP. We will now work closely with our manufacturing site to ensure new stock with the enclosed safety update is available to patients as soon as possible.

We remain at your disposal for any further information you may need.

Yours sincerely,



Tony Whitehead

Medical Director

Sanofi-aventis UK