

# Appendix D

## SUMMARY OF PRODUCT CHARACTERISTICS



## 1. NAME OF THE MEDICINAL PRODUCT

Levviax 400 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Levviax contains 400 mg of telithromycin as active substance.  
For excipients, see 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 Levviax, consideration should be given to official guidance on the appropriate use of antibacterial agents (See also sections 4.4 and 5.1).

Levviax 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).
- 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.

### 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.

*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 Group A *beta streptococci*: 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 Group A *beta streptococci*: 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:

The safety and efficacy of Levviax in patient populations less than 12 years old have not yet been established.

Impaired renal function:

No dosage adjustment is necessary in patients with mild or moderate renal impairment. In the presence of severe renal impairment (creatinine clearance <30ml/min) with or without co-existing hepatic impairment, the dose should be halved.

In haemodialysed patients, the tablets should be given after the dialysis session on dialysis days.

Impaired hepatic function:

No dosage adjustment is necessary in patients with mild, moderate, or severe hepatic impairment, unless renal function is severely impaired.

### 4.3 Contraindications

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

Concomitant administration of Levviax 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).

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

Levviax 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.

### 4.4 Special warnings and special precautions for use

As with macrolides, due to a potential to increase QT, Levviax 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 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 Levviax 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.

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

Treatment with Levviax should be avoided during and 2 weeks after treatment with CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, St John's wort, see section 4.5 *Effects of other drugs on Levviax*).

Levviax is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4. Caution should be exercised during concomitant administration of CYP2D6 substrates for which the dose is individually titrated (see section 4.5 *Effects of Levviax on other drugs*).

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*.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### 4.5 Interaction with other medicinal products and other forms of interaction

##### Effect of Levviax on other medicinal product

Telithromycin is an inhibitor of CYP3A4 and *in vitro* 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, Levviax 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 Levviax. Caution should be exercised during concomitant administration of CYP2D6 substrates for which the dose is individually titrated.

##### Medicinal products with a potential to prolong QT interval

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

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

##### Ergot alkaloid derivatives (such as ergotamine and dihydroergotamine)

By extrapolation from erythromycin A and josamycin, concomitant medication of Levviax 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 Levviax, 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 simvastatin acid AUC. *In vivo* interaction studies with other statins have not been performed, but Levviax may produce a similar interaction with lovastatin and atorvastatin, a lesser interaction with cerivastatin and little or no interaction with pravastatin and fluvastatin. Levviax should not be used concomitantly with simvastatin, atorvastatin and lovastatin. Treatment with these agents should be interrupted during Levviax 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 Levviax, 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 Levviax 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 Levviax is unlikely.

### Cyclosporin, tacrolimus, sirolimus

Due to its CYP3A4 inhibitory potential, telithromycin can increase blood concentrations of these CYP3A4 substrates. Thus, when initiating telithromycin in patients already receiving any of these 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.

### Digoxin

Levviax 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 Levviax.

### Theophylline

There is no clinically relevant pharmacokinetic interaction of Levviax 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.

### Warfarin

Levviax has no clinically relevant pharmacokinetic or pharmacodynamic interaction with warfarin after single dose administration. However, a pharmacodynamic interaction after multiple dose administration cannot be ruled out.

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

### **Effect of other medicinal products on Levviax**

Concomitant administration of CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, St John's wort) could result in major reductions of the telithromycin plasma concentrations and loss of effect. The induction gradually decreases during 2 weeks after cessation of treatment with CYP3A4 inducers. Treatment with Levviax should be avoided 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 Levviax) and antacid containing aluminium and magnesium hydroxide has no clinically relevant influence on telithromycin pharmacokinetics.

#### 4.6 Pregnancy and lactation

##### Pregnancy

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

##### Lactation

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. Levviax should not be used by breast-feeding women.

#### 4.7 Effects on ability to drive and use machines

Levviax may cause undesirable effects which may reduce the capacity for the completion of certain tasks. Patients should be informed of the potential for these undesirable effects and should be aware of how they react to this medication before driving or operating machinery.

#### 4.8 Undesirable effects

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

Organ systems	Very common side effects ≥ 10 % of patients	Common side effects 1 to 10 % of patients	Uncommon side effects 0.1 to 1 % of patients	Rare side effects 0.01 to 0.1 % of patients
Gastro-intestinal disorders	Diarrhoea	Nausea, vomiting, gastrointestinal pain, flatulence	Constipation, anorexia, oral moniliasis, stomatitis	
Hepato-biliary disorders		Increase in liver enzymes (AST, ALT, alkaline phosphatase)		Cholestatic jaundice
Nervous system disorders		Dizziness, headache	Somnolence, insomnia, nervousness	Paraesthesia
Blood and the lymphatic system disorders			Eosinophilia	
Eye and sensory organs disorders		Disturbance of taste	Blurred vision	
Reproductive system disorders		Vaginal moniliasis		
Skin disorders			Rash, urticaria, pruritus	Eczema
Cardiovascular disorders			Flush Palpitations	Atrial arrhythmia, hypotension, bradycardia

In addition, the following undesirable effects have been reported in one isolated case each: *pseudomembranous colitis*, hepatitis, erythema multiforme, parosmia, face oedema, muscle cramps

In clinical trials the effect on QTc was small (mean of approximately 1 msec). In comparative trials, similar effects to those observed with clarithromycin were seen with an on-therapy  $\Delta$ QTc >30 msec in 7.6% and 7.0% of cases, respectively. No patient in either group developed a  $\Delta$ QTc >60 msec. There were no reports of TdP or other serious ventricular arrhythmias or related syncope in the clinical program and no subgroups at risk were identified.

### **Overdose**

In the event of acute overdose the stomach should be emptied. The patients should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained. Blood electrolytes (especially potassium) must be controlled. Due to the potential for the prolongation of the QT interval and increased risk of arrhythmia, ECG monitoring must take place

## **5. PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamic properties**

Pharmacotherapeutic group: antibacterial for systemic use, ATC Code: J01

Telithromycin is a semisynthetic derivative of erythromycin A belonging to the ketolides, a class of antibacterial agents related to macrolides.

### **Mode of action**

Telithromycin inhibits protein synthesis by acting at the ribosome level.

The affinity of telithromycin for the 50S bacterial subunit of ribosome is 10 fold higher than that of erythromycin A when the strain is susceptible to erythromycin A. Against erythromycin A resistant strains, due to an MLS<sub>B</sub> mechanism of resistance, telithromycin shows a more than 20 fold affinity compared to erythromycin A in the 50S bacterial subunit.

Telithromycin interferes with the ribosome translation at the 23S ribosomal RNA level, where it interacts with domain V and II. Furthermore, telithromycin is able to block the formation of the 50S and 30S ribosomal subunits.

### **Breakpoints**

The recommended MIC breakpoints for telithromycin, separating susceptible organisms from intermediately susceptible organisms and intermediately susceptible organisms from resistant organisms, are: susceptible  $\leq 0.5$  mg/l, resistant >2mg/l.

### **Antibacterial spectrum**

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to telithromycin. Where resistance patterns for particular species are known to vary within the European Union, this is shown below.

	Category with European range of resistance where this is known to vary
<b>Susceptible</b>	
<u>Aerobic Gram-positive bacteria</u>	
<i>Streptococcus pneumoniae</i> penicillin G susceptible or resistant and erythromycin A susceptible or resistant*	<1 %
<i>Streptococcus pyogenes</i> *	1 – 22%
<i>Streptococcus agalactiae</i>	
Viridans group <i>streptococci</i>	
Lancefield group C and G ( $\beta$ haemolytic ) <i>streptococci</i>	
<i>Staphylococcus aureus</i> erythromycin A susceptible* or resistant by inducible MLS <sub>B</sub> mechanism	
<u>Aerobic Gram- negative bacteria</u>	
<i>Moraxella catarrhalis</i> *	
<u>Other</u>	
<i>Legionella spp</i> <i>Legionella pneumophila</i> <i>Chlamydia pneumoniae</i> * <i>Chlamydia psittaci</i> <i>Mycoplasma pneumoniae</i> *	
<b>Intermediately susceptible</b>	
<i>Haemophilus influenzae</i> * <i>Haemophilus parainfluenzae</i>	
<b>Resistant</b>	
<i>Staphylococcus aureus</i> erythromycin A resistant by constitutive mechanism* * <i>Enterobacteriaceae</i> <i>Pseudomonas</i> <i>Acinetobacter</i>	

\* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications

\* \* Among MRSA the rate of MLS<sub>Bc</sub> resistant strains is more than 80%.

### Resistance

Telithromycin does not induce MLS<sub>B</sub> resistance in vitro to *S. aureus*, *S. pneumoniae*, and *S. pyogenes*, an attribute related to its 3 keto function. Development of in vitro resistance to telithromycin due to spontaneous mutation is rare. The majority of MRSA are resistant to erythromycin A by a constitutive MLS<sub>B</sub> mechanism.

In vitro results have shown that telithromycin is affected by the erythromycin *ermB* or *mefA* related resistance mechanisms but to lesser extent than erythromycin. While exposure to telithromycin did select for pneumococcal mutants with increased MICs, the MICs remained within the proposed susceptibility range.

For *S. pneumoniae*, there is no cross-resistance between telithromycin and other antibacterial classes

For *S. pyogenes*, cross-resistance occurs for high-level erythromycin A resistant strains.

### **Effect on oral and faecal flora**

In a comparative study in healthy human volunteers, telithromycin 800 mg daily and clarithromycin 500 mg twice daily for 10 days showed a similar and reversible reduction of oral and faecal flora. However, in contrast to clarithromycin, no resistant strains of alpha streptococci emerged in saliva on treatment with telithromycin.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Following oral administration, telithromycin is fairly rapidly absorbed. A mean maximum plasma concentration of about 2 mg/l is reached within 1-3 hour after dose with once-daily dosing of telithromycin 800 mg. The absolute bioavailability is about 57 % after a single dose of 800 mg. The rate and extent of absorption is unaffected by food intake, and thus Levviac tablets can be given without regard to food.

Mean steady-state trough plasma concentrations of between 0.04 and 0.07 mg/l are reached within 3 to 4 days with once-daily dosing of telithromycin 800 mg. At steady-state AUC is approximately 1.5 fold increased compared to the single dose.

Mean peak and trough plasma concentrations at steady state in patients were  $2.9 \pm 1.6$  mg/l (range 0.02-7.6 mg/l) and  $0.2 \pm 0.2$  mg/l (range 0.010 to 1.29 mg/l), during a therapeutic 800 mg once-daily dose regimen.

### **Distribution**

The in vitro protein binding is approximately 60 % to 70 %. Telithromycin is widely distributed throughout the body. The volume of distribution is  $2.9 \pm 1.0$  l/kg. Rapid distribution of telithromycin into tissues results in significantly higher telithromycin concentrations in most target tissues than in plasma. The maximum tissue concentration in epithelial lining fluid, alveolar macrophages, bronchial mucosa and tonsils were 14.9 mg/l, 318.1 mg/l, 3.88 mg/kg and 3.95 mg/kg, respectively. The tissue concentration 24 h after dose in epithelial lining fluid, alveolar macrophages, bronchial mucosa and tonsils were 0.84 mg/l, 166 mg/l, 0.78 mg/kg and 0.72 mg/kg, respectively. The mean maximum white blood cell concentration of telithromycin was 83 mg/l.

### **Metabolism**

Telithromycin is metabolized primarily by the liver. After oral administration, two-thirds of the dose is eliminated as metabolites and one-third unchanged. The main circulating compound in plasma is telithromycin. Its principal circulating metabolite represents approximately 13 % of telithromycin AUC, and has little antimicrobial activity compared with the parent medicinal product. Other metabolites were detected in plasma, urine and faeces and represent less or equal than 3 % of plasma AUC.

Telithromycin is metabolized both by CYP450 isoenzymes and non-CYP enzymes. The major CYP450 enzyme involved in the metabolism of telithromycin is CYP3A4. Telithromycin is an

inhibitor of CYP3A4 and CYP2D6, but has no or limited effect on CYP1A, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1.

## Elimination

After oral administration of radiolabelled telithromycin, 76 % of the radioactivity was recovered from faeces, and 17 % from the urine. Approximately one-third of telithromycin was eliminated unchanged; 20 % in faeces and 12 % in urine. Telithromycin displays moderate non-linear pharmacokinetics. The non-renal clearance is decreased as the dose is increased. The total clearance (mean  $\pm$ SD) is approximately  $58 \pm 5$  l/h after an intravenous administration with renal clearance accounting for about 22 % of this. Telithromycin displays a tri-exponential decay from plasma, with a rapid distribution half-life of 0.17 h. The main elimination half-life of telithromycin is 2-3 h and the terminal, less important, half-life is about 10 h at the dose 800 mg once daily.

## Special populations

### Renal impairment

The effect of renal impairment was evaluated after single dose administration.

In patients with mild to severe renal impairment, mean  $C_{max}$  and AUC values increased by an average of 37-38 % and 41-52 %, respectively, compared to normal healthy subjects. The inter-individual variability was increased in patients with renal impairment, but plasma exposure remained in the well tolerated range. The effect of dialysis on the elimination of telithromycin has not been assessed.

### Hepatic impairment

The effect of hepatic impairment was evaluated after single dose administration. AUC of telithromycin was not affected but  $C_{max}$  decreased 20 %, trough concentration increased two fold and half-lives increased 20 to 40 % in patients with mild to severe hepatic insufficiency. The effect of hepatic impairment on the pharmacokinetics after multiple dose administration cannot be predicted from these data. Levviax should be used with caution in patients with hepatic impairment.

Elderly subjects: In subjects over 65 (median 75 years), the maximum plasma concentration and AUC of telithromycin were increased approximately 2 fold compared with those achieved in young healthy adults. These changes in pharmacokinetics do not necessitate dosage adjustment.

Paediatric patients: The pharmacokinetics of telithromycin in paediatric population less than 12 years old have not yet been studied. Limited data, obtained in paediatric patients 13 to 17 years of age, showed that telithromycin concentrations in this age group were similar to the concentrations in patients 18 to 40 years of age.

### Gender

The pharmacokinetics of telithromycin are similar between males and females.

## 5.3 Preclinical safety data

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, phospholipidosis and histological evidence of damage. These effects showed a tendency to regress after cessation of treatment. Plasma exposures based on free fraction of drug, at the no observed adverse effect levels ranged from 1.6 to 13 times the expected clinical exposure.

In similarity to some macrolides, telithromycin caused a prolongation of QTc in dogs and on action potential duration in rabbit Purkinje fibers in vitro. Effects were evident at plasma levels of free drug 8 to 13 times the expected clinical level. Hypokalaemia and quinidine had additive/supra-additive effects in vitro while potentiation was evident with sotalol. Telithromycin, but not its major human metabolites, had inhibitory activity on HERG and Kv1.5 channels.

Reproduction toxicity studies showed reduced gamete maturation in rat and adverse effects on fertilization. At high doses embryotoxicity was apparent and an increase in incomplete ossification and in skeletal anomalies was seen. Studies in rats and rabbits were inconclusive with respect to potential for teratogenicity, there was equivocal evidence of adverse effects on foetal development at high doses.

Telithromycin, and its principal human metabolites, were negative in tests on genotoxic potential *in vitro* and *in vivo*. No carcinogenicity studies have been conducted with telithromycin.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core:

Maize starch  
Microcrystalline cellulose  
Povidone K25  
Croscarmellose sodium  
Magnesium stearate  
Lactose monohydrate

#### Tablet coating:

Talc  
Macrogol 8000  
Hypromellose 6 cp  
Titanium dioxide E171  
Yellow iron oxide E172  
Red iron oxide E172

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

### **6.4 Special precautions for storage**

No special precautions for storage.

### **6.5 Nature and contents of container**

Opaque PVC/Aluminium blisters.  
Two tablets are contained in each blister cavity.  
Available as packs of 10, 14, 20 and 100 tablets.

### **6.6 Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Aventis Pharma S.A.  
20, Avenue Raymond Aron  
F-92160 ANTONY  
France

**8. MARKETING AUTHORISATION NUMBER(S)**

EU1/01/192/001-004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

9 July 2001

**10. DATE OF REVISION OF THE TEXT**