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貯　　法：室温保存
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指定医薬品、処方せん医薬品：注意－医師等の処方せんにより使用すること

ケトライド系経口抗菌剤

ケテック®錠300mg
Ketek®

テリスロマイシン錠

sanofi aventis

【 禁忌（次の患者には投与しないこと）】
1. 本剤の成分に対し、過敏症の既往歴のある患者
2. ピモジド又はシサプリドを投与中の患者［「3. 相互作用」の項参照］

【 組成・性状 】

1. 組成

成分・含量（1錠中）	テリスロマイシン　300mg（力価）
添加物	結晶セルロース、ポビドン、クロスカルメロースナトリウム、ステアリン酸マグネシウム、ヒドロキシプロピルメチルセルロース2910、マクロゴール6000、タルク、酸化チタン、黄色三二酸化鉄、三二酸化鉄

2. 製剤の性状

剤形	色	外形、大きさ、重量			識別コード
		表	裏	側面	
フィルムコーティング錠	うすいだいだい色				38AV
		直径	厚さ	重量	
		長径 約12.6mm 短径 約7.9mm	約5.5mm	約460.1mg	

【 効能又は効果 】

〈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

肺炎球菌にはペニシリン耐性肺炎球菌及びマクロライド耐性肺炎球菌を含む。［【 臨床成績 】【 薬効薬理 】の項参照］

【 用法及び用量 】

通常、成人にはテリスロマイシンとして600mg（力価）を1日1回、5日間経口投与する。なお、歯周組織炎、歯冠周囲炎及び顎炎には、1日1回、3日間経口投与とし、肺炎には症状により1日1回最大7日間まで投与できる。

〈用法及び用量に関連する使用上の注意〉
1. 高度の腎機能障害（クレアチニンクリアランス30mL/min未満）のある患者では、1日1回、300mg（力価）への減量を考慮すること。血液透析患者に対しては、透析日には通常用量600mg（力価）を透析終了後に投与し、透析日以外には1日1回、300mg（力価）への減量を考慮すること。
2. 本剤の使用にあたっては、耐性菌の発現等を防ぐため、原則として感受性を確認すること。
3. 6日目以降（歯周組織炎、歯冠周囲炎及び顎炎の場合は4日目以降、肺炎の場合は8日目以降）においても臨床症状が不変もしくは悪化の場合には、医師の判断で適切な他の薬剤に変更すること。

【 使用上の注意 】

1. 慎重投与（次の患者には慎重に投与すること）
(1)マクロライド系抗菌剤に対し、過敏症の既往歴のある患者
(2)重症筋無力症の患者［症状を悪化させるおそれがある。］
(3)QT延長を起こすおそれのある患者［先天性QT延長症候群の患者、補正されていない低カリウム血症、低マグネシウム血症、徐脈のある患者、あるいはクラスIa、クラスIII抗不整脈剤又はQT延長が報告されている薬剤の投与を受けている患者では、QT延長を起こすおそれがある。］

2. 重要な基本的注意
(1)意識消失、視調節障害、霧視等があらわれることがあるので、自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。投与にあたっては、これらの副作用が発現する場合があることを患者等に十分に説明し、これらがあらわれた場合には、直ちに投与を中止し、医師の診察を受けるよう指導すること。［「4. 副作用」の項参照］
(2)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。

3. 相互作用
本剤は主としてCYP3A4及び一部CYP1Aで代謝される。また、CYP3A4及び軽度にCYP2D6を阻害する。CYP3A4により代謝される薬剤は併用に注意すること。

(1)併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
ピモジド（オーラップ）	マクロライド系抗菌剤とピモジドの併用において、ピモジドの血中濃度が上昇する。ピモジドの血中濃度を上昇させ、QT延長及び心室頻拍、心室細動及びtorsades de pointesなどの不整脈があらわれると考えられる。	本剤はこれらの薬剤の主たる代謝酵素（CYP3A4）を阻害する。
シサプリド	併用試験において、シサプリドの血中濃度が上昇しQTが延長した。［【 薬物動態 】の項参照］ QT延長及び心室頻拍、心室細動及びtorsades de pointesなどの不整脈があらわれるおそれがある。	

(2)併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
シンバスタチン アトルバスタチン	併用試験において、シンバスタチンの血中濃度が上昇した。［【 薬物動態 】の項参照］ミオパシーの発現を助長するおそれがあるので、筋肉痛、筋脱力、顕著なCK（CPK）上昇などに注意すること。CYP3A4で代謝されるスタチンとの併用は避けることが望ましい。併用する際には、12時間あけることを考慮すること。	本剤はこれらの薬剤の主たる代謝酵素（CYP3A4）を阻害する。

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A4で代謝されるベンゾジアゼピン類 ミダゾラム トリアゾラム 等	併用試験において、ミダゾラムのAUCが上昇した。[【 薬物動態 】の項参照] 鎮静作用が増強するおそれがあるので、用量調節を考慮すること。また、患者の状態を十分観察すること。	本剤はこれらの薬剤の主たる代謝酵素（CYP3A4）を阻害する。
テオフィリン	悪心、嘔吐など消化器系副作用を避けるために、両剤の投与間隔を1時間あけること。	ともに局所の消化器系副作用があらわれる。
ジゴキシン	併用試験において、ジゴキシンの血中濃度が上昇した。[【 薬物動態 】の項参照] 血中ジゴキシン濃度をモニタリングし、副作用発現に注意すること。	腸内細菌叢への影響により、ジゴキシンの不活性化が抑制され、ジゴキシンの血中濃度が上昇する。
リファンピシン	併用試験において、本剤の血中濃度が低下したので、併用を避けることが望ましい。[【 薬物動態 】の項参照]	リファンピシンは本剤の主たる代謝酵素(CYP3A4)を誘導する。
ソタロール	併用試験において、ソタロールの血中濃度とAUCが低下した。[【 薬物動態 】の項参照]	併用することによりソタロールの吸収が阻害される。
ワルファリン	ワルファリンの作用を増強したとの報告があるので、プロトロンビン時間/INRをモニタリングすることが望ましい。	機序は不明である。

(3)マクロライド系抗菌剤において、下記薬剤による相互作用が報告されている。

1)ジソピラミド、シクロスポリン、タクロリムス水和物、リトナビル、カルバマゼピン、フェニトイン、イトラコナゾール[これらの薬剤の血中濃度が上昇し、作用が増強されるおそれがある。]

2)エルゴタミン含有製剤［末梢の壊死を伴う重篤な血管収縮がおこることがある。］

4. 副作用

国内での承認時までの試験において1日1回テリスロマイシンとして600又は800mg（力価）が投与された安全性評価対象例613例中113例（18.4%）に自他覚的副作用が認められた。主な副作用は、下痢28例（4.6%）、軟便16例（2.6%）、肝機能異常12例（2.0%）、頭痛11例（1.8%）、腹部膨満9例（1.5%）、嘔気・悪心6例（0.98%）であった。

副作用としての主な臨床検査値異常は、ALT(GPT)上昇4.9%(26/536)、AST(GOT)上昇1.9%(10/536)、好酸球増加1.5%(8/521)、γ-GTP上昇1.5%(8/524)、血中アミラーゼ上昇1.4%(7/510)であった。

副作用の発現頻度は比較試験対照薬群と同程度であった。

（承認時：2003年10月）

（注）国内における承認用量は、1日1回600mg（力価）である。

(1)重大な副作用

1)ショック、アナフィラキシー様症状(頻度不明[注])…ショック、アナフィラキシー様症状があらわれることがあるので、観察を十分に行い、蕁麻疹、血管浮腫等の異常が認められた場合には投与を中止し、適切な処置を行うこと。

2)重症筋無力症の悪化（頻度不明[注])…重症筋無力症の患者で症状の悪化が報告されている。

3)意識消失（頻度不明[注])…意識消失、意識レベルの低下等があらわれることがあるので、このような場合には投与中止等の適切な処置を行うこと。

＊4)肝炎、肝機能障害、黄疸（頻度不明[注])…肝炎、AST(GOT)、ALT(GPT)、Al-Pの著しい上昇等を伴う肝機能障害、黄疸があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

＊5)QT延長（頻度不明[注])…QT延長があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

注）自発報告において認められている副作用のため頻度不明。

(2)その他の副作用

以下のような副作用があらわれた場合には、症状に応じ適切な処置を行うこと。

1)国内データ

	1～5%未満	1%未満	頻度不明[注]
消化器	下痢、軟便、血中アミラーゼ上昇、腹部膨満	嘔気・悪心、嘔吐、腹痛、便秘、口内炎、食欲不振	
肝臓	肝機能異常、ALT(GPT)上昇、AST(GOT)上昇、γ-GTP上昇	Al-P上昇	
血液	好酸球増加		
精神・神経系	頭痛	めまい、不眠、傾眠	錯感覚
感覚器		味覚異常、視調節障害、霧視	複視
皮膚		そう痒、発疹	蕁麻疹、湿疹
筋骨格		筋痙攣	
循環器系		低血圧、ほてり	心房性不整脈、徐脈
＊その他			浮腫(顔面、末梢性等)、膣カンジダ症、動悸

注）自発報告において認められている副作用のため頻度不明。

＊2)外国データ

外国での承認時までの試験において1日1回テリスロマイシンとして800mg（力価）が投与された安全性評価対象例3,265例中1,005例（30.8%）に副作用が認められた。主な副作用の種類及び発生頻度は国内と同程度であった。外国のみで認められている副作用は、口腔モニリア症、神経過敏、胆汁うっ滞性黄疸、多形紅斑である。

また、大規模臨床試験（1日1回800mg（力価））において、12,159例中に発現した主な副作用は、下痢（3.2%）、悪心（2.8%）、頭痛（1.3%）、浮動性めまい（1.2%）、味覚障害、腹痛（各0.8%）、嘔吐、口渇、鼓腸（各0.6%）及び霧視（0.5%）であった。なお、霧視は可逆性の眼の調節障害であり、多くは軽度かつ一過性で、投与後数時間以内に認められ発現後数時間で消失し、後遺症はみられなかった。

（注）国内における承認用量は、1日1回600mg(力価)である。

5. 高齢者への投与

高齢者での薬物動態試験で、本剤の血中濃度が非高齢者に比べて高くなることが認められている。[【 薬物動態 】7. 高齢者の項参照]

年齢による用量調節は必要ないが、高度の腎障害（クレアチニンクリアランス30mL/min未満）を伴う患者では、1日1回、300mg（力価）への減量を考慮すること。[【 薬物動態 】6. 腎機能障害患者の項参照]

6. 妊婦、産婦、授乳婦等への投与

(1)妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。[妊娠中の投与に関する安全性は確立していない。生殖に及ぼす影響の検討において、ラットにおける生殖細胞の成熟低下、受胎率の低下傾向がみられ、ラット及びウサギにおける胎児器官形成期投与試験において、母体毒性（体重低下あるいは摂餌量低下）がみられる高用量投与時(ラット：300mg/kg/日、NZWウサギ：60mg/kg/日）では、胎児体重の低値、胎児の化骨遅延等の異常のわずかな増加に加え、無尾・短尾等の外表異常、泌尿器系の発生異常が認められた。]

(2)授乳中の婦人には投与しないこと。やむを得ず投与する場合には授乳を避けさせること。[動物実験（ラット）で乳汁中へ移行することが認められている。]

7. 小児等への投与

小児等に対する安全性は確立していない。[使用経験がない。]

8. 過量投与

急性過量投与例においては嘔吐又は胃内洗浄により胃内薬物の除去を行うこと。患者を注意深く観察し、対症的、補助的療法を行うこと。また、十分な水分補給を行い、血液電解質（特にカリウム)を管理すること。また、心電図モニタリングを実施すること。

9. 適用上の注意

薬剤交付時：PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。[PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。]

10. その他の注意

(1)本剤の投与中又は投与後に下痢があらわれることがある。頻回又は出血を伴う場合は、偽膜性大腸炎のおそれがあるので、本剤の投与を直ちに中止し、補助療法や対症療法による処置を行うこと。

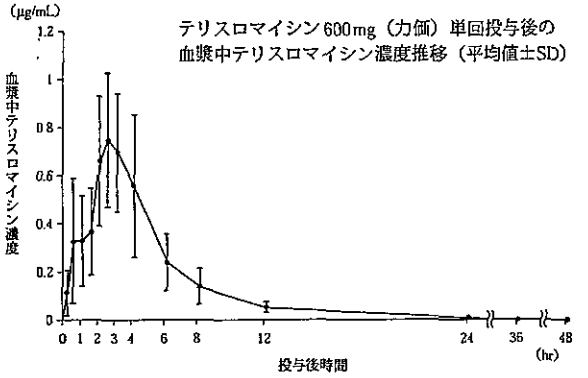
(2)動物（ラット、イヌ）に150mg/kg/日以上を4週間反復経口投与した場合、あるいは4週間以上の長期間投与では150mg/kg/日未満の用量で様々な組織（肝臓、肺、腎臓、脾臓、腸間膜リンパ節等）にリン脂質症に関連する所見がみられた。この所見は、投薬中止により消失し、マクロライド系抗菌剤にも認められる毒性学的意義の低い変化である。

【 薬物動態 】

1. 血漿中濃度

(1)単回投与[1)]

健康成人６名に本剤600mg（力価）を空腹時単回経口投与したとき、血漿中テリスロマイシン濃度の推移及び薬物動態パラメータは以下のとおりであった。



テリスロマイシン600mg（力価）単回投与後の血漿中テリスロマイシン濃度推移（平均値±SD）

C_{max} (μg/mL)	t_{max} (hr)	AUC_{0-24h} (μg·h/mL)	$t_{1/2\beta}$# (hr)
0.91±0.18	2.5	4.00±1.33	9.6±2.3

#：コンパートメントモデルによる解析(平均値±SD、t_{max}は中央値　n＝６)

(2)反復投与[1)]

健康成人８名に本剤600mg（力価）を１日１回10日間食後に反復経口投与したとき、最終回投与時における血漿中テリスロマイシンのC_{max}、AUC_{0-24h}、C_{24h}はそれぞれ1.18±0.39μg/mL、7.47±1.86μg·h/mL、0.039±0.013μg/mLであった（平均値±SD）。

血漿中テリスロマイシン濃度及び尿中排泄の推移から、蓄積性は認められなかった。

(3)食事の影響（外国人データ）[2)]

健康成人18名に本剤800mg(力価)をクロスオーバー法で、空腹時又は食後に単回経口投与したとき、血漿中テリスロマイシンのC_{max}及びAUCの空腹時投与に対する食後投与時の比の90%信頼区間は、いずれも生物学的同等の許容範囲内(80～125%)であった。本剤の吸収に及ぼす食事の影響はないと考えられた。

(注) 国内における承認用量は、１日１回600mg（力価）である。

2. 吸収・代謝・排泄（外国人データ）

健康成人（18～28歳）及び高齢者（65～84歳）各12名に本剤800mg（力価）を単回経口投与したときの絶対的バイオアベイラビリティは、ともに約57%であった[3)]。

健康成人男子６名に^{14}C-テリスロマイシン800mg（力価）を単回経口投与したとき、投与後７日までに投与放射能の約76及び17%がそれぞれ糞及び尿中に排泄された。投与放射能の約20及び12%がそれぞれ糞及び尿中に未変化体テリスロマイシンとして排泄された。血漿中においては、放射能AUCの約57%がテリスロマイシンであった。主要な代謝物として脱芳香環体、その他の代謝物として脱メチル体、オキサイド体、脱芳香環体酸化物が確認された[4)]。

健康成人男子４名にテリスロマイシン480mg（力価）を静脈内投与したとき、全身クリアランス(CLt)は61.3±10.5L/hであり（平均値±SD）、肝及び腎クリアランスは、CLtのそれぞれ約65及び23%であった[5)]。

なお、ヒト血清蛋白結合率(*in vitro* 平衡透析法)は、約60～70%であった[6)]。

(注) 国内における承認用量は、１日１回600mg（力価）である。

3. 組織移行性

健康成人における白血球、気管支肺胞分泌液、肺胞マクロファージ、また、患者における喀痰、副鼻腔粘膜、口蓋扁桃、歯肉、抜歯創貯留液などへの本剤の良好な組織移行が認められ、各組織中の薬物濃度は、血漿中濃度と同等もしくはそれ以上の濃度であった。

組織	対象	組織中薬物濃度 (μg/g又はμg/mL)	組織移行率 (組織/血漿比)	備考 (投与後時間)
白血球[1)]	健康成人	53.9±12.5	99倍	6
肺組織[7)]：気管支肺胞分泌液	健康成人	2.3±1.2	5.9倍	8
肺胞マクロファージ	健康成人	51.0±15.9	129倍	8
喀痰[8)]	患者	8.5±3.4 (C_{max}値)	4.8倍 (C_{max}比)	—
耳鼻咽喉組織[9)]：副鼻腔粘膜	患者	1.7±0.4	4.0倍	3～6
口蓋扁桃	患者	2.6±1.9	7.8倍	3～6
唾液[1)]	健康成人	0.6±0.2	1.2倍	6
口腔組織[10)]：歯肉	患者	1.7±1.7	3.3倍	3～6
抜歯創貯留液	患者	1.1±1.0	2.2倍	3～6

1回投与量として本剤600mg（力価）を用いた。平均値±SD

4. 薬物相互作用（外国人データ）

健康成人を対象にした薬物相互作用試験の結果は、以下のとおりであった。

なお、本剤の血漿中濃度はCYP3A4を阻害するグレープフルーツジュースの影響を受けなかった[11)]。

	併用薬剤 C_{max}	併用薬剤 AUC	テリスロマイシン C_{max} (μg/mL)	テリスロマイシン AUC (μg·h/mL)
シサプリド[12)]	2.0倍	3.0倍	3.0±1.1	14.7±5.0
シンバスタチン[13)] シンバスタチン	5.3倍	8.6倍	2.2±0.8	9.4±2.4
シンバスタチン酸	15倍	11倍		
ミダゾラム[14)] (静脈内)	1.1倍	2.2倍	1.5±0.4	10.3±4.1
(経口)※	2.6倍	6.1倍	1.6±0.5	11.4±4.1
イトラコナゾール[15)]	測定せず	測定せず	3.1±0.8 (1.2倍)	23.2±9.1 (1.6倍)
リファンピシン[16)]	0.4倍	0.4倍	0.4±0.2 (0.2倍)	1.4±0.5 (0.1倍)
テオフィリン[17)]	1.2倍	1.2倍	算出せず	算出せず トラフ値：0.047±0.020μg/mL
ジゴキシン[18)]	1.7倍	1.4倍	2.0±0.9	9.0±2.5
メトプロロール[19)]	1.4倍	1.4倍	1.5±0.3 (0.9倍)	9.7±1.8 (0.9倍)
ソタロール[20)]	0.7倍	0.8倍	1.2±0.3	5.8±2.1

いずれの試験においても、テリスロマイシンの１回投与量は800mgを用いた。

併用薬剤のC_{max}、AUCは単独投与時と比較した倍率を示した。

テリスロマイシンでは、併用時C_{max}（μg/mL）及びAUC（μg·h/mL）、又はトラフ値（μg/mL）の平均値±SDをそれぞれ示した。テリスロマイシン単独投与時と比較したものについては、その倍率を（　）中に示した。

※：他の経口ベンゾジアゼピン類では検討されていない。

(注) 国内における承認用量は、１日１回600mg（力価）である。

5. 肝機能障害患者（外国人データ）[21)]

健康成人及び肝機能障害患者（Child Pughスコア：平均7.4）各13名に本剤800mg（力価）を１日１回７日間反復経口投与したとき、肝機能障害患者におけるテリスロマイシンの薬物動態に、健康成人との有意な差は認められなかった。脱芳香環体のC_{max}及びAUCでは、肝機能障害患者において健康成人に比べ約50%低い値を示した。テリスロマイシンのC_{max}及びAUCにおいて、肝機能障害患者と健康成人との間に差が認められなかった理由の一つとして、肝機能障害患者におけるテリスロマイシンの腎クリアランスの増大が考えられた。なお、忍容性はいずれも良好であった。

(注) 国内における承認用量は、１日１回600mg（力価）である。

6. 腎機能障害患者（外国人データ）[22,23)]

健康成人及び腎機能障害患者に本剤800mg（力価）を１日１回５日間反復経口投与したとき、健康成人（９名）に比べ、軽度及び中等度の腎機能障害患者（クレアチニンクリアランスCcr値：50～80及び30～49mL/min、それぞれ８名）において、テリスロマイシンの定常状態におけるC_{max}及びAUCに有意な差は認められなかった。これに対し、高度の腎機能障害患者(Ccr値：<30mL/min、８名)におけるC_{max}及びAUCは健康成人に比べて有意に増加し、それぞれ健康成人の約1.5及び2.0倍であった。なお、テリスロマイシンの腎クリアランスは、腎機能の低下に応じて低下した。血液透析患者（10名）に透析終了後２時間以上あけて本剤800mg（力価）を単回経口投与したとき、健康成人（10名）との比較において、テリスロマイシンのC_{max}及びAUCに有意な差は認められなかった。

(注) 国内における承認用量は、１日１回600mg（力価）である。

7. 高齢者（外国人データ）[24,25)]

健康成人12名及び65歳以上の健康高齢者14名に本剤800mg（力価）を１日１回10日間反復経口投与したとき、高齢者の最終回投与時における血漿中テリスロマイシンのC_{max}及びAUC_{0-24h}は、それぞれ3.6±1.5μg/mL及び17.2±5.5μg·h/mLであった（平均値±SD）。これは、健康成人における値のそれぞれ約2倍であった。なお、忍容性はいずれも良好であった。

また、感染症患者を対象として検討した薬物動態試験では、非高齢患者に比べ高齢患者のC_{max}及びAUCは約1.4倍であった。

(注) 国内における承認用量は、１日１回600mg（力価）である。

【 臨床成績 】

二重盲検比較試験（肺炎）を含む国内臨床試験のうち327例の投与終了時の臨床効果は以下のとおりであった。

疾患名		投与期間	臨床効果
呼吸器感染症[8, 26, 27]	急性気道感染症群	5日間投与	95.7%(45/47)
	咽頭・喉頭炎 扁桃炎 急性気管支炎		93.8%(15/16) 100%(10/10) 95.2%(20/21)
	肺炎	5日間投与 (7日間投与)	88.5%(23/26) (92.8%(154/166))
	慢性呼吸器病変の二次感染(慢性気管支炎、びまん性汎細気管支炎、気管支拡張症、肺気腫、気管支喘息等)	5日間投与	91.3%(21/23)
耳鼻科領域感染症[9]	副鼻腔炎	5日間投与	85.4%(35/41)
歯科・口腔外科領域感染症[10]	歯科・口腔外科領域感染症	3日間投与	91.7%(22/24)
	歯周組織炎 歯冠周囲炎 顎炎		100%(5/ 5) 100%(4/ 4) 86.7%(13/15)

また、ペニシリン耐性あるいはマクロライド耐性肺炎球菌を含む主な起炎菌に対する臨床効果及び微生物学的効果（消失率）は以下のとおりであった。

疾患名	起炎菌	臨床効果	微生物学的効果
呼吸器感染症[8, 26, 27] 耳鼻科領域感染症[9] 歯科・口腔外科領域感染症[10]	ブドウ球菌属	94.7%(18/19)	89.5%(17/19)
	レンサ球菌属	86.7%(26/30)	100%(29/29)
	肺炎球菌	93.5%(43/46)	93.5%(43/46)
	PRSP	100%(7/ 7)	100%(7/ 7)
	PISP	100%(13/13)	100%(13/13)
	ERSP	96.9%(31/32)	93.8%(30/32)
	EISP	(1/1)	(1/1)
	PRSP/PISPもしくはERSP/EISP	97.1%(33/34)	94.1%(32/34)
	モラクセラ(ブランハメラ)・カタラーリス	92.3%(12/13)	100%(13/13)
	インフルエンザ菌	93.8%(60/64)	71.9%(46/64)
	ペプトストレプトコッカス属	100%(10/10)	100%(10/10)
	プレボテラ属	100%(6/ 6)	100%(6/ 6)
	肺炎マイコプラズマ(マイコプラズマ・ニューモニエ)	100%(5/ 5)	100%(5/ 5)

PRSP（ペニシリン耐性肺炎球菌）：ペニシリンGのMIC≧2μg/mL
PISP（ペニシリン中等度耐性肺炎球菌）：
0.12μg/mL≦ペニシリンGのMIC＜2μg/mL
ERSP（エリスロマイシン耐性肺炎球菌）：エリスロマイシンのMIC≧1μg/mL
EISP（エリスロマイシン中等度耐性肺炎球菌）：
0.5μg/mL≦エリスロマイシンのMIC＜1μg/mL

【 薬効薬理 】

1. 抗菌作用

(1) *In vitro* において、ブドウ球菌属、レンサ球菌属、肺炎球菌等のグラム陽性菌及びモラクセラ(ブランハメラ)・カタラーリス、インフルエンザ菌、プレボテラ属等のグラム陰性菌、レジオネラ属、ペプトストレプトコッカス属、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）に対し抗菌力を示す。肺炎球菌のペニシリン耐性株、エリスロマイシン耐性株あるいはキノロン耐性株に対しても、抗菌力を示す[28~38]。

(2) 肺炎球菌及びインフルエンザ菌に対して、1 MIC 濃度から殺菌的な作用を示す[39]。

(3) 黄色ブドウ球菌、肺炎球菌、インフルエンザ菌、レジオネラ等の各種細菌を用いた感染症モデルにおいて、*in vitro* の抗菌力を反映し、マクロライド系抗菌剤に比べ強い防御効果及び治療効果を示す[40~43]。

2. 作用機序

(1) 細菌の70Sリボソームの50Sサブユニット中の23S rRNAドメインVの2058位及び2059位アデニン残基に加えて、ドメインIIの752位アデニン残基に結合し、蛋白合成を阻害する[44, 45]。

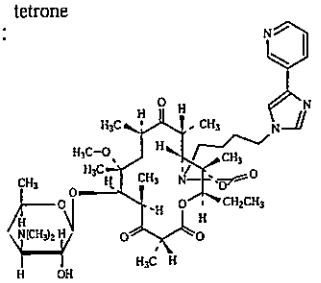
(2) 黄色ブドウ球菌、化膿レンサ球菌、肺炎球菌においてマクロライド・リンコマイシン・ストレプトグラミンB(MLS$_B$)耐性を誘導しない[46]。

【 有効成分に関する理化学的知見 】

一般名：テリスロマイシン Telithromycin（JAN） 略号：TEL

化学名：(+)-(3a*S*, 4*R*, 7*R*, 9*R*, 10*R*, 11*R*, 13*R*, 15*R*, 15a*R*)-4-Ethyloctahydro-11-methoxy-3a, 7, 9, 11, 13, 15-hexamethyl-1-{4-[4-(3-pyridyl)imidazol-1-yl]butyl}-10-{[3, 4, 6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-2*H*-oxacyclotetradecino[4, 3-*d*]oxazole-2, 6, 8, 14(1*H*, 7*H*, 9*H*)-tetrone

構造式：



分子式：$C_{43}H_{65}N_5O_{10}$ 分子量：812.00

性 状：テリスロマイシンは白色～微帯黄白色の粉末である。ジクロロメタンに極めて溶けやすく、アセトニトリル、*N*, *N*-ジメチルホルムアミド又はメタノールに溶けやすく、水又はヘキサンにほとんど溶けない。

分配係数：log P＝1.6（1-オクタノール／水系、pH 7）

【 包 装 】

100錠〔10錠(PTP)×10〕

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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-06000422	第2報	報告日 2007年03月30日	第一報入手日 2007年02月13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	サノフィ・アベンティス（本社）のプレスリリース (http://intranet.sanofi-aventis.com/uDocuments/press_release/2007/02/KETEK_FDA_DECISION_ENG_120207.pdf) FDAのホームページ (http://www.fda.gov/bbs/topics/NEWS/2007/NEW01561.html)	公表国 アメリカ		
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（USPI改訂）
ケテックのUSPIが変更されるとの情報を入手した。また、処方時に患者に配布するPatient Medication Guideも作成された。本情報はFDAのホームページにも掲載されている。
USPIの変更点は以下のとおりである。
・今までの適応のうち「急性増悪慢性気管支炎」「急性細菌性副鼻腔炎」については削除し、「軽度～中等度の市中肺炎」のみの適応となった。
・重症筋無力症患者での使用を「禁忌」に記載した。
・視覚障害、意識消失（失神）を「警告」に記載した。
本改訂は、2006年12月14ー15日に行われたFDA諮問委員会にて、ケテックによる肺炎治療のベネフィットはリスクを上回るが、副鼻腔炎（細菌性副鼻腔炎：ABS）、気管支炎（慢性気管支炎の増悪：AECB）に対してはリスクがベネフィットを上回るとしてケテックの使用制限を勧告されたことによる。
【2007年3月27日入手の追加情報】
上記のUSPI改訂に伴い、Dear Healthcare Professional LetterがFDAのWebsiteに掲載された。内容はUSPIの改訂内容、および処方時の患者への説明に関するものである。
（処方時には注意すべき副作用（重症筋無力症の悪化、肝毒性、視覚障害、意識消失）についての説明を行うこと。患者へMedication Guideを配布し、服用前に読むよう指導すること。）

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2月16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。
今回のUSPI改訂に伴い、Dear Healthcare Professional LetterがFDAのWebiteに掲載された。

報告企業の意見

ケテックのUSPIの改訂に伴い、Dear Healthcare Professional LetterがFDAのWebsiteに掲載されたとの情報を入手したため報告を行う。今後の対応については現在、厚生労働省　安全対策課と協議中である。

今後の対応

今後の対応については現在、厚生労働省　安全対策課と協議中である。対応が確定次第、追加報告を行う。

P5

17-060004 22
(ケテック錠300mg)

IMPORTANT PRESCRIBING INFORMATION

sanofi aventis
Because health matters

KETEK® (telithromycin) DEAR HEALTHCARE PROFESSIONAL LETTER

March 2007

IMPORTANT INFORMATION ABOUT KETEK® (telithromycin)

Dear Healthcare Professional:

Sanofi-aventis U.S. would like to inform you of important updated information regarding KETEK® (telithromycin) tablets. **The prescribing information has been revised to add a boxed warning and contraindication for myasthenia gravis patients. In addition, the indications for the treatment of acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS) have been removed from the labeling.** These revisions follow discussions with the Food and Drug Administration (FDA) regarding its decision to follow recommendations of a December 2006 Advisory Committee that the balance of the benefits and risks no longer support continued marketing of Ketek for these two indications. It is important to note that Ketek continues to be indicated only for the treatment of community-acquired pneumonia (CAP) of mild to moderate severity due to *Streptococcus pneumoniae,* (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae, or Mycoplasma pneumoniae,* for patients 18 years old and older.

Safety information regarding visual disturbances and loss of consciousness, previously in the precautions section, has been added to the warnings section. **In prescribing KETEK, it is important for healthcare professionals to inform and discuss with patients the four highlighted toxicities: exacerbation of myasthenia gravis, hepatotoxicity, visual disturbances, and loss of consciousness.**

A Medication Guide has been developed that replaces the Patient Information section of the US prescribing information for KETEK, to better inform and educate patients. The Medication Guide must be provided by pharmacists to patients when KETEK® is dispensed. Healthcare professionals should advise patients to read the medication guide prior to taking KETEK.

Important changes to the updated KETEK® Prescribing Information include:

IMPORTANT DRUG SAFETY INFORMATION:

1. Add a **BOXED WARNING** regarding what is now a **CONTRAINDICATION** for patients with myasthenia gravis;
2. Include a **WARNING** concerning visual disturbances and loss of consciousness, including information previously listed in the **PRECAUTIONS** section;
3. Include a Medication Guide for patients that replaces the Patient Information section

sanofi-aventis U.S., 55 Corporate Drive, PO Box 5925, Bridgewater, NJ 08807-0890
Tel 1-908-981-5600 - www.sanofi-aventis.com

IMPORTANT PRESCRIBING INFORMATION:

1. ***Remove*** from the labeling recommendations for the use of Ketek in the treatment of acute exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS) in the **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION and CLINICAL STUDIES** sections.

These changes have been approved by the US Food and Drug Administration.

The most important changes in the prescribing information relating to the above are as follows:

MYASTHENIA GRAVIS

Clinicians are advised to review carefully the Boxed Warning shown below, which has been added to the prescribing information.

Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek. (See **CONTRAINDICATIONS.**)

CONTRAINDICATIONS

Added:

"KETEK is contraindicated in patients with myasthenia gravis. Exacerbations of myasthenia gravis have been reported in patients and sometimes occurred within a few hours of the first dose of telithromycin. Reports have included fatal and life-threatening acute respiratory failure with a rapid onset and progression."

VISUAL DISTURBANCES AND SYNCOPE

WARNINGS

Added 2 new subsections:

"Visual disturbances*"

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.

"Loss of Consciousness*"

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome.

***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 **PRECAUTIONS, Information for Patients.**)"

REMOVED: *ACUTE EXACERBATION of CHRONIC BRONCHITIS (AECB) and ACUTE BACTERIAL SINUSITIS (ABS) INDICATIONS*

INDICATIONS AND USAGE

***Removed* from the indications section acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS).**

DOSAGE AND ADMINISTRATION

Revised the dosing information to delete references to infection type and to be specific for the community acquired-pneumonia indication as follows:

"The dose of KETEK tablets is 800 mg (2 tablets of 400 mg) taken orally once every 24 hours, for 7–10 days. KETEK tablets can be administered with or without food."

We also remind healthcare professionals of the June 2006 labeling changes concerning hepatotoxicity. The current version of the warning follows.

"WARNINGS

"Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK.

"Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. ***Patients with signs or symptoms of* hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests.** If clinical hepatitis or transaminase elevations combined with other systemic symptoms occur, KETEK should be permanently discontinued.

"Ketek must not be re-administered to patients with a previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic.

"In addition, less severe hepatic dysfunction associated with increased liver enzymes, hepatitis and in some cases jaundice was reported with the use of KETEK. These events associated with less severe forms of liver toxicity were reversible."

At sanofi-aventis U.S., patient safety is our highest priority and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe KETEK appropriately. Please carefully review this information and the revised labeling including the Medication Guide which are enclosed. Contact sanofi-aventis if you have any questions about this information or the safe and effective use of KETEK.

We also encourage you to report any adverse events experienced by your patients. Call sanofi-aventis U.S. at 1-800-633-1610 (option #2) to report adverse events occurring in connection with the use of KETEK. Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

The revised product information including the Medication Guide will be included in Ketek® (telithromycin) packages manufactured after February 12, 2007, and is available on the company and product websites (www.sanofi-aventis.us and www.ketek.com) or by contacting Medical Information Services at 1-800-633-1610 (option #1) from 9 am to 5 pm (EST) Monday–Friday.

Sincerely,

Douglas Greene, MD

Senior Vice President US Medical Affairs & Chief Medical Officer
Sanofi-aventis U.S.

Enclosures: KETEK® (telithromycin) Full Prescribing Information

US.TEL.07.02.022

About Ketek

Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek.

KETEK tablets are indicated for the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years old and above.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

KETEK is contraindicated in patients with myasthenia gravis. Exacerbations of myasthenia gravis have been reported in patients and sometimes occurred within a few hours of the first dose of telithromycin. Reports have included fatal and life-threatening acute respiratory failure with a rapid onset and progression.

KETEK is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic.

KETEK is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of KETEK tablets, or any macrolide antibiotic.

Concomitant administration of KETEK with cisapride or pimozide is contraindicted.

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK.

Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. **Patients with signs or symptoms of hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests.** If clinical hepatitis or transaminase elevations combined with other systemic symptoms occur, KETEK *should be permanently discontinued.*

Ketek must not be re-administered to patients with a previous history of hepatitis and/or jaundice *associated with the use of KETEK tablets, or any macrolide antibiotic.*

In addition, less severe hepatic dysfunction associated with increased liver enzymes, hepatitis and in some cases jaundice was reported with the use of KETEK. These events associated with less severe forms of liver toxicity were reversible.

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (e.g., quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

Cases of torsades de pointes have been reported post-marketing with KETEK. In clinical trials, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical trials, including 204 patients having a prolonged QTc at baseline.

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.

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome.

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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including KETEK, and may range in severity from mild diarrhea to fatal colitis. Treatment *with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile,* and surgical evaluation should be instituted as clinically indicated.

Therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of KETEK treatment. Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided.

Most adverse events were mild to moderate and included diarrhea, nausea, headache, dizziness, and vomiting.

7-060004422
(ケテック錠300mg)

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.
DYNABAC® (dirithromycin) is a registered trademark of Eli Lilly and Company.
PROPULSID® (cisapride) is a registered trademark of Johnson & Johnson.
ORAP® (pimozide) is a registered trademark of Teva Pharmaceuticals USA, Inc.
LIPITOR® (atorvastatin) is a registered trademark of Pfizer Inc.
ZOCOR® (simvastatin) is a registered trademark of Merck & Co Inc.
VYTORIN® (simvastatin and ezetimibe) is a registered trademark of Merck/Schering Plough Pharmaceuticals.
MEVACOR® (lovastatin) is a registered trademark of Merck & Co Inc..

7-06000422
(ケテック錠300mg.

NDA 21-144/S-012

Rev February 2007
KETEK®
(telithromycin) Tablets

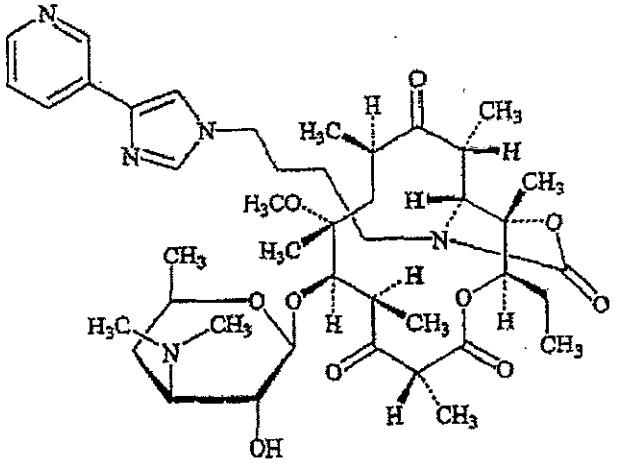
Ketek is contraindicated in patients with myasthenia gravis. *There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek.* (See **CONTRAINDICATIONS.**)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

KETEK® tablets contain telithromycin, a semisynthetic antibacterial in the ketolide class for oral administration. Chemically, telithromycin is designated as Erythromycin, 3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-.

Telithromycin, a ketolide, differs chemically from the macrolide group of antibacterials by the lack of α-L-cladinose at position 3 of the erythronolide A ring, resulting in a 3-keto function. It is further characterized by a C11-12 carbamate substituted by an imidazolyl and pyridyl ring through a butyl chain. Its empirical formula is $C_{43}H_{65}N_5O_{10}$ and its molecular weight is 812.03. Telithromycin is a white to off-white crystalline powder. The following represents the chemical structure of telithromycin.



KETEK tablets are available as light-orange, oval, film-coated tablets, each containing 400 mg or 300 mg of telithromycin, and the following inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Following oral administration, telithromycin reached maximal concentration at about 1 hour (0.5 - 4 hours).

It has an absolute bioavailability of 57% in both young and elderly subjects.

The rate and extent of absorption are unaffected by food intake, thus KETEK tablets can be given without regard to food.

In healthy adult subjects, peak plasma telithromycin concentrations of approximately 2 µg/mL are attained at a median of 1 hour after an 800-mg oral dose.

Steady-state plasma concentrations are reached within 2 to 3 days of once daily dosing with telithromycin 800 mg.

Following oral dosing, the mean terminal elimination half-life of telithromycin is 10 hours.

The pharmacokinetics of telithromycin after administration of single and multiple (7 days) once daily 800-mg doses to healthy adult subjects are shown in Table 1.

Table 1

	Mean (SD)	
Parameter	**Single dose (n=18)**	***Multiple dose (n=18)***
C_{max} (µg/mL)	1.9 (0.80)	2.27 (0.71)
T_{max} (h)*	1.0 (0.5-4.0)	1.0 (0.5-3.0)
$AUC_{(0-24)}$ (µg·h/mL)	8.25 (2.6)	12.5 (5.4)
Terminal $t_{1/2}$ (h)	7.16 (1.3)	9.81 (1.9)
C_{24h} (µg/mL)	0.03 (0.013)	0.07 (0.051)

* Median (min-max) values
SD=Standard deviation
C_{max}=Maximum plasma concentration
T_{max}=Time to C_{max}
AUC=Area under concentration vs. time curve
$t_{1/2}$=Terminal plasma half-life
C_{24h} =Plasma concentration at 24 hours post-dose

In a patient population, mean peak and trough plasma concentrations were 2.9 µg/mL (±1.55), (n=219) and 0.2 µg/mL (±0.22), (n=204), respectively, after 3 to 5 days of KETEK 800 mg once daily.

Distribution: Total *in vitro* protein binding is approximately 60% to 70% and is primarily due to human serum albumin.

Protein binding is not modified in elderly subjects and in patients with hepatic impairment.

The volume of distribution of telithromycin after intravenous infusion is 2.9 L/kg.

Telithromycin concentrations in bronchial mucosa, epithelial lining fluid, and alveolar macrophages after 800 mg once daily dosing for 5 days in patients are displayed in Table 2.

Table 2

	Hours post-dose	Mean concentration (µg/mL) Tissue or fluid	Plasma	Tissue/ Plasma Ratio
Bronchial mucosa	2	3.88*	1.86	2.11
	12	1.41*	0.23	6.33
	24	0.78*	0.08	12.11
Epithelial lining fluid	2	14.89	1.86	8.57
	12	3.27	0.23	13.8
	24	0.84	0.08	14.41
Alveolar macrophages	2	65	1.07	55
	8	100	0.605	180
	24	41	0.073	540

*Units in mg/kg

Telithromycin concentration in white blood cells exceeds the concentration in plasma and is eliminated more slowly from white blood cells than from plasma. Mean white blood cell concentrations of telithromycin peaked at 72.1 µg/mL at 6 hours, and remained at 14.1 µg/mL 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days, repeated dosing of 600 mg once daily, white blood cell concentrations remained at 8.9 µg/mL 48 hours after the last dose.

Metabolism: In total, metabolism accounts for approximately 70% of the dose. In plasma, the main circulating compound after administration of an 800-mg radiolabeled dose was parent compound, representing 56.7% of the total radioactivity. The main metabolite represented 12.6% of the AUC of telithromycin. Three other plasma metabolites were quantified, each representing 3% or less of the AUC of telithromycin.

It is estimated that approximately 50% of its metabolism is mediated by CYP 450 3A4 and the remaining 50% is CYP 450-independent.

Elimination: The systemically available telithromycin is eliminated by multiple pathways as follows: 7% of the dose is excreted unchanged in feces by biliary and/or intestinal secretion; 13% of the dose is excreted unchanged in urine by renal excretion; and 37% of the dose is metabolized by the liver.

Special populations

Gender: There was no significant difference between males and females in mean AUC, C_{max}, and elimination half-life in two studies; one in 18 healthy young volunteers (18 to 40 years of age) and the other in 14 healthy elderly volunteers (65 to 92 years of age), given single and multiple once daily doses of 800 mg of KETEK.

Hepatic insufficiency: In a single-dose study (800 mg) in 12 patients and a multiple-dose study (800 mg) in 13 patients with mild to severe hepatic insufficiency (Child Pugh Class A, B and C), the C_{max}, AUC and $t_{1/2}$ of telithromycin were similar to those obtained in age- and sex-matched healthy subjects. In both studies, an *increase in renal elimination was observed in hepatically impaired patients indicating that this pathway may* compensate for some of the decrease in metabolic clearance. No dosage adjustment is recommended due to hepatic impairment. (See **PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION.**)

Renal insufficiency: In a multiple-dose study, 36 subjects with varying degrees of renal impairment received 400 mg, 600 mg, or 800 mg KETEK once daily for 5 days. There was a 1.4-fold increase in $C_{max,ss}$, and a 1.9-fold increase in AUC $(0\text{-}24)_{ss}$ at 800 mg multiple doses in the severely renally impaired group (CL_{CR} < 30 mL/min) compared to healthy volunteers. Renal excretion may serve as a compensatory elimination pathway for telithromycin in situations where metabolic clearance is impaired. Patients with severe renal impairment are prone to conditions that may impair their metabolic clearance. Therefore, in the presence of severe renal

impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION.**)

In a single-dose study in patients with end-stage renal failure on hemodialysis (n=10), the mean C_{max} and AUC values were similar to normal healthy subjects when KETEK was administered 2 hours post-dialysis. However, the effect of dialysis on removing telithromycin from the body has not been studied.

Multiple insufficiency: The effects of co-administration of ketoconazole in 12 subjects (age ≥ 60 years), with impaired renal function were studied (CL_{CR}= 24 to 80 mL/min). In this study, when severe renal insufficiency (CL_{CR} < 30 mL/min, n=2) and concomitant impairment of CYP 3A4 metabolism pathway were present, telithromycin exposure (AUC (0-24)) was increased by approximately 4- to 5-fold compared with the exposure in healthy subjects with normal renal function receiving telithromycin alone. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, a reduced dosage of KETEK is recommended. (**See PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION.**)

Geriatric: Pharmacokinetic data show that there is an increase of 1.4-fold in exposure (AUC) in 20 patients ≥ 65 years of age with community acquired pneumonia in a Phase III study, and a 2.0-fold increase in exposure (AUC) in 14 subjects ≥ 65 years of age as compared with subjects less than 65 years of age in a Phase I study. No dosage adjustment is required based on age alone.

Drug-drug interactions

Studies were performed to evaluate the effect of CYP 3A4 inhibitors on telithromycin and the effect of telithromycin on drugs that are substrates of CYP 3A4 and CYP 2D6. In addition, drug interaction studies were conducted with several other concomitantly prescribed drugs.

CYP 3A4 inhibitors:

Itraconazole: A multiple-dose interaction study with itraconazole showed that C_{max} of telithromycin was increased by 22% and AUC by 54%.

Ketoconazole: A multiple-dose interaction study with ketoconazole showed that C_{max} of telithromycin was increased by 51% and AUC by 95%.

Grapefruit juice: When telithromycin was given with 240 mL of grapefruit juice after an overnight fast to healthy subjects, the pharmacokinetics of telithromycin were not affected.

CYP 3A4 substrates:

Cisapride: Steady-state peak plasma concentrations of cisapride (an agent with the potential to increase QT interval) were increased by 95% when co-administered with repeated doses of telithromycin, resulting in significant increases in QTc. (See **CONTRAINDICATIONS.**)

Simvastatin: When simvastatin was co-administered with telithromycin, there was a 5.3-fold increase in simvastatin C_{max}, an 8.9-fold increase in simvastatin AUC, a 15-fold increase in the simvastatin active metabolite C_{max}, and a 12-fold increase in the simvastatin active metabolite AUC. (See **PRECAUTIONS.**)

In another study, when simvastatin and telithromycin were administered 12 hours apart, there was a 3.4-fold increase in simvastatin C_{max}, a 4.0-fold increase in simvastatin AUC, a 3.2-fold increase in the active metabolite C_{max}, and a 4.3-fold increase in the active metabolite AUC. (See **PRECAUTIONS.**)

Midazolam: Concomitant administration of telithromycin with intravenous or oral midazolam resulted in 2- and 6-fold increases, respectively, in the AUC of midazolam due to inhibition of CYP 3A4-dependent metabolism of midazolam. (See **PRECAUTIONS.**)

CYP 2D6 substrates:

Paroxetine: There was no pharmacokinetic effect on paroxetine when telithromycin was co-administered.

Metoprolol: When metoprolol was co-administered with telithromycin, there was an increase of approximately 38% on the C_{max} and AUC of metoprolol, however, there was no effect on the elimination half-life of metoprolol. Telithromycin exposure is not modified with concomitant single-dose administration of metoprolol. (See **PRECAUTIONS, Drug interactions.**)

Other drug interactions:

Digoxin: The plasma peak and trough levels of digoxin were increased by 73% and 21%, respectively, in healthy volunteers when co-administered with telithromycin. However, trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations has been achieved) ranged from 0.74 to 2.17 ng/mL. There were no significant changes in ECG parameters and no signs of digoxin toxicity. (See **PRECAUTIONS.**)

Theophylline: When theophylline was co-administered with repeated doses of telithromycin, there was an increase of approximately 16% and 17% on the steady-state C_{max} and AUC of theophylline. Co-administration of theophylline may worsen gastrointestinal side effects such as nausea and vomiting, especially in female patients. It is recommended that telithromycin should be taken with theophylline 1 hour apart to decrease the likelihood of gastrointestinal side effects.

Sotalol: Telithromycin has been shown to decrease the C_{max} and AUC of sotalol by 34% and 20%, respectively, due to decreased absorption.

Warfarin: When co-administered with telithromycin in healthy subjects, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin.

Oral contraceptives: When oral contraceptives containing ethinyl estradiol and levonorgestrel were co-administered with telithromycin, the steady-state AUC of ethinyl estradiol did not change and the steady-state AUC of levonorgestrel was increased by 50%. The pharmacokinetic/pharmacodynamic study showed that telithromycin did not interfere with the antiovulatory effect of oral contraceptives containing ethinyl estradiol and levonorgestrel.

Ranitidine, antacid: There was no clinically relevant pharmacokinetic interaction of ranitidine or antacids containing aluminum and magnesium hydroxide on telithromycin.

Rifampin: During concomitant administration of rifampin and KETEK in repeated doses, C_{max} and AUC of telithromycin were dereased by 79%, and 86%, respectively. (See **PRECAUTIONS, Drug Interactions.**)

Microbiology

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP*]).

*MDRSP=Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Mechanism of action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g., *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in subinhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*])

*MDRSP=Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other microorganisms

Chlamydophila (Chlamydia) pneumoniae

Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Other microorganisms

Legionella pneumophila

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in Table 3.

Table 3. Susceptibility Test Result Interpretive Criteria for Telithromycin

	Minimal Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Haemophilus influenzae	≤ 4	8	≥ 16	≥ 15	12-14	≤ 11

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors

from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in Table 4. For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in Table 4.

Table 4. Acceptable Quality Control Ranges for Telithromycin

QC Strain	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (Zone diameter in mm)
Streptococcus pneumoniae ATCC 49619	0.004-0.03	27-33
Haemophilus influenzae ATCC 49247	1.0-4.0	17-23

ATCC = American Type Culture Collection

INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis, Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years old and above.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

KETEK is contraindicated in patients with myasthenia gravis. Exacerbations of myasthenia gravis have been reported in patients and sometimes occurred within a few hours of the first dose of telithromycin. Reports have included fatal and life-threatening acute respiratory failure with a rapid onset and progression.

KETEK is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic.

KETEK is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of KETEK tablets, or any macrolide antibiotic.

Concomitant administration of KETEK with cisapride or pimozide is contraindicated. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions** and **PRECAUTIONS**.)

WARNINGS

Hepatotoxicity

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. *These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver* transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK. (See **ADVERSE REACTIONS**.) Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. **Patients with signs or symptoms of hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests.** (See **ADVERSE REACTIONS, PRECAUTIONS**, Information to Patients.) If clinical hepatitis or transaminase elevations combined with other systemic symptoms occur, KETEK should be permanently discontinued.

Ketek must not be re-administered to patients with a previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic. (See **CONTRAINDICATIONS**.)

In addition, less severe hepatic dysfunction associated with increased liver enzymes, hepatitis and in some cases jaundice was reported with the use of KETEK. These events associated with less severe forms of liver toxicity were reversible.

QTc prolongation

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (e.g., quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

Cases of torsades de pointes have been reported post-marketing with KETEK. In clinical trials, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical trials, including 204 patients having a prolonged QTc at baseline.

Visual disturbances*

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.

Loss of consciousness*

There have been post-marketing adverse event reports of transient loss of consciousness including *some cases associated with vagal syndrome.*

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 **PRECAUTIONS, *Information for Patients.)

PSEUDOMEMBRANOUS COLITIS

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including KETEK, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C *difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Prescribing KETEK in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CL_{CR} < 30 *mL/min), a reduced dosage of* KETEK is recommended. (See **DOSAGE AND ADMINISTRATION.**)

Information for patients

A Medication Guide is provided to patients when Ketek is dispensed. Patients should be instructed to read the *MedGuide when Ketek is received. In addition, the complete text of the MedGuide is reprinted at the end of this* document.

The following information and instructions should be communicated to the patient.

- KETEK may cause problems with vision particularly when looking quickly between objects close by and objects far away. These events include blurred vision, difficulty focusing, and objects looking doubled. Most events were mild to moderate; however, severe cases have been reported. Problems with vision were reported as having occurred after any dose during treatment, but most occurred following the first or second dose. These problems lasted several hours and in some patients came back with the next dose. (See **WARNINGS** and **ADVERSE REACTIONS.**)

Patients should be advised that avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.

- **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 difficulties or loss of consciousness / fainting
- patients should seek advice from their physician before taking another dose
- patients should not drive a motor vehicle, operate heavy machinery, or engage in otherwise hazardous activities.

Patients should also be advised:
- **Ketek is contraindicated in patients with myasthenia gravis.** (See **CONTRAINDICATIONS.**)

- of the possibility of liver injury, associated with KETEK, which in rare cases may be severe. **Patients developing signs or symptoms of liver injury should be instructed to discontinue KETEK and seek medical attention immediately.** Symptoms of liver injury may include nausea, fatigue, anorexia, jaundice, dark urine, light-colored stools, pruritus, or tender abdomen. Ketek must not be taken by patients with a

previous history of hepatitis/jaundice associated with the use of KETEK or macrolide antibiotics. (See **CONTRAINDICATIONS** and **WARNINGS.**)

- antibacterial drugs including KETEK should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When KETEK is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance *and will not be treatable by KETEK or other antibacterial drugs in the future.*

- KETEK has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.

- KETEK should be avoided in patients receiving Class 1A (e.g., quinidine, procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

- *to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions* such as uncorrected hypokalemia, or clinically significant bradycardia.

- diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

- simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving KETEK. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment.

- KETEK tablets can be taken with or without food.

- to inform their physician of any other medications taken concurrently with KETEK, including over-the-counter medications and dietary supplements.

Drug interactions

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Co-administration of KETEK tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug co-administered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug co-administered with telithromycin.

The use of KETEK is contraindicated with cisapride. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY, *Drug-drug interactions.*)**

The use of KETEK is contraindicated with pimozide. Although there are no studies looking at the interaction between KETEK and pimozide, there is a potential risk of increased pimozide plasma levels by inhibition of CYP 3A4 pathways by KETEK as with macrolides. (See **CONTRAINDICATIONS.**)

In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**) Similarly, an interaction may occur with lovastatin or *atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the* risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment.

Monitoring of digoxin side effects or serum levels should be considered during concomitant administration of digoxin and KETEK. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Patients should be monitored with concomitant administration of midazolam and dosage adjustment of midazolam should be considered if necessary. Precaution should be used with other benzodiazepines, which are metabolized by CYP 3A4 and undergo a high first-pass effect (e.g., triazolam). (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided. Concomitant administration of other CYP 3A4 inducers such as phenytoin, carbamazepine, or phenobarbital is likely to result in subtherapeutic levels of telithromycin and loss of effect. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**)

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP 2D6 substrate, may be of clinical importance. Therefore, co-administration of KETEK and metoprolol in patients with heart failure should be considered with caution. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Spontaneous post-marketing reports suggest that administration of KETEK and oral anticoagulants concomitantly may potentiate the effects of the oral anticoagulants. Consideration should be given to monitoring *prothrombin times/INR while patients are receiving KETEK and oral anticoagulants simultaneously.*

No specific drug interaction studies have been performed to evaluate the following potential drug-drug interactions with KETEK. However, these drug interactions have been observed with macrolide products.
Drugs metabolized by the cytochrome P450 system such as carbamazepine, cyclosporine, tacrolimus, sirolimus, hexobarbital, and phenytoin: elevation of serum levels of these drugs may be observed when co-administered with telithromycin. As a result, increases or prolongation of the therapeutic and/or adverse effects of the concomitant drug may be observed.
Ergot alkaloid derivatives (such as ergotamine or dihydroergotamine): acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has been reported when macrolide antibiotics were co-administered. *Without further data, the co-administration of KETEK and these drugs is not recommended.*

Laboratory test interactions

There are no reported laboratory test interactions.

Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals to determine the carcinogenic potential of KETEK have not been conducted.

Telithromycin showed no evidence of genotoxicity in four tests: gene mutation in bacterial cells, gene mutation in mammalian cells, chromosome aberration in human lymphocytes, and the micronucleus test in the mouse.

No evidence of impaired fertility in the rat was observed at doses estimated to be 0.61 times the human daily dose on a mg/m^2 basis. At doses of 1.8-3.6 times the human daily dose, at which signs of parental toxicity were observed, moderate reductions in fertility indices were noted in male and female animals treated with telithromycin.

Pregnancy

Teratogenic effects: Pregnancy Category C. Telithromycin was not teratogenic in the rat or rabbit. Reproduction studies have been performed in rats and rabbits, with effect on pre-post natal development studied in the rat. At doses estimated to be 1.8 times (900 mg/m^2) and 0.49 times (240 mg/m^2) the daily human dose of 800 mg (492 mg/m^2) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the 900 mg/m^2 and 240 mg/m^2 in rats and rabbits, respectively, maternal toxicity may have resulted in delayed fetal maturation. No adverse effects on prenatal and postnatal development of rat pups were observed at 1.5 times (750 mg/m^2/d) the daily human dose.

There are no adequate and well-controlled studies in pregnant women. Telithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

Telithromycin is excreted in breast milk of rats. Telithromycin may also be excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KETEK is administered to a nursing mother.

Pediatric use

The safety and effectiveness of KETEK in pediatric patients has not been established.

Geriatric use

In all Phase III clinical trials (n=4,780), KETEK was administered to 694 patients who were 65 years and older, *including 231 patients who were 75 years and older. Efficacy and safety in elderly patients ≥ 65 years were* generally similar to that observed in younger patients; however, greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is required based on age alone. (See **CLINICAL PHARMACOLOGY, Special populations, Geriatric** and ***DOSAGE AND ADMINISTRATION.***)

ADVERSE REACTIONS

In Phase III clinical trials, 4,780 patients (n=2702 in controlled trials) received daily oral doses of KETEK 800 mg once daily for 5 days or 7 to 10 days. Most adverse events were mild to moderate in severity. In the combined Phase III studies, discontinuation due to treatment-emergent adverse events occurred in 4.4% of KETEK-treated patients and 4.3% of combined comparator-treated patients. Most discontinuations in the KETEK group *were due to treatment-emergent adverse events in the gastrointestinal body system, primarily diarrhea (0.9% for* KETEK vs. 0.7% for comparators), nausea (0.7% for KETEK vs. 0.5% for comparators).

All and possibly related treatment-emergent adverse events (TEAEs) occurring in controlled clinical studies in ≥ 2.0% of all patients are included below:

Table 5

All and Possibly Related Treatment-Emergent Adverse Events Reported in Controlled Phase III Clinical Studies (Percent Incidence)

Adverse Event*	All TEAEs		Possibly-Related TEAEs	
	KETEK n= 2702	Comparator† n= 2139	KETEK n= 2702	Comparator† n= 2139
Diarrhea	10.8%	8.6%	10.0%	8.0%
Nausea	7.9%	4.6%	7.0%	4.1%
Headache	5.5%	5.8%	2.0%	2.5%
Dizziness (excl. vertigo)	3.7%	2.7%	2.8%	1.5%
Vomiting	2.9%	2.2%	2.4%	1.4%
Loose Stools	2.3%	1.5%	2.1%	1.4%
Dysgeusia	1.6%	3.6%	1.5%	3.6%

*Based on a frequency of all and possibly related treatment-emergent adverse events of ≥ 2% in KETEK or comparator groups.
† Includes comparators from all controlled Phase III studies.

The following events judged by investigators to be at least possibly drug related were observed infrequently (≥ 0.2% and < 2%), in KETEK-treated patients in the controlled Phase III studies.

Gastrointestinal system: abdominal distension, dyspepsia, gastrointestinal upset, flatulence, constipation, gastroenteritis, gastritis, anorexia, oral candidiasis, glossitis, stomatitis, watery stools.

Liver and biliary system: abnormal liver function tests: increased transaminases, increased liver enzymes (*e.g.*, ALT, AST) *were usually asymptomatic and reversible. ALT elevations above 3 times the upper limit of* normal were observed in 1.6%, and 1.7% of patients treated with KETEK and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with KETEK, and was reversible. (See **PRECAUTIONS, General.**)

Nervous system: dry mouth, somnolence, insomnia, vertigo, increased sweating

Body as a whole: abdominal pain, upper abdominal pain, fatigue

Special senses: Visual adverse events most often included blurred vision, diplopia, or difficulty focusing. Most events were mild to moderate; however, severe cases have been reported. Some patients discontinued therapy due to these adverse events. Visual adverse events were reported as having occurred after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Visual events *lasted several hours and recurred upon subsequent dosing in some patients. For patients who continued* treatment, some resolved on therapy while others continued to have symptoms until they completed the full course of treatment. (See **WARNINGS** and **PRECAUTIONS, Information for patients.**)

Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events. (See **CLINICAL STUDIES.**)

Urogenital system: vaginal candidiasis, vaginitis, vaginosis fungal

Skin: rash

Hematologic: increased platelet count

Other possibly related clinically-relevant events occurring in <0.2% of patients treated with KETEK from the controlled Phase III studies included: anxiety, bradycardia, eczema, elevated blood bilirubin, erythema multiforme, flushing, hypotension, increased blood alkaline phosphatase, increased eosinophil count, paresthesia, pruritus, urticaria.

Post-Marketing Adverse Event Reports:

In addition to adverse events reported from clinical trials, the following events have been reported from worldwide post-marketing experience with KETEK.
Allergic: face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.
Cardiovascular: atrial arrhythmias, palpitations
Gastrointestinal system: pancreatitis
Liver and biliary system: Hepatic dysfunction has been reported.
Severe and in some cases fatal hepatotoxicity, including fulminant hepatitis, hepatic necrosis and hepatic failure have been reported in patients treated with KETEK. These hepatic reactions were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of only a few doses of KETEK. (See **CONTRAINDICATIONS** and **WARNINGS.**) Severe reactions, in some but not all cases, have been associated with serious underlying diseases or concomitant medications.
Data from post-marketing reports and clinical trials show that most cases of hepatic dysfunction were mild to moderate. (See **PRECAUTIONS, General.**)

Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See **CONTRAINDICATIONS.**)
Nervous system: loss of consciousness, in some cases associated with vagal syndrome.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by gastric lavage. The patient should be carefully monitored (e.g., ECG, electrolytes) and given symptomatic and supportive treatment. Adequate hydration should be maintained. The effectiveness of hemodialysis in an overdose situation with KETEK is unknown.

DOSAGE AND ADMINISTRATION

The dose of KETEK tablets is 800 mg (2 tablets of 400 mg) taken orally once every 24 hours, for 7–10 days. KETEK tablets can be administered with or without food.

KETEK may be administered without dosage adjustment in the presence of hepatic impairment.

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), including patients who need dialysis, the dose should be reduced to KETEK 600 mg once daily. In patients undergoing hemodialysis, KETEK should be given after the dialysis session on dialysis days. (See **CLINICAL PHARMACOLOGY, Renal insufficiency.**)

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, the dose should be reduced to KETEK 400 mg once daily. (See **CLINICAL PHARMACOLOGY, Multiple insufficiency.**)

HOW SUPPLIED

KETEK® 400 mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "H3647" on one side and "400" on the other side. These are packaged in bottles and blister cards (Ketek Pak™ and unit dose) as follows:

Bottles of 60	(NDC 0088-2225-41)
Ketek Pak™, 10-tablet cards (2 tablets per blister cavity)	(NDC 0088-2225-07)
Unit dose package of 100 (blister pack)	(NDC 0088-2225-49)

KETEK® 300 mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "38AV" on one side and blank on the other side. These are packaged in bottles as follows:

Bottles of 20	(NDC 0088-2223-20)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

CLINICAL STUDIES

Community-acquired pneumonia (CAP)

KETEK was studied in four randomized, double-blind, controlled studies and four open-label studies for the treatment of community-acquired pneumonia. Patients with mild to moderate CAP who were considered appropriate for oral outpatient treatment were enrolled in these trials. Patients with severe pneumonia were excluded based on any one of the following: ICU admission, need for parenteral antibiotics, respiratory rate > 30/minute, hypotension, altered mental status, < 90% oxygen saturation by pulse oximetry, or white blood cell count < 4000/mm^3. Total number of clinically evaluable patients in the telithromycin group included 2016 patients.

Table 6. CAP: Clinical cure rate at post-therapy follow-up (17-24 days)

	Patients (n)		Clinical cure rate	
Controlled Studies	*KETEK*	*Comparator*	*KETEK*	*Comparator*
KETEK vs. clarithromycin 500 mg BID for 10 days	162	156	88.3%	88.5%
KETEK vs. trovafloxacin* 200 mg QD for 7 to 10 days	80	86	90.0%	94.2%
KETEK vs. amoxicillin 1000 mg TID for 10 days	149	152	94.6%	90.1%
KETEK for 7 days vs. clarithromycin 500 mg BID for 10 days	161	146	88.8%	91.8%

*This study was stopped prematurely after trovafloxacin was restricted for use in hospitalized patients with severe infection.

Clinical cure rates by pathogen from the four CAP controlled clinical trials in microbiologically evaluable patients given KETEK for 7-10 days or a comparator are displayed in Table 7.

Table 7. CAP: Clinical cure rate by pathogen at post-therapy follow-up (17-24 days)

Pathogen	KETEK	Comparator
Streptococcus pneumoniae	73/78 (93.6%)	63/70 (90.0%)
Haemophilus influenzae	39/47 (83.0%)	42/44 (95.5%)
Moraxella catarrhalis	12/14 (85.7%)	7/9 (77.8%)
Chlamydophila (Chlamydia) pneumoniae	23/25 (92.0%)	18/19 (94.7%)
Mycoplasma pneumoniae	22/23 (95.7%)	20/22 (90.9%)

Clinical cure rates for patients with CAP due to *Streptococcus pneumoniae* were determined from patients in controlled and uncontrolled trials. Of 333 evaluable patients with CAP due to *Streptococcus pneumoniae*, 312 (93.7%) achieved clinical success. Only patients considered appropriate for oral outpatient therapy were included in these trials. More severely ill patients were not enrolled. Blood cultures were obtained in all patients participating in the clinical trials of mild to moderate community-acquired pneumonia. In a limited number of outpatients with incidental pneumococcal bacteremia treated with KETEK, a clinical cure rate of 88% (67/76) has been observed. KETEK is not indicated for the treatment of severe community-acquired pneumonia or suspected pneumococcal bacteremia.

Clinical cure rates for patients with CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP*) were determined from patients in controlled and uncontrolled trials. Of 36 evaluable patients with CAP due to MDRSP, 33 (91.7%) achieved clinical success.

*MDRSP: Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Table 8. Clinical cure rate for 36 evaluable patients with MDRSP treated with KETEK in studies of community-acquired pneumonia

Screening Susceptibility	*Clinical Success in Evaluable MDRSP* Patients	
	n/N[a]	%
Penicillin-resistant	20/23	86.9
2nd generation cephalosporin-resistant	20/22	90.9
Macrolide-resistant	25/28	89.3
Trimethoprim/ sulfamethoxazole-resistant	24/27	88.9
Tetracycline-resistant[b]	11/13	84.6

[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

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.
DYNABAC® (dirithromycin) is a registered trademark of Eli Lilly and Company.
PROPULSID® (cisapride) is a registered trademark of Johnson & Johnson.
ORAP® (pimozide) is a registered trademark of Teva Pharmaceuticals USA, Inc.
LIPITOR® (atorvastatin) 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	使用上の注意記載状況・その他参考事項等
□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。	【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	今後の対応
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。	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。

7-0700028(ケトライド系300mg

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 (Ssee 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.

System organ class	Very common (≥ 1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)
Blood and the lymphatic system disorders			Eosinophilia		
Nervous system disorders		Dizziness, headache, disturbance of taste	Vertigo somnolence, nervousness, insomnia,	Transient loss of consciousness, paraesthesia	Parosmia
Eye disorders			Blurred vision	Diplopia	
Cardiovascular disorders			Flush Palpitations	Atrial arrhythmia, hypotension, bradycardia	
Gastro-intestinal disorders	Diarrhoea	Nausea, vomiting, gastrointestinal pain, flatulence	Oral *Candida* infection, stomatitis anorexia, constipation, ,		Pseudomembranous colitis
Hepato-biliary disorders		Increase in liver enzymes (AST, ALT, alkaline phosphatase)	Hepatitis	Cholestatic jaundice	
Skin and subcutaneous tissue disorders			Rash, urticaria, pruritus	Eczema	Erythema multiforme
Musculoskeletal, connective tissue					Muscle cramps
Reproductive system disorders		Vaginal *Candida* infection			

Visual disturbances (<1%) associated with the use of Ketek, including blurred vision, difficulty focusing and diplopia, were mostly mild to moderate. They typically occurred within a few hours after the first or second dose, recurred upon subsequent dosing, lasted several hours and were fully reversible either during therapy or following the end of treatment. These events have not been associated with signs of ocular abnormality (see sections 4.4 and 4.7).
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 ΔQTc >30 msec in 7.6% and 7.0% of cases, respectively. No patient in either group developed a ΔQTc >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.

During post-marketing experience the following reactions have been reported (frequency unknown):
-Immune system disorders: Angioneurotic oedema, anaphylactic reactions including anaphylactic shock
-Cardiac disorders: QT/QTc interval prolongation
-Gastrointestinal disorders: Pancreatitis,
-Hepato-biliary disorders: Severe hepatitis and liver failure (see section 4.4)
-Nervous system disorders: Cases of rapid onset of exacerbation of myasthenia gravis have been reported (see sections 4.43 and 4.4).

4.9 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: macrolides, lincosamides and streptogramins, ATC Code: J01FA15.

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_B 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 ≤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. -As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
This information provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to telithromycin.

Commonly susceptible species

Aerobic Gram-positive bacteria

Staphylococcus aureus methicillin susceptible (MSSA)*

Lancefield group C and G (ß haemolytic) streptococci
Streptococcus agalactiae
Streptococcus pneumoniae *
Viridans group streptococci

Aerobic Gram- negative bacteria *Legionella pneumophila* *Moraxella catarrhalis**
Other *Chlamydophila pneumoniae** *Chlamydia psittaci* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem Aerobic Gram-positive bacteria *Staphylococcus aureus* methicillin resistant (MRSA)+ *Streptococcus pyogenes** Aerobic Gram- negative bacteria *Haemophilus influenzae*$*$ *Haemophilus parainfluenzae*$
Inherantly resistant organisms Aerobic Gram- negative bacteria *Acinetobacter* *Enterobacteriaceae* *Pseudomonas*

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
$ natural intermediate susceptibility
+Among MRSA the rate of MLSBc resistant strains is more than 80%, telithromycin is not active against MLS_Bc.

Resistance

Telithromycin does not induce MLS_B resistance in vitro to *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus 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_B 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 *Streptococcus pneumoniae*, there is no cross- or co-resistance between telithromycin and other antibacterial classes including erythromycin A and/or penicillin resistance-.

For *Streptococcus 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 Ketek 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±1.6 mg/l (range 0.02-7.6 mg/l) and 0.2±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±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 total tissue concentration in epithelial lining fluid, alveolar macrophages, bronchial mucosa, tonsils and sinus tissue were 14.9±11.4 mg/l, 318.1±231 mg/l, 3.88±1.87 mg/kg, 3.95±0.53 mg/kg and 6.96±1.58 mg/kg, respectively. The total tissue concentration 24 h after dose in epithelial lining fluid, alveolar macrophages, bronchial mucosa, tonsils and sinus tissue were 0.84±0.65 mg/l, 162±96 mg/l, 0.78±0.39 mg/kg, 0.72±0.29 mg/kg and 1.58±1.68 mg/kg, respectively. The mean maximum white blood cell concentration of telithromycin was 83±25 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 ±SD) is approximately 58±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
In a multiple-dose study, 36 subjects with varying degrees of renal impairment, a 1.4-fold increase in $C_{max,ss}$, and a 2-fold increase in AUC $(0\text{-}24)_{ss}$ at 800 mg multiple doses in the severe renally impaired group (CLCR < 30 mL/min) compared to healthy volunteers were observed and a reduced dosage of Ketek is recommended (See Section 4.2.). Based on observed data, a 600 mg daily dose is approximately equivalent with the target exposure observed in healthy subjects. Based on simulation data, an alternating daily dosing regimen of 800 mg and 400 mg in patients with severe renal impairment can approximate the AUC (0-48h) in healthy subjects receiving 800 mg once daily.

The effect of dialysis on the elimination of telithromycin has not been assessed.

-Hepatic impairment
In a single-dose study (800 mg) in 12 patients and a multiple-dose study (800 mg) in 13 patients with mild to severe hepatic insufficiency (Child Pugh Class A, B and C), the C_{max}, AUC and $t_{1/2}$ of telithromycin were similar compared to those obtained in age- and sex-matched healthy subjects. In both studies, higher renal elimination was observed in the hepatically impaired patients. Due to limited experience in patients with decreased metabolic capacity of the liver, Ketek should be used with caution in patients with hepatic impairment (see also section 4.4).

-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, and histological evidence of damage. These effects showed a tendency to regress after cessation of treatment. Plasma exposures based on free fraction of active substance, at the no observed adverse effect levels ranged from 1.6 to 13 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 in rats and dogs administered telithromycin at repeated doses of 150 mg/kg/day or more for 1 month and 20 mg/kg/day or more for 3-6 months. This administration corresponds to free active substance systemic exposure levels of at least 9 times the expected levels in human after 1 month and less than the expected level in humans after 6 months, respectively. There was evidence of reversibility upon cessation of treatment. The significance of these findings for humans is unknown.

In similarity to some macrolides, telithromycin caused a prolongation of Qtc interval- 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:

Microcrystalline cellulose
Povidone K25
Croscarmellose sodium
Magnesium stearate

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

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Two tablets are contained in each blister cavity.

Available as packs of 10, 14, 20 and 100 tablets.
Opaque PVC/Aluminium blisters

Available as pack of 5 x 2 tablets.
Opaque PVC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/191/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first ~~authorizaton~~ authorisation: 9 July 2001
Date of first renewal: 9 July 2006

10. DATE OF REVISION OF THE TEXT

PACKAGE LEAFLET

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ketek 400 mg film-coated tablets
Telithromycin

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

In this leaflet:

1. WHAT KETEK IS AND WHAT IT IS USED FOR

Ketek belongs to one of a group of medicines called ketolides, a new class of antibiotics related to macrolides. Antibiotics stop the growth of bacteria which cause infections.

Ketek is used in adults and adolescents of 12 years and older to treat infections due to bacteria against which the medicine is active. In adolescents of 12 years and older, Ketek can be used to treat: infections of the throat. In adults, Ketek can be used to treat infections of the throat, infections of the sinuses, chest infections in patients with long standing breathing difficulties and pneumonia.

2. BEFORE YOU TAKE KETEK

Do not take Ketek:

- if you suffer from myasthenia gravis, a rare disease which causes muscle weakness.
- if you are allergic (hypersensitive) to telithromycin, to any of the macrolide antibiotics or to any of the other ingredients of Ketek. If in doubt, talk to your doctor or pharmacist.
  if you have had a hepatitis and/or jaundice while taking Ketek in the past.
- if you are taking certain medicinal products to control the blood level of cholesterol or other lipids.
- if you or someone in your family are known to have an abnormality of electrocardiogram (ECG) called "long QT syndrome".
- while taking other medicines containing any of the following active substances:
  - ergotamine or dihydroergotamine (tablets or inhaler for migraine)
  - terfenadine or astemizole (allergic problems)
  - cisapride (digestive problems)
  - pimozide (psychiatric problems)

-if you have severely impaired renal function and/or severely impaired hepatic function, do not take Ketek while taking other medicines containing any of the following active substances:
  - ketoconazole (anti fungal treatment)
  - a medicine called protease inhibitor (HIV treatment)

Refer also to section "Taking other medicines".

Take special care with Ketek:
- if you have had certain heart problems such as coronary heart disease, ventricular arrhythmias, bradycardia or if you have had certain abnormal blood tests due to medical conditions such as hypokalaemia, hypomagnesaemia.
- if you develop severe or prolonged or bloody diarrhoea during or after taking Ketek tablets, consult your doctor immediately since it may be necessary to interrupt the treatment. This may be a sign of bowel inflammation (*pseudomembranous colitis*) which can occur following treatment with antibiotics.
- ~~if you suffer from myasthenia gravis, a rare disease which causes muscle weakness.~~
- ~~if you experience any worsening of your symptoms of myasthenia gravis during treatment with Ketek, you should interrupt treatment with Ketek and immediately seek medical attention.~~
- if you have liver disease.
- if you experience visual disturbances (blurred vision, difficulty in focusing, double vision)
- if you experience transient loss of consciousness (fainting).
- Ketek tablets are not recommended for use in children and adolescents less than 12 years old.

Refer also to sections "Do not take Ketek"~~ and~~, "Taking other medicines" and "Driving and using machines".

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medecines, including medicines obtained without a prescription, as some of them could have an interaction with Ketek.

You should not use Ketek with medicines containing ergotamine or dihydroergotamine tablets or ergotamine inhalers for migraine, terfenadine or astemizole for allergic problems, cisapride for digestive problems and pimozide for psychiatric problems. You should not use Ketek if you are taking certain medicinal products to control the blood level of cholesterol or other lipids, like simvastatin. Refer also to section "Do not take Ketek".

It is particularly important for your doctor to know if you are taking medicines containing phenytoin, and carbamazepine (for epilepsy), rifampicin (antibiotic), phenobarbital or St John's wort, medicines like tacrolimus, cyclosporin and sirolimus (for organ transplantation), or metoprolol (against heart disorder) or the anti HIV medicine ritonavir.

Taking Ketek with food and drink
Ketek may be taken with or without food.

Pregnancy and Breast-feeding
If you are pregnant do not take Ketek tablets as the safety of Ketek in pregnancy is insufficiently established. If you are breast-feeding do not take Ketek tablets.

Driving and using machines
Limit driving or other hazardous activities while taking Ketek. If you have vision problems or faint while taking Ketek, do not drive, operate heavy machinery, or engage in dangerous activities.
Taking Ketek tablets may cause side effects such as visual disturbances, which may reduce the capacity to carry out certain tasks. Rare cases of transient loss of consciousness (fainting), which may be preceded by vagal symptoms (malaise, gastrointestinal distress), have been reported. These symptoms may appear as early as after the first dose of Ketek. ~~You should be aware of the potential effect of these symptoms on your ability to drive or operate machinery~~

3. HOW TO TAKE KETEK

Your doctor will tell you how many Ketek tablets to take, at what time and for how long.

The usual duration of treatment is 5 days for infections of the throat, infections of the sinuses, chest infections in patients with long standing breathing difficulties and 7 to 10 days for pneumonia.

The recommended dose of Ketek for adults and children of 12 years and older is two tablets of 400 mg once daily (800 mg once daily).
If you have severe renal insufficiency you should take alternating daily doses of 800 mg (two tablets of 400 mg) and 400 mg (one tablet of 400 mg), starting with the 800 mg dose.

Swallow the tablets whole with a glass of water.
It is best to take tablets at the same time each day. If possible take the tablets before going to bed, to reduce the potential impact of visual disturbances and loss of consciousness.

If you take more Ketek than you should
If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or pharmacist. If possible, take your tablets or the box with you to show the doctor or pharmacist.

If you forget to take Ketek
If you forget to take a dose, take it as soon as possible. However, if it is nearly time for your next dose *skip the missed dose and take the next tablet at the usual time.*

If you stop taking Ketek
Take the complete course of tablets prescribed by your doctor, even if you begin to feel better before you have finished them all. If you stop taking the tablets too soon, the infection may return, or your condition may get worse.
If you stop taking the tablets too soon you may also create a bacterial resistance to the medicine.
If you feel you are suffering from a side effect, tell a doctor immediately to get advice before taking the next dose.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines Ketek can cause side effects, although not everybody gets them. Most of them are mild and transient, but very rare cases of serious adverse liver reactions and liver failure, including fatal cases, have been reported. So, if any of the following happens, stop taking Ketek and tell your doctor immediately:

- Allergic or skin reactions such as face swelling, general allergic reactions including allergic shock, or serious skin conditions associated with red spots, blisters.
- Severe, persistent or bloody diarrhoea associated with abdominal pain or fever, which can be a sign of serious bowel inflammation which may occur very rarely following treatment with antibiotics.
- Signs and symptoms of hepatitis (liver disease) such as yellowing of skin and eyes, dark urine, itching, loss of appetite or abdominal pain.
- Worsening of a condition called myasthenia gravis, a rare disease which causes muscle weakness. ~~Reports have included death and life threatening breathing trouble that happens fast in myasthenia gravis patients~~.

The above serious side effects are uncommon (1 out of 1000 to less than 1 out of 100), rare (1 out of 10,000 to less than 1 out of 1000 patients) or very rare (less than 1/10,000 patients including isolated report), but may require urgent medical attention.

The other side effects listed below are given with an estimation of the frequency with which they may occur.

The most common side effect (10 or more out of 100 patients) which may occur with Ketek is diarrhoea, usually mild and temporary.

Other side effects which may commonly (1 to 10 out of 100 patients) occur with Ketek are:
Nausea, vomiting, abdominal pain, flatulence (excess wind), dizziness, headaches, disturbance of taste, vaginal *Candida* infection (fungal infection associated with local itching, burning and white discharge), increase in liver enzymes (detected by blood test).

Uncommon or rare side effects (1 out of 10,000 to less than 1 out of 100 patients) which may occur with Ketek are:
Constipation, anorexia (loss of appetite), stomatitis (inflammation in themouth), oral *Candida* infection (fungal infection), hepatitis, rash, urticaria (hives), pruritus (itching), eczema, somnolence, insomnia, nervousness, vertigo, paraesthesia (tingling of the hands or feet), , visual disturbances (blurred vision, difficulty in focusing, double vision), , flushes, transient loss of consciousness (fainting), arrhythmia, bradycardia or palpitations (changes in heart rate or in ECG), hypotension (low blood pressure), eosinophilia (increase of certain white blood cells, detected by blood test).
Very rare side effects(less than 1 out of 10,000 patients) which may occur with Ketek are :
Disturbance of smell, muscle cramps.

Additional side effects which may occur with Ketek are:
abnormality of electrocardiogram (ECG) called prolongation of QT interval and inflamed pancreas (pancreatitis).
During post-marketing experience, liver failure has been reported (frequency unknown).

If any of these undesirable effects are troublesome, severe, or do not wear off as treatment goes on, tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KETEK

Keep out of the reach and sight of children.

Do not use Ketek after the expiry date which is stated on the pack.

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

6. FURTHER INFORMATION

What Ketek contains

- The active substance is telithromycin
- The other ingredients are microcrystalline cellulose, povidone K25, croscarmellose sodium, magnesium stearate in the tablet core as well as talc, macrogol 8000 , hypromellose 6 cp, titanium dioxide E171, yellow iron oxide E172, red iron oxide E172 in the film-coating.

What Ketek looks like and contents of the pack

Ketek 400 mg tablets are light orange, oblong, biconvex, film-coated tablet imprinted with "H3647" on one side and "400" on the other.

Ketek tablets are presented in blister packs. Two tablets are contained in each blister cavity.
They are available in packs of 10, 5x2, 14, 20 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder of Ketek is:
Aventis Pharma S.A.
20 Avenue Raymond Aron
F-92160 ANTONY
France

The manufacturer of Ketek is:
Aventis Pharma S.p.A.
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I-67019 Scoppito (L'Aquila), Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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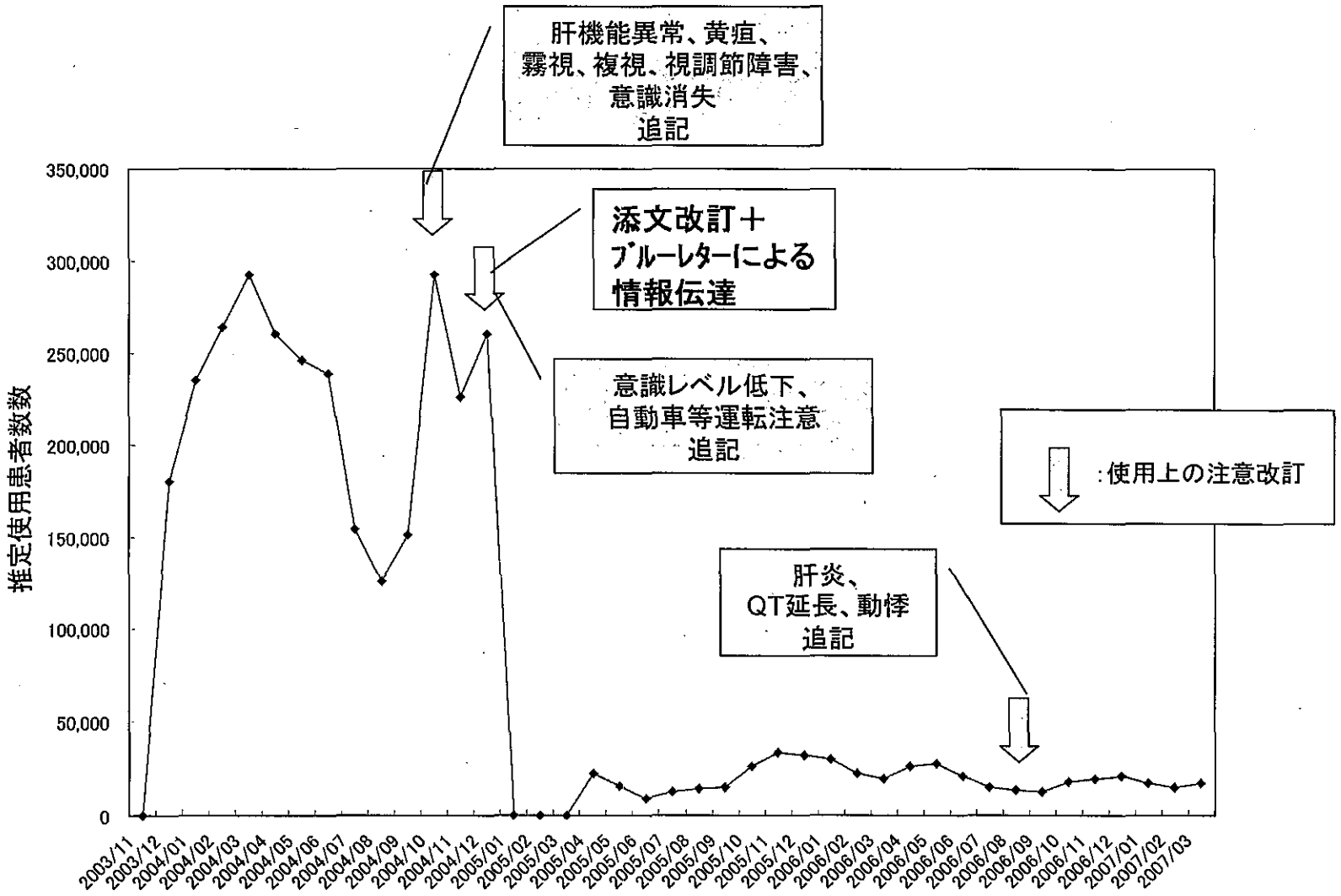

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