

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB 04-424)

In re Application of:)
)
Constantin Agouridas et al.)
)
U.S. Patent No.: 5,635,485)
)
Issued: June 3, 1997)
)
For: ERYTHROMYCIN COMPOUNDS)
)

2007 04 SEP -3 01:05

Examiner: Elli Peselev

Group Art Unit: 1623

RECEIVED

MAY 28 2004

REEXAM UNIT

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

In regard to the above-identified patent application:

1. We are transmitting herewith the attached:
 - a. Request for Patent Term Extension and Exhibits (1 Original and 4 Copies)
 - b. Postcard
2. With respect to additional fees:
 A. No additional fee is required.
 B. Attached is a check in the amount of \$1120.00
3. Please charge any additional fees or credit over-payments to the Deposit Account No.13-2490.
4. The undersigned hereby certifies that this Transmittal Letter and this paper, as described in paragraph 1 hereinabove, are being hand-delivered, in an envelope addressed to: Examiner Jim Engel, Crystal Plaza 3, Room 3D11, Washington, D.C. 20231 on the 27th day of May 2004.

Dated: May 27, 2004

By: _____
Kevin E. Noonan
Reg. No. 35,303

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 04-424)

U.S. Patent No.:	5,635,485)
Granted:	June 3, 1997)
Inventors:	Agouridas <i>et al.</i>)
Serial No.:	08/426,067)
Filed:	April 21, 1995)
For:	Erythromycin Compounds)

RECEIVED
MAY 28 2004
REEXAM UNIT

APPLICATION FOR PATENT TERM EXTENSION
PURSUANT TO 35 U.S.C. §156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22303-1450

Dear Sir:

Applicant, Aventis S.A., the owner of record of U.S. Patent No. 5,635,485 (“the - 485 patent”; *attached hereto* as Exhibit A) submits this Application for Patent Term Extension pursuant to the provisions of 35 U.S.C. §156. In making this application for patent term extension, Applicant relies upon the activity of its marketing agent, Aventis Pharmaceuticals, Inc., who has received regulatory approval of a new human antibiotic drug as disclosed below and claimed in the ‘485 patent.

I. Eligibility

Applicant is entitled to patent term extension for this patent on the grounds that the circumstances fulfill the requirements of 35 U.S.C. §156. Specifically:

- a) U.S. Patent 5,635,485 claims a product according to the provisions of §156(a);
- b) The term of this patent has not expired before submission of this application for patent term extension pursuant to §156(a)(1);
- c) The term of this patent has never been extended, pursuant to §156(a)(2);
- d) Applicant is the owner of record of the patent according to the assignment documents appended to this application, pursuant to §156(a)(3);
- e) The product has been subject to a regulatory review period before commercial marketing and use pursuant to §156(a)(4); and
- f) Permission for commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provisions of the law under which the regulatory review period was conducted pursuant to §156(a)(5).

Applicant, Aventis S.A., is the owner of all right, title and interest in U.S. Patent 5.635,485, as recorded by assignment in the U.S. Patent and Trademark Office at reel 7586 and frame 0264 (attached hereto as **Exhibit B**). The assignment was originally to Roussel Uclaf, which assignee changed its name to Hoechst Marion Roussel (recorded at reel 9168 and frame 0986), and then was conveyed to the current owner pursuant to merger, recorded at reel 11497 and frame 0001 (**Exhibit B**).

Aventis S.A.'s marketing agent, Aventis Pharmaceuticals, Inc., a wholly-owned subsidiary of Aventis S.A., received regulatory approval for the approved product on April 1, 2004. Aventis S.A. relies upon the activities of its marketing agent, Aventis Pharmaceuticals, Inc. according to their authorization letter (attached hereto as **Exhibit C**).

The term of U.S. Patent No. 5,635,485 has not expired prior to submission of this application.

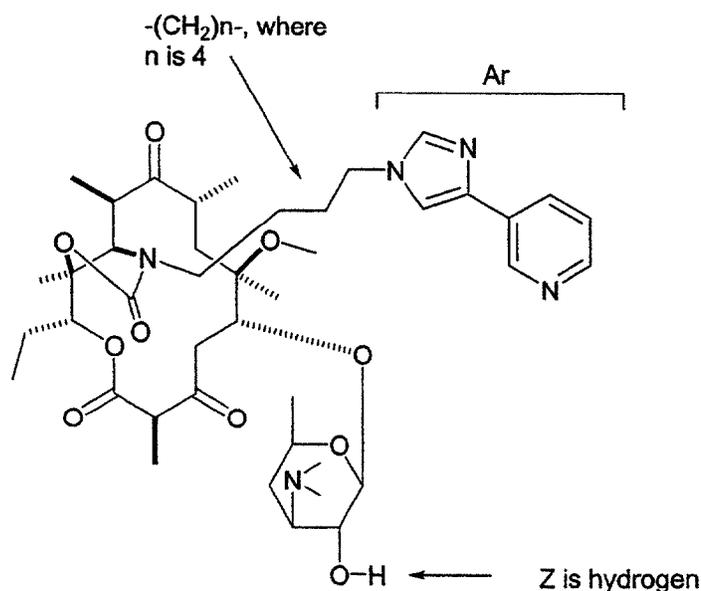
II. Requirements

Applicant provides the following information, pursuant to the requirements of 35 U.S.C. §156(d) and 37 C.F.R. 1.740 *et seq.*:

(a) An application for extension of patent term must be made in writing to the Commissioner. A formal application for the extension of patent term must include:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is Ketek™ (generic name: telithromycin), an antibiotic drug having the chemical name 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]]]-. This compound has the structural formula:



(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

The approved product was subject to regulatory review pursuant to 21 U.S.C. §355(a)

and Title 505(b)(1) of the Federal Food, Drug and Cosmetic Act, *codified at* 21 U.S.C. §355(b)(1).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

The product received permission for commercial marketing or use on April 1, 2004, pursuant to NDA 21-144 by the letter of that date from Mark Goldberger, M.D., M.P.H., Director, Office of Drug Evaluation IV, Center for Drug Evaluation and Research, Food and Drug Administration, Public Health Services, Department of Health and Human Services (attached hereto as **Exhibit D**).

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of the approved drug product is 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]]-, generic name telithromycin. This active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

The product has been approved for acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*, for patients 18 years old or older; acute bacterial sinusitis due to

Streptococcus pneumoniae, *Haemophilus influenzae*, *Staphylococcus aureus*, or *Moraxella catarrhalis*, for patients 18 year old or older; and community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae* (including multidrug resistant *Streptococcus pneumoniae* (MDRSP) strains), *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*, or *Mycoplasma pneumoniae*, for patients 18 year old or older.

The product has been approved pursuant to 21 U.S.C. §355(a) and Title 505(b)(1) of the Federal Food, Drug and Cosmetic Act, *codified at* 21 U.S.C. §355(b)(1).

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f) and an identification of the date of the last day on which the application could be submitted;

This application is submitted within 60 days of the date that the product first received permission for commercial marketing or use under the provisions of law under which the regulatory review period occurred, the last day for such submission being June 1, 2004.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

This application is made for U.S. Patent No. 5,635,485, issued June 3, 1997 to Constantin Agouridas, Jean-Francois Chantot, Alexis Denis, Solange Gouin D'Ambrieres and Odile Le Matret, and will expire on April 21, 2015.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A copy of this patent is attached hereto as **Exhibit A**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

A copy of a receipt for payment of the first maintenance fee, paid July 24, 2000, is attached hereto as **Exhibit E**.

A copy of a Certificate of Correction, filed May 26, 2004, is attached hereto as **Exhibit F**. The correction was of typographical errors.

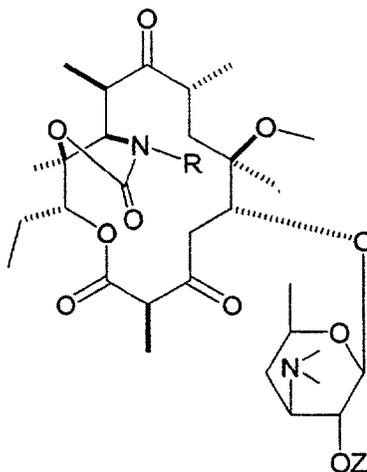
(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

This patent claims the approved product and methods for using the approved product.

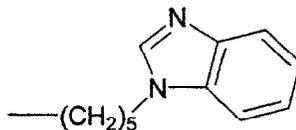
Specifically, the approved product and methods for using the approved product are claimed in the following claims of U.S. Patent No. 5,635,485:

.....

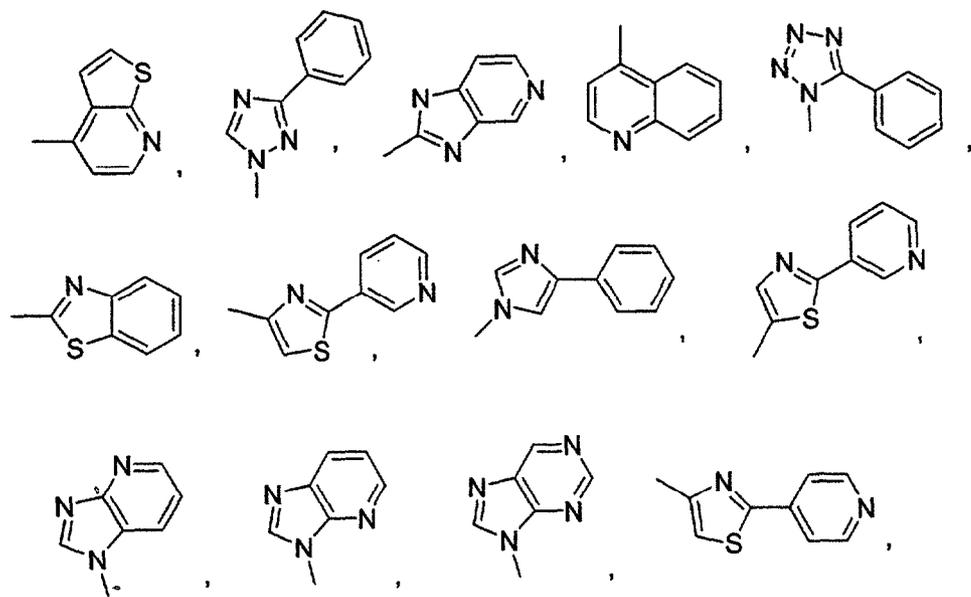
Claim 1. A compound of the formula

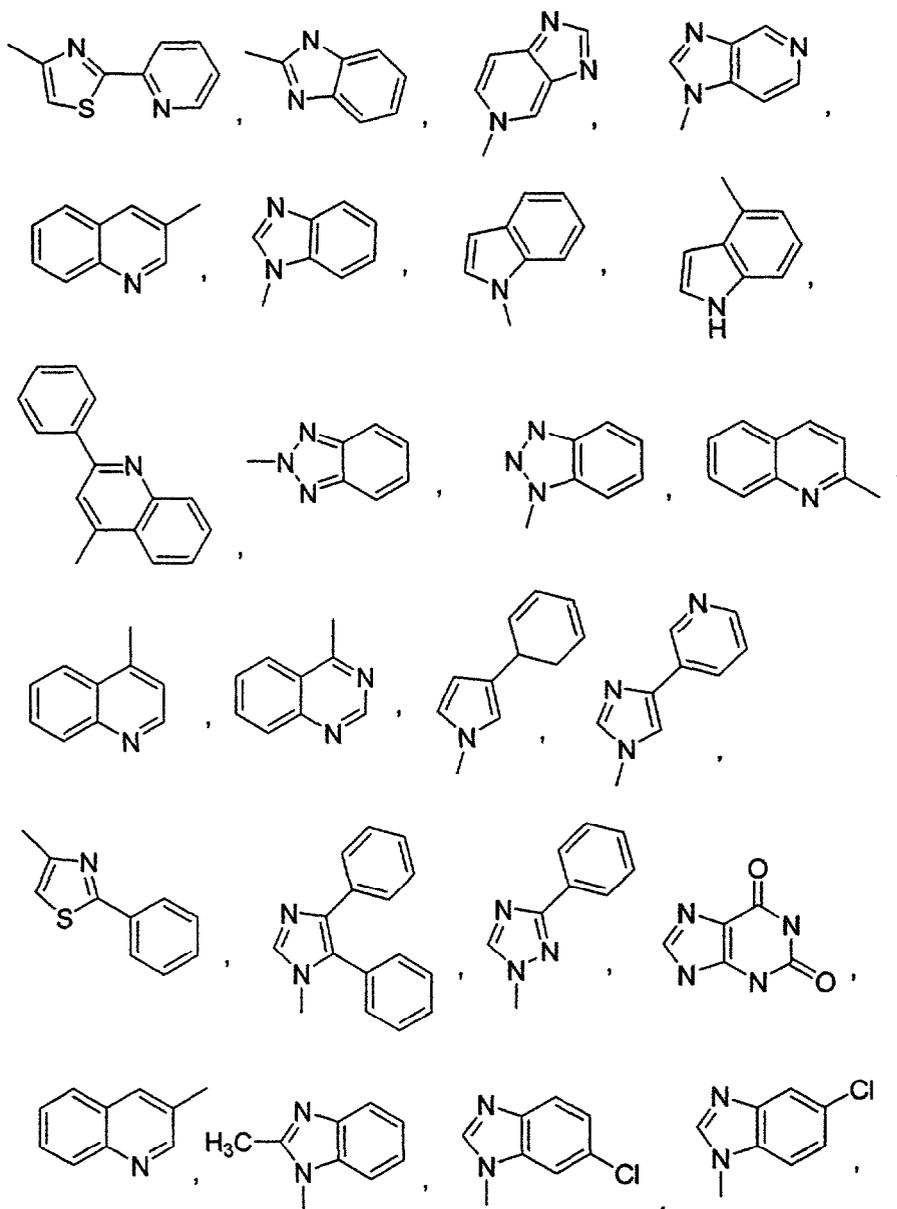


wherein R is

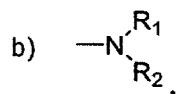


or $-(CH_2)_n$ --Ar, n is an integer from 3 to 5, Ar is an optionally substituted heterocyclic selected from the group consisting of

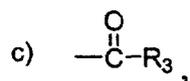




the optional substituents are at least one member selected from the group consisting of a free, salted, esterified and amidified carboxyl, hydroxyl, halogen, --NO₂, --CN, alkyl, cycloalkyl, alkenyl, alkynyl, O-alkyl, O-alkenyl, O-alkynyl, S-alkyl, S-alkenyl, S-alkynyl, N-alkyl, N-alkenyl and N-alkynyl of up to 12 carbon atoms optionally substituted by one or more halogens,

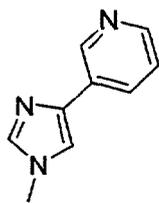


R₁ and R₂ are individually hydrogen or alkyl of up to 12 carbon atoms,



R₃ is alkyl of up to 12 carbon atoms, and d) an optionally substituted carbocyclic O-aryl and S-aryl and heterocyclic aryl, O-aryl and S-aryl and Z is hydrogen or an acid remainder or its non-toxic, pharmaceutically acceptable acid addition salts.

Claim 1 reads on the approved product when Z is H, and R is $\text{—}(\text{CH}_2)_n\text{—Ar}$, where n is 4



and Ar is

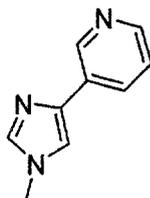
Claim 2. A compound of claim 1 wherein Z is hydrogen.

Claim 2 reads on the approved product because it requires Z to be hydrogen.

Claim 3. A compound of claim 1 wherein Z is 4.

A Certificate of Correction (**Exhibit F**) has been filed to correct this claim to read that “n is 4” rather than “Z is 4,” and this claim reads on the approved product because n is 4 in the approved product.

Claim 7. A compound of claim 1 wherein Ar is



optionally substituted.

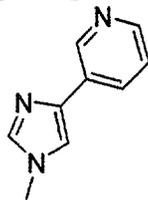
Claim 7 reads on the approved product because it recites the approved product when n is 4 and Z is H.

Claim 9. A compound of claim 1 which is 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino)]-erythromycin.

Claim 9 recites the approved product, and thus reads on it.

Claim 10. An antibacterial composition comprising an antibiologically effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

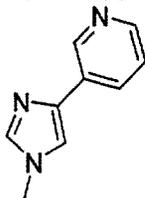
Claim 10 reads on a composition comprising the approved product when Z is H, and R



is $-(\text{CH}_2)_n\text{-Ar}$, where n is 4 and Ar is

Claim 11. A method of treating bacterial infections in warm-blooded animals comprising administering to warm-blooded animals having a bacterial infection an antibiologically effective amount of a compound of claim 1.

Claim 11 reads on a method for using the approved product when Z is H, and R is –



$(\text{CH}_2)_n\text{-Ar}$, where n is 4 and Ar is

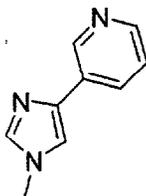
Claim 12. A method of claim 11 wherein Z is hydrogen.

Claim 12 reads on a method for using the approved product because it requires Z to be hydrogen.

Claim 13. A method of claim 11 wherein n is 4.

Claim 13 reads on a method for using the approved product because it n is 4 in the approved product.

Claim 17. A method of claim 11 wherein Ar is



optionally substituted.

Claim 17 covers reads on a method for using the approved product because it recites the approved product when n is 4 and Z is H.

Claim 19. A method of claim 11 wherein the compound is 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino)]-erythromycin.

Claim 19 recites a method of using the approved product and thus reads on it.

Thus,

Claim 1 reads on the approved product.

Claim 2 reads on the approved product.

Claim 3 reads on the approved product (when corrected by Certificate of Correction).

Claim 7 reads on the approved product.

Claim 9 reads on the approved product.

Claim 10 reads on the approved product.

Claim 11 reads on a method for using the approved product.

Claim 12 reads on a method for using the approved product.

Claim 13 reads on a method for using the approved product.

Claim 17 reads on a method for using the approved product.

Claim 19 reads on a method for using the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

The following dates are relevant for a determination of the length of the Patent Term Extension available to applicant:

An Investigational New Drug (IND) application, No. 55,283 was filed February 18, 1998 (copy of FDA letter acknowledgment attached hereto as **Exhibit G**).

A New Drug Application (NDA), No. 21-144 was filed February 28, 2000 (copy of FDA letter acknowledgment attached hereto as **Exhibit H**).

An Approval letter for NDA No. 21-144 was signed April 1, 2004 (copy of FDA letter attached hereto as **Exhibit D**).

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

Applicant submits its log of activities before the FDA as **Exhibit I**. The following provides a brief description of significant activities undertaken by the marketing applicant during the regulatory review period with respect to the approved product, with significant dates:

- The original IND submission (IND 55,283) for KETEK™ (telithromycin) was submitted on **February 19, 1998**.
- On **June 2 and July 7, 1998**, two End-of-Phase II (EoPII) meetings were held between Aventis (then HMR) and the FDA Division of Anti-Infective Drug Products (DAIDP). The meetings discussed plans for clinical development and chemistry, manufacturing and controls (CMC) of telithromycin.
- In 1999, Aventis met with the FDA DAIDP on five occasions to discuss planning and preparation of the NDA. A CMC Pre-NDA meeting occurred on **May 25, 1999**, and a clinical Pre-NDA meeting was held on **June 2, 1999**. On **July 6, 1999**, Aventis discussed the analysis and presentation of electrocardiograph QT interval prolongation data with both the DAIDP and the Division of Cardio-Renal Drug Products. Meetings to discuss the preparation of the electronic NDA and review aids occurred on **November 16 and December 20, 1999**.
- On **February 28, 2000**, Aventis submitted an application (NDA 21-144) for Ketek for the treatment of respiratory tract infections (RTIs) to the United States Food and Drug Administration (FDA). Telithromycin, the first of a new class of antibiotics known as the ketolides, was designed to deliver a targeted spectrum of activity for the treatment of upper and lower RTIs – including those caused by antibiotic-resistant *S. pneumoniae* isolates – with a convenient, once daily, short-course treatment option for most indications.

- On **June 29, 2000**, Aventis submitted a 4-Month Safety Update to the NDA, which included one additional clinical study report.
- On **February 28, 2001**, Aventis submitted the first major Amendment to the NDA. The Amendment included three additional controlled clinical studies examining the efficacy and safety of telithromycin.
- In **April 2001**, the FDA Anti-Infective Drugs Advisory Committee (AIDAC) reviewed data relating to NDA 21-144. The Committee's recommendations included collecting safety data from a larger sample of patients, particularly from older adults and subjects with co-morbid conditions. On **June 1, 2001**, the FDA deemed telithromycin approvable for the indications of community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute bacterial sinusitis (ABS), pending review of additional efficacy and safety data. In collaboration with the Division of Anti-Infective Drug Products (DAIDP), Aventis designed a large supplemental clinical program, including a 24,000-patient safety study (Study 3014) with a large proportion of older adults – comparing telithromycin to amoxicillin-clavulanic acid in a usual-care setting – that primarily focused on the identification and evaluation of cardiac, hepatic, visual, and vasculitic adverse events (AEs).
- Aventis filed a complete response to the first Approvable letter on **July 24, 2002** as major Amendment 2 to the NDA. This Amendment included the reports for four additional clinical efficacy studies and the report for Study 3014, the above mentioned comparative large safety study. On **January 8, 2003**, the AIDAC reviewed the additional efficacy and safety data. At that time, the Aventis pharmacovigilance database (Clintrace[®]) included data from more than 16,000 clinical trial subjects and postmarketing spontaneous reports following more than 1.5 million patient exposures. This data was submitted to FDA and presented at AIDAC. The AIDAC voted to approve telithromycin for the treatment of CAP, AECB, and ABS.

- Subsequent to the Advisory Committee meeting, Aventis received an Approvable letter (dated **January 24, 2003**), in which the Agency requested additional analyses and information relating to preapproval studies and postmarketing experience from other countries, prior to granting approval for marketing telithromycin in the United States.
- Amendment 3 to NDA 21-144, *Amendment to Pending Application: Complete Response to January 24, 2003, Approvable Letter*, was submitted on **October 17, 2003**. This submission focused on the presentation and analyses of safety data from postmarketing experience in other countries and additional analyses of safety data from clinical trials previously submitted to the NDA.
- Ketek NDA 21-144 was approved by the FDA on **April 1, 2004** following multiple interactions with the Agency regarding the content of final product labeling.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

Applicant submits that U.S. Patent No. 5,635,485 is entitled to patent term extension according to the provisions of 35 U.S.C. §156. Applicant believes that the length of the extension of the patent term is equal to 1,076 days, pursuant to the provisions of 35 U.S.C. §§156(c) and (g).

The length of the patent term extension requested in this application is 1,076 days, comprising half of the period from February 19, 1998 to February 28, 2000 (a total of $739/2 = 369.5$ days) plus the period from February 28, 2000 until April 1, 2004 (1,494 days), for a total of 1,864 days, as limited by the proviso of 35 U.S.C. §156(g)(6) that the total patent term extension is limited to be no longer than five (5) years (1,825 days), and further limited by the proviso of 35 U.S.C. §156(c)(3) that the total patent term is limited to be no longer than fourteen (14) years from the date of marketing approval, calculated as follows:

Length of regulatory review period under IND:

February 19, 1998 - February 18, 1999	= 365 days
February 19, 1999 - February 18, 2000	= 365 days
<u>February 19, 2000 - February 27, 2000</u>	<u>= 9 days</u>
Total	= 739 days

Length of regulatory review under NDA:

February 28, 2000 - February 27, 2001	= 365 days
February 28, 2001 - February 27, 2002	= 365 days
February 28, 2002 - February 27, 2003	= 365 days
February 28, 2003 - February 27, 2004	= 365 days
<u>February 28, 2004 - April 1, 2004</u>	<u>= 34 days</u>
Total	=1494 days

Length of time from current expiration date of U.S. Patent No. 5,635,485 and fourteen years from April 1, 2004:

April 21, 2015 - April 21, 2016	= 366 days
April 21, 2016 - April 21, 2017	= 365 days
<u>April 21, 2017 - April 1, 2018</u>	<u>= 345 days</u>
Total	=1076 days

Applicant is applying for a patent term extension to the fullest extent that the patent deserves under the circumstances of regulatory delay set forth herein. Applicant believes the length of the patent term extension determined above is the appropriate length pursuant to the statute. Despite Applicant's diligent efforts, if the total number of days to which U.S. Patent No. 5,635,485 is greater than the number of days (1,076) requested here, Applicant requests the U.S. Patent and Trademark Office recalculate the correct length of patent term extension and award a patent term extension to U.S. Patent No. 5,635,485 for the correct number of days.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought;

Applicant and its undersigned agent acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the patent term extension sought in this application.

(14) The prescribed fee for receiving and acting upon the application for extension pursuant to 37 C.F.R. § 120(j)

The prescribed fee of one thousand one hundred twenty dollars (\$1,120.00) as set forth in 37 C.F.R. § 1.20(j) accompanies this application. The U.S. Patent and

Trademark Office is authorized to charge Deposit Account 13-2490 for the full amount of any deficiency in this fee.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Inquiries and correspondence relating to this patent term extension application should be addressed to:

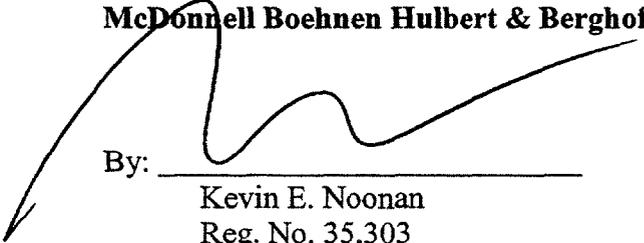
Kevin E. Noonan
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606
(312) 913-2145 (direct)
(312) 913-0002 (facsimile)
noonan@mbhb.com

An associate power of attorney from the attorneys of record during prosecution of U.S. Patent No. 5,635,485 to the undersigned and the attorneys of McDonnell Boehnen Hulbert & Berghoff is appended hereto as **Exhibit J**.

If the Examiner reviewing this application believes it to be helpful, he or she is invited to contact the undersigned attorney by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: May 26, 2004

By: 

Kevin E. Noonan
Reg. No. 35,303

LIST OF EXHIBITS

1. **Exhibit A:** U.S. Patent No. 5,635,485
2. **Exhibit B:** U.S. Patent and Trademark Office assignment record for U.S. Patent No. 5,635,485
3. **Exhibit C:** Authorization letter from the marketing agent, Aventis Pharmaceuticals, Inc., to the owner of all right, title and interest in U.S. Patent No. 5,635,485, Aventis S.A.
4. **Exhibit D:** Ketek™ FDA approval letter
5. **Exhibit E:** Copy of a receipt for payment of the first maintenance fee, paid July 24, 2000
6. **Exhibit F:** Copy of a Certificate of Correction, filed May 26, 2004
7. **Exhibit G:** FDA acknowledgement letter for filing an New Drug (IND) application, No. 55,283
8. **Exhibit H:** FDA acknowledgment letter for filing a New Drug Application (NDA), No. 21-144
9. **Exhibit I:** FDA Log
10. **Exhibit J:** Associate Power of Attorney from patent prosecution attorneys of record





US005635485A

United States Patent [19]

[11] **Patent Number:** **5,635,485**

Agouridas et al.

[45] **Date of Patent:** **Jun. 3, 1997**

[54] **ERYTHROMYCIN COMPOUNDS**

FOREIGN PATENT DOCUMENTS

[75] **Inventors:** **Constantin Agouridas; Jean-Francois Chantot, both of Nogent sur Maine; Alexis Denis, Paris; Solange G. D'Ambrieres, Paris; Odile L. Martret, Paris, all of France**

0487411 5/1992 European Pat. Off. .
0596802 5/1994 European Pat. Off. .
0606062 7/1994 European Pat. Off. .
0606024 7/1994 European Pat. Off. .
2692579 12/1993 France .

[73] **Assignee:** **Roussel Uclaf, France**

OTHER PUBLICATIONS

[21] **Appl. No.:** **426,067**

Copy of J. Org. Cgem. 1988 53, 2340-2345 No. 10, Baker et al.

[22] **Filed:** **Apr. 21, 1995**

[30] **Foreign Application Priority Data**

May 3, 1994 [FR] France 94 05368

Primary Examiner—Elli Peselev
Attorney, Agent, or Firm—Bierman, Muscerlian and Lucas LLP

[51] **Int. Cl.⁶** **A61K 31/70; C07H 17/08**

[52] **U.S. Cl.** **514/29; 536/7.2; 536/7.3; 536/7.4**

[58] **Field of Search** **536/7.2, 7.3, 7.4; 514/29**

[57] **ABSTRACT**

[56] **References Cited**

An erythromycin compound of Formula I or its non-toxic acid addition salt having antibiotic activity.

U.S. PATENT DOCUMENTS

5,403,923 4/1995 Kaulimura et al. 536/7.2
5,527,780 6/1996 Agouridas et al. 536/7.4

19 Claims, No Drawings

1
ERYTHROMYCIN COMPOUNDS

OBJECTS OF THE INVENTION

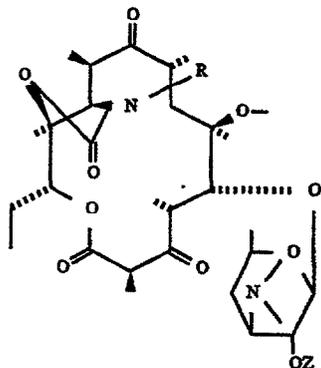
It is an object of the invention to provide the novel erythromycin compounds of formula I and their non-toxic, pharmaceutically acceptable acid addition salts and a process and intermediates for their preparation.

It is another object of the invention to provide novel antibiotic compositions and a method of treating bacterial infections in warm-blooded animals.

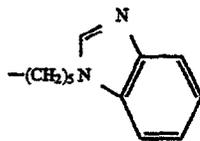
These and other objects and advantages of the invention will become obvious from the following detailed description.

THE INVENTION

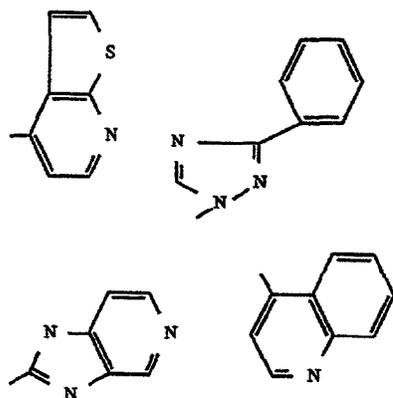
The novel compounds of the invention are compounds selected from the group consisting of a compound of the formula



wherein R is

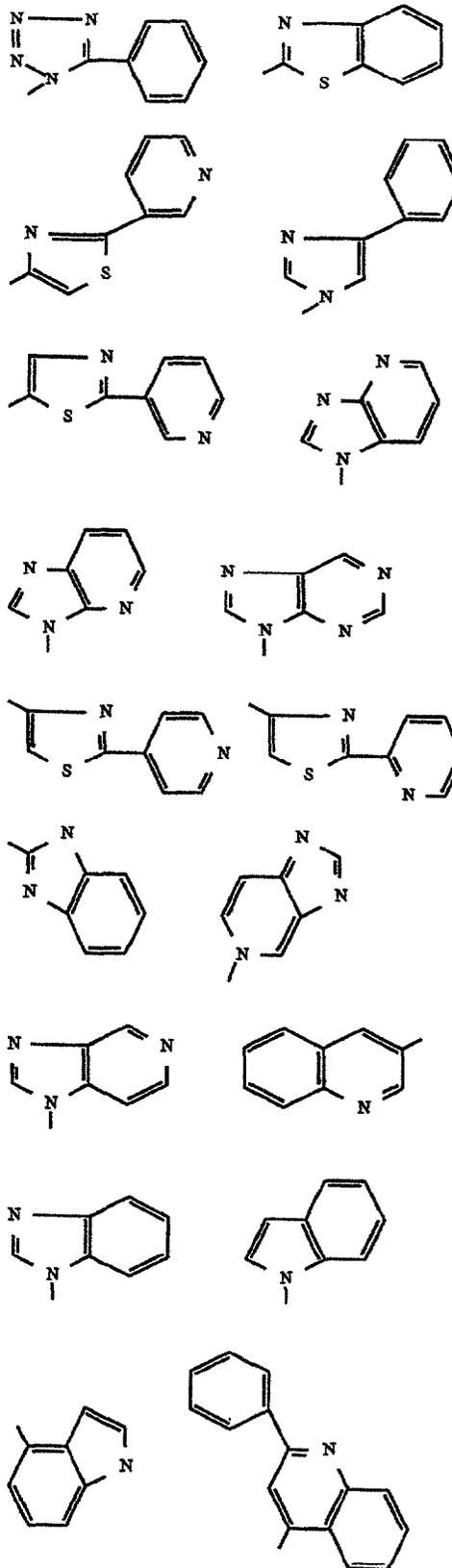


or $-(CH_2)_n-Ar$, n is an integer from 3 to 5, Ar is an optionally substituted heterocyclic selected from the group consisting of



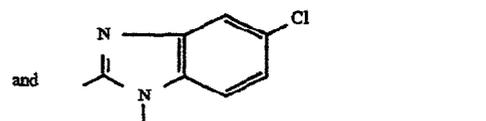
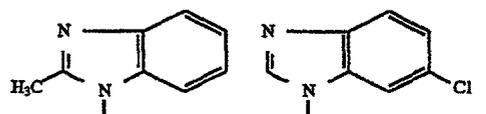
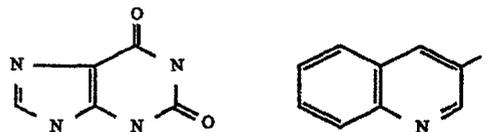
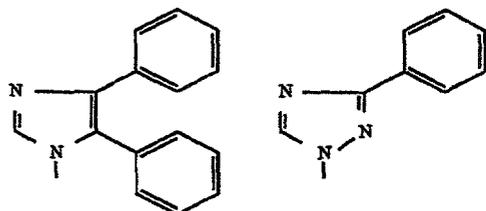
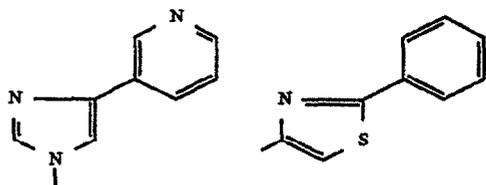
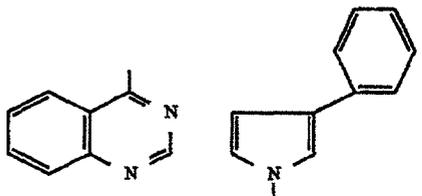
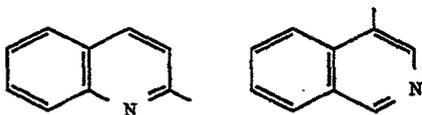
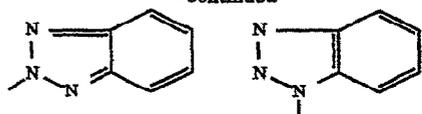
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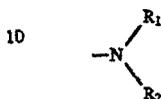


and Z is hydrogen or an acid remainder and their non-toxic, pharmaceutically acceptable acid addition salts.

Examples of suitable acids for the non-toxic, pharmaceutically acceptable acid addition salts are acetic acid, propionic acid, trifluoroacetic acid, maleic acid, tartaric acid, methane-sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric and especially stearic acid, ethylsuccinic acid and laurylsulfuric acid.

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The heterocyclics may be substituted with at least one member of the group consisting of free, salted, esterified and amidified carboxyl, hydroxyl, halogen, $-\text{NO}_2$, $-\text{CN}$, alkyl, cycloalkyl, alkenyl, alkynyl, O-alkyl, O-alkenyl, O-alkynyl, S-alkyl, S-alkenyl, S-alkynyl, N-alkyl, N-alkenyl and N-alkynyl of up to 12 carbon atoms optionally substituted by one or more halogens,



R_1 and R_2 are individually hydrogen or alkyl of up to 12 carbon atoms,

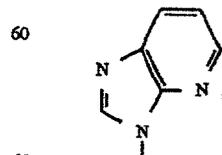
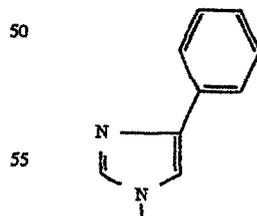


R_3 is alkyl of up to 12 carbon atoms, or an optionally substituted carbocyclic or heterocyclic aryl, O-aryl or S-aryl or heterocyclic aryl, O-aryl or S-aryl with one or more heteroatoms optionally substituted by one or more of the substituents mentioned above.

When the heterocyclic radical contains several rings linked together, or condensed, the substituent or substituents can be found on one and/or the other of the heterocyclic or carbocyclic rings. For example, if a heterocyclic nucleus is linked to or condensed with an aryl, the heterocyclic nucleus and the aryl nucleus can both carry one or more substituents.

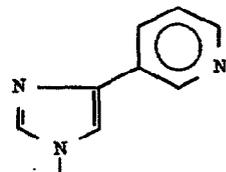
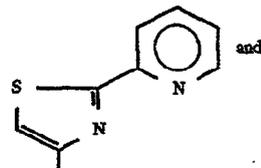
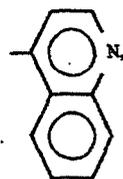
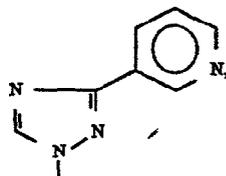
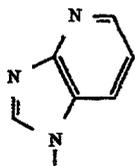
The aryl is preferably phenyl or naphthyl. Examples of alkyl, alkenyl or alkynyl are preferably methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertbutyl, decyl, dodecyl, vinyl, allyl, ethynyl, propynyl, propargyl, cyclobutyl, cyclopentyl or cyclohexyl. Halogen is preferably fluorine, chlorine or bromine and alkyl substituted by at least one halogen is preferably $-\text{CHCl}_2$, $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CCl}_3$ or $-\text{CH}_2\text{CH}_2\text{CF}_3$. The carboxylic acid remainder is preferably acetyl, propionyl, butyryl, isobutyryl, n-valeryl, isovaleryl, tert-valeryl and pivalyl.

Among the preferred compounds of formula I are those wherein Z is hydrogen, those wherein n is 4, those wherein Ar is the following optionally substituted



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Specific preferred compounds of formula I are

- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-phenyl-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3H-imidazo(4,5-b)pyridin-3-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1H-imidazo(4,5-b)pyridin-1-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-chlorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-fluorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,
- 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-

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(oxycarbonyl-((4-(7-methoxy-4-quinoleinyl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-(2-pyridinyl)-4-thiazolyl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butyl)-imino))-erythromycin, erythromycin and their non-toxic, pharmaceutically acceptable acid addition salts and most preferably

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin.

The antibiotic compositions of the invention are comprised of an antibiotically effective amount of a compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, granules, suppositories, ointments, creams, gels and injectable solutions or suspensions.

Examples of suitable pharmaceutical carriers or excipients are talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and preservatives.

These compositions can also be presented in the form of a powder intended to be dissolved extemporaneously in a suitable vehicle, for example apyrogenic sterile water.

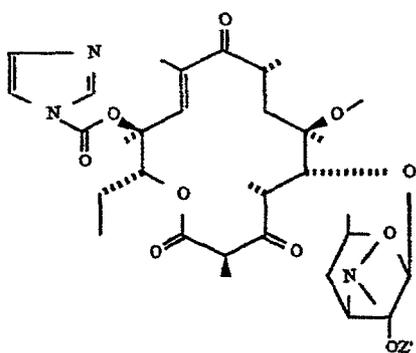
The compositions possess a very good antibiotic activity on gram bacteria such as staphylococci, streptococci, pneumococci. They are useful in the treatment of infections caused by sensitive germs and particularly that of staphylococci, such as staphylococcal septicemia, malignant staphylococci of the face or skin, pyodermitis, septic or suppurating sores, boils, anthrax, phlegmons, erysipelas and acne, staphylococci such as primary or post-influenzal acute anginas, bronchopneumonia, pulmonary suppurations, streptococcal infections such as acute anginas, otitis, sinusitis, scarlet fever, pneumococcal infections such as pneumonia, bronchitis; brucellosis, diphtheria, gonococcal infection.

The compositions of the invention are also active against infections caused by germs such as *Haemophilus influenzae*, Rickettsia, *Mycoplasma pneumoniae*, Chlamydia, Legionella, Ureaplasma, Toxoplasma or by germs of the Mycobacterium, Listeria, Meningococci and Campylobacter type. Particularly preferred are compositions using the compounds of Examples 1, 2, 3 and 29 to 35.

The novel method of the invention for treating bacterial infections in warm-blooded animals, including humans, comprises administering to warm-blooded animals an antibiotically effective amount of a compound of formula I or its non-toxic, pharmaceutically acceptable acid addition salts. The compounds may be administered buccally, rectally, parenterally or topically by application to the skin or mucous membrane. The usual daily dose is 0.6 to 4.0 mg/kg depending on the condition treated, the specific compound administered and the method of administration.

The novel process of the invention for the preparation of the compounds of formula I comprises reacting a compound of formula

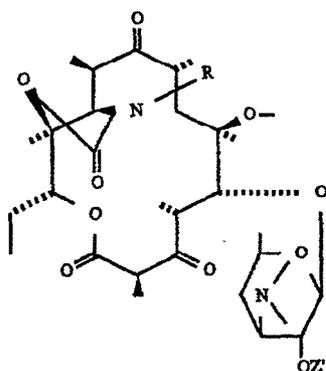
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wherein Z' is the remainder of an organic carboxylic acid with a compound of the formula



wherein R has the above definition to form a compound of the formula



wherein R and Z' have the above definition, optionally subjecting the latter to the action of an agent releasing the Z' hydroxyl function and optionally reacting the latter with an acid to form the acid addition salt thereof.

The reaction of the compounds of the formulae II and III is effected in a solvent such as acetonitrile, dimethylformamide, tetrahydrofuran, dimethoxyethane or dimethylsulfoxide. The hydrolysis of the Z'-ester group is preferably effected with methanol or aqueous hydrochloric acid and the salification is effected by known procedures.

The compounds of formula II are described in European patent application No. 0,596,802. The new compounds of formula III may be prepared by the process described in J. Med. Chem. (1982), Vol. 25, p. 947 and subsequent, Tetrahedron Letters, Vol. 32, No. 14, pp. 1699-1702, (1991); J. Org. Chem., Vol. 54, No. 18, p. 4298-4301 (1989); J. Org. Chem. Vol. 28 No. 101, pp. 2589-2591 (1963) or the German Patent No. 3,406,416; J. Org. Chem., Vol. 6, pp. 895-901 (1941) or Synth. Commun., Vol. 17, No. 14, pp. 1741-1748 (1987).

Preferred compounds of formula III are
 4-phenyl-1H-imidazole-1-butanamine,
 3H-imidazo(4,5-b)-pyridine-3-butanamine,
 1H-imidazo(4,5-b)-pyridine-3-butanamine,
 2-phenyl-4-quinolinebutanamine,
 1H-benzotriazole-1-butanamine,
 2H-benzotriazole-2-butanamine,
 1-methyl-1H-imidazo(4,5-c)-pyridine-2-butanamine,
 3-methyl-3H-imidazo(4,5-c)-pyridine-2-butanamine,
 5-chloro-1H-benzimidazole-1-butanamine,

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- II 7-methoxy-4-quinolinebutanamine,
 1H-imidazo(4,5-c)-pyridine-1-butanamine,
 9H-purine-9-butanamine,
 1-methyl-1H-indole-4-butanamine,
 5 3-phenyl-1H-1,2,4-triazole-1-butanamine-(hydrochloride),
 5-phenyl-1H-tetrazole-1-butanamine-(hydrochloride),
 2-benzothiazolebutanamine,
 4-(thieno(2,3-b)-pyridine-4-yl)-butanamine,
 5,6-dimethyl-1H-benzimidazole-1-butanamine,
 10 3-quinoleine-butanamine,
 2-quinoleine-butanamine,
 5H-imidazo-[4,5-c]-pyridine-5-butanamine,
 1-methyl-1H-benzimidazol-2-butanamine,
 6-chloro-1H-benzimidazol-2-butanamine,
 15 2-methyl-1H-benzimidazol-2-butanamine,
 4-(4-chlorophenyl)-1H-imidazol-1-butanamine,
 2-(3-pyridinyl)-thiazol-5-butanamine,
 7-methoxyquinoleine-4-butanamine,
 III 4-(4-fluorophenyl)-1H-imidazol-1-butanamine,
 20 4-(2-methoxyphenyl)-1H-imidazol-1-butanamine,
 3-(3-pyridinyl)-1H-1,2,4-triazol-1-butanamine,
 4-(3-pyridinyl)-1H-imidazol-1-butanamine,
 IA 2-(2-pyridinyl)-thiazol-4-butanamine,
 2-phenylthiazol-4-butanamine,
 25 4-(4-methoxyphenyl)-1H-imidazol-1-butanamine,
 isoquinoleine-4-butanamine,
 quinazoline-4-butanamine,
 4,5-diphenyl-1H-imidazol-1-butanamine,
 4-(3-methoxyphenyl)-1H-imidazol-1-butanamine,
 30 4-(4-(trifluoromethoxy)-phenyl)-1H-imidazol-1-butanamine,
 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purine-7-butanamine,
 2-(4-pyridinyl)-thiazol-4-butanamine,
 35 1H-indol-1-butanamine,
 2-(3-pyridinyl)-thiazol-4-butanamine and their non-toxic, pharmaceutically acceptable acid addition salts.
- In the following Examples, there are described several preferred embodiments to illustrate the invention. However, it is to be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLE 1

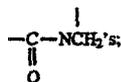
11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-[(4-(4-phenyl-1H-imidazol-1-yl)-butyl)-imino]]-erythromycin

A mixture of 0.705 g of 11-déoxy-10,11-didéhydro-3-de-(2,6-didéoxy-3-C-méthyl-3-O-méthyl- α -L-ribohexopyranosyl)-oxy)-12-O-((1H-imidazol-1-yl)-carbonyl)-6-O-méthyl-3-oxo-érythromycine-2'-acétate obtained as indicated in example 1C of European Patent application 0,596,802, 3 ml of acetonitrile with 10% water and 1.08 g of 4-(4-phenyl-1H-imidazol-1-yl)-butanamine was taken to 63° C. and the reaction mixture was maintained at this temperature for 5 hours and then left to return to ambient temperature. The reaction mixture was poured into a solution of sodium acid phosphate and extraction was carried out with ethyl acetate. The organic phases were washed with water, dried, filtered and concentrated to obtain 1.5 g of a product to which 210 ml of methanol were added. The mixture was stirred for 16 hours under a nitrogen atmosphere and at ambient temperature. After concentration, 1.4 g of product were obtained which was purified by chromatography on silica, eluant CH₂Cl₂-MeOH-NH₄OH (93-7-0.4) to obtain after concentration 0.305 g of the crude

desired product which was crystallized from isopropyl ether, followed by washing and drying at 50° C. under reduced pressure to obtain 0.267 g of the desired product melting at 222°C.-231° C. and having a specific rotation of $[\alpha]_D^{25} = +18^\circ$ (C.=0.9% in CHCl_3).

NMR CDCl_3 ppm

0.84 (t): $\text{CH}_2\text{-CH}_2$; 1.01 (d)-1.17 (d)-1.24 (d): the $\text{CH}_2\text{-CH}'$'s; 1.30 (d)-1.38 (d)-1.34 to 1.47: 6 and 12-Me; 2.27 (s): $\text{N}(\text{Me})_2$; 2.45 (-): H'_3 ; 2.61 (m): H_6 ; 2.63 (s): 6-OMe; 3.04 (-): H_4 ; 3.13 (q): H_{10} ; 3.18 (dd): H'_2 ; 3.53 (-): H'_5 ; 3.56 (s): H_{11} ; 3.67 (-)-3.75 (-): the



3.87 (q): H_2 ; 3.99 (t): CH_2NC ; 4.23 (d): H_5 ; 4.27 (d): H'_1 ; 4.94 (dd): H_{13} ; 7.26 (s): H'_5 ; 7.5 (s): H''_2 ; 7.20: H in para position; 7.35: H in meta position; 7.76: H in ortho position.

PREPARATION 1: 4-(4-phenyl-1H-imidazol-1-yl)-butanamine

Stage A: 2-(4-(4-phenyl-1H-imidazol-1-yl)-butyl)-1H-indole-1,3(2H)dione

A solution of 5.05 g of 4-phenyl-1H-imidazole in 25 ml of DMF was introduced dropwise over 90 minutes into a mixture of 7 ml of DMF dried on siliporite and 2.02 g of sodium hydride and then, 10.86 g of 2-(4-bromobutyl)-1H-indole-1,3(2H)dione-N-4-bromobutylphthalimide in solution in 25 ml of DMF were introduced. The solution was taken to 70° C. for about 90 minutes and was then allowed to return to ambient temperature. The solution was concentrated, taken up in water and extracted with ethyl acetate. The organic phases were washed with water, dried, filtered and concentrated to obtain 15 g of product which was crystallized from ethyl acetate. The product was separated off, washed with ethyl acetate and dried under reduced pressure at 50° C. to obtain 5.5 g of the desired product melting at 130°-132° C.

NMR CDCl_3 ppm

1.75 (m) (2H)-1.86 (m) (2H): central CH_2 's; 3.74 (t): 2H; 4.03: 2H; 7.22 (t): 2H H_4 ; 7.26 (m): 1H H'_3 ; 7.36 (t): 2H H_3 and H_5 ; 7.56 (d): H'_5 ; approx. 7.73 (m): 4H; approx. 7.86 (m): H_2 and H_6 .

Stage B: 4-(4-phenyl-1H-imidazol-1-yl)-butanamine

A mixture of 3.45 g of the product of Stage A, 100 ml of ethanol and 0.97 ml of hydrazine hydrate was refluxed for 8 hours and the reaction mixture was then concentrated. About 50 ml of 2N sodium hydroxide were added and extraction was carried out with ethyl acetate. The organic phases were washed with 2N sodium hydroxide, then with sodium chloride. After drying, filtering and concentrating, 2.21 g of the desired product were obtained.

NMR CDCl_3 ppm

1.47 (m)-1.87 (m): central CH_2 's; 2.73 (t)-3.97: $-\text{CH}_2\text{-NH}_2$; 7.20(d): H'_3 ; 7.50 (d): H'_5 ; 7.37 (wt) 2H: H_3 H_5 ; 7.24 (it) 1H: H_4 ; 7.77 (m) 2H: H_2 and H_6 .

EXAMPLE 2

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-[(4-(3H-imidazo(4,5-b)-pyridin-3-yl)-butyl)-iraino]-erythromycin

708.2 mg of 11-déoxy-10,11-didéhydro-3-de(2,6-didéoxy-3-C-méthyl-3-O-méthyl- α -L-ribohexopyranosyl)-

oxy)-12-O-((1H-imidazol-1-yl)-carbonyl)-6-O-méthyl-3-oxo-érythromycine-2'-acétate obtained as Example 1C of European Patent application 0,596,802, and 958 mg of 3H-imidazo(4,5-b)-pyridin-3-butanamine were dissolved in 2.82 ml of acetonitrile and 0.28 ml of water. The reaction mixture was heated to 80° C. and was then allowed to return to ambient temperature and was poured into a solution of sodium acid phosphate. Extraction was carried out with methylene chloride followed by washing with water. The aqueous phases were collected and extraction was carried out again. After drying, filtering and rinsing, 826 mg of product were obtained which was dissolved in 16.5 ml of methanol. The reaction solution was stirred at ambient temperature for 20 hours to obtain 789 g of crude desired product which was purified by chromatography, eluting with a mixture of methylene chloride, methanol and ammonium hydroxide (94-6-0.4) to obtain 327 mg of the desired product melting at 200° C. and having a specific rotation $[\alpha]_D^{25} = +13^\circ$ (C=1% in CHCl_3).

NMR CDCl_3 400 MHz ppm

0.85 (t): $\text{CH}_2\text{-CH}_2$; 1.01 (d)-1.16 (d)-1.25 (d)-1.30 (d)-1.26 (d): the $\text{CH}_2\text{-CH}'$'s; 1.35 and 1.47: 6 and 12 Me; approx. 1.63 and approx. 1.98: the central CH_2 's of the chain; 2.27 (s): $\text{N}(\text{CH}_3)_2$; 2.46 (m): H'_3 ; approx. 2.59 (m): H_6 ; 2.61 (s): 6-OMe; 3.07 (m): H_4 ; 3.12 (wq): H_{10} ; 3.18 (dd): H'_2 ; 3.54 (m): H'_5 ; 3.57 (s): H_{11} ; 3.6 to 3.8:



3.85 (q): H_2 ; 4.24 (d): H_5 ; 4.29 (d): H'_1 ; approx. 4.35 (m): $\text{CH}_2\text{NC}=\text{O}$; 4.93 (dd): H_{13} ; 7.21 (dd): H_6 aromatic; 8.04 (dd): H_7 aromatic; 8.11 (s): H_2 aromatic; 8.38 (dd): H_5 aromatic.

EXAMPLE 3

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-[(4-(1H-imidazo(4,5-b)-pyridin-1-yl)-butyl)-imino]-erythromycin

708.3 mg of 11-déoxy-10,11-didéhydro-3-de(2,6-didéoxy-3-C-méthyl-3-O-méthyl- α -L-ribohexopyranosyl)-oxy)-12-O-((1H-imidazol-1-yl)-carbonyl)-6-O-méthyl-3-oxo-érythromycine-2'-acétate obtained as in Example 1C of the European Patent application 0,596,802, were added to a solution of 953 mg of 1H-imidazo(4,5-b)-pyridine-3-butanamine, 2.82 ml of acetonitrile and 0.28 ml of water and the reaction mixture was taken to 55° C. and maintained at this temperature for 44 hours. 0.5 ml of acetonitrile were added and the mixture was maintained at 55° C. for a further 20 hours. It was allowed to return to ambient temperature and was poured into a saturated solution of sodium acid phosphate. The aqueous phase was extracted with methylene chloride and the chloromethylene phases were washed with water. Drying over sodium sulfate was carried out, followed by filtration and evaporation to obtain 806 mg of product to which 16.1 ml of methanol were added. The reaction mixture was maintained at ambient temperature for 24 hours and evaporated to dryness to obtain 656 mg of a product which was chromatographed on silica, eluting with a $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$ mixture (94-6-0.4). The crude desired product was obtained which was purified by chromatography on silica, eluting with a $\text{CHCl}_3\text{-MeOH-NH}_4\text{OH}$ mixture (94-6-0.4). The residue was dissolved in an ethyl acetate-isopropyl ether mixture, followed by filtra-

tion and evaporation to dryness to obtain the desired product melting at 203° C. and having a specific rotation of $[\alpha]_D^{25} = 17.6^\circ$ (C=1% in CHCl_3).

0.81 (t): $\text{CH}_3\text{—CH}_2$; 1.00 (d)—1.17 (d)—1.25 (d)—1.31 (d)—1.38 (d): the $\text{CH}_3\text{—CH}'\text{s}$; 1.35 (s)—1.47 (s): 6 and 12- CH_3 ; 1.68 (m) and 1.93 (m): the central CH_2 's of the chain; 2.27 (s): $\text{N}(\text{CH}_3)_2$; 2.61 (s): 6- OCH_3 ; 2.45 (m): H'_3 ; approx. 2.60 (m in masked part): H_8 ; 3.07 (m): H_4 ; approx. 3.15 (wq): H_{10} ; 3.18 (dd): H'_2 ; 3.56 (s): H_{11} ; 3.53 (m): H'_5 ; 3.60 to 3.80 (m): CO—N—CH_2 ; 3.87 (q): H_2 ; approx. 4.25 (m): $\text{CH}_2\text{—N—C=}$; 4.24 (d): H_5 ; 4.28 (d): H'_1 ; 4.91 (dd): H_{13} ; 7.21 (dd, J=5 and 8): H_6 ; 7.80 (dd, J=8 and 1.5): aromatic $\text{H}'\text{s}$; 8.56 (dd, J=5 and 1.5): H_5 ; 8.15 (s): $\text{H}_2 + \text{CH}_2\text{Cl}_2$.

PREPARATION 2: Preparation of the starting products of Examples 2 and 3

3H-imidazo(4,5-b)pyridine-3-butanamine and 1H-imidazo(4,5-b)pyridine-1-butanamine

Stage A:

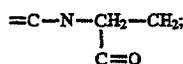
10.3 g of potassium carbonate were added to a solution of 5.95 g of 4-azabenzimidazole and 15.5 g of N-4-bromobutyl-phthalimide in 30 ml of dimethylformamide and the mixture was stirred for 20 hours at ambient temperature. The insoluble part was filtered off and rinsed with methylene chloride. The organic phase was washed with water, then dried over magnesium sulfate and evaporated. The oily residue obtained was washed with petroleum ether, then with isopropyl ether to obtain 16.3 g of a yellow solid which was purified by chromatography on silica, eluting with a methylene chloride—acetone mixture to obtain 4.9 g of product (A) melting at 143° C., and 3.9 g of product (B) melting at 172° C.

Stage B1: 3H-imidazo(4,5-b)-pyridine-3-butanamine (starting product of Example 2)

A mixture of 32.86 g of product (A) of the previous stage, 697 ml of ethanol and 20 ml of hydrazine was refluxed for 19 hours and then, the mixture was allowed to return to ambient temperature, filtered, rinsed and evaporated to dryness. The residue was taken up in methylene chloride, filtered, rinsed and evaporated to dryness to obtain 18.87 g of the desired product.

NMR CDCl_3 —250 MHz

1.52 (m)—2.00 (m): 2 central CH_2 's; 1.63 (wide s): 2 mobile $\text{H}'\text{s}$; 2.76 (t): $\text{CH}_2\text{—CH}_2\text{—NH}_2$; 4.33 (t):



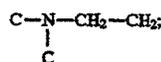
7.24 (dd, J=8 and 5): H_6 ; 8.08 (dd, J=8 and 1.5): H_7 ; 8.40 (dd, J=5 and 1.5): H_5 ; 8.08 (s): H_2 .

Stage B2: 1H-imidazo(4,5-b)-pyridine-1-butanamine (starting product of Example 3)

A mixture of 32 g of product (B) of Preparation 3, 640 ml of ethanol and 24.8 ml of hydrazine was refluxed for 21 hours and then, the mixture was allowed to return to ambient temperature. Filtration was carried out, followed by rinsing with ethanol and evaporating under reduced pressure. The residue was taken up in methylene chloride, followed by filtration, rinsing and evaporating to dryness to obtain 19.5 g of the desired product.

NMR CDCl_3

1.45 (m)—1.96 (m): 2 central CH_2 's; 2.74 (t): $\text{CH}_2\text{—NH}_2$; approx. 1.45 (m): mobile; 4.23 (t):



7.24 (dd, J=8 and 5): H_6 ; 7.75 (dd, J=8 and 1.5): H_7 ; 8.58 (dd, J=5 and 1.5): H_5 ; 8.13 (s): $\text{H}_2 + \text{EtOH}$.

Operating as previously, the following products were obtained:

EXAMPLE 4

11,12-dideoxy-3-de-[(2,6-dideoxy-3-O-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(thieno(2,3-b)-pyridin-4-yl)-butyl)-imino)]-erythromycin melting at 176°–178° C. and having a specific rotation of $[\alpha]_D^{25} = +17^\circ$ (C=0.9% in CHCl_3).

EXAMPLE 5

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(3-phenyl-1H-1,2,4-triazol-1-yl)-butyl)-imino)]-erythromycin melting at 208°–210° C. and having a specific rotation of $[\alpha]_D^{25} = +17^\circ$ (C=1% in CHCl_3).

EXAMPLE 6

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(1-methyl-1H-imidazo(4,5-c)pyridin-2-yl)-butyl)-imino)]-erythromycin and having a specific rotation of $[\alpha]_D^{25} = +19^\circ$ (C=1% in CHCl_3).

EXAMPLE 7

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(3-methyl-3H-imidazo(4,5-c)pyridin-2-yl)-butyl)-imino)]-erythromycin and having a specific rotation of $[\alpha]_D^{25} = +16^\circ$ (C=1% in CHCl_3).

EXAMPLE 8

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-methyl-((4-(7-methoxy-4-quinoliny)-butyl)-imino)]-erythromycin and having a specific rotation of $[\alpha]_D^{25} = +15.8^\circ$ (C=1% in CHCl_3).

EXAMPLE 9

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(5-phenyl-1H-tetrazol-1-yl)-butyl)-imino)]-erythromycin melting at 132°–134° C. and having a specific rotation of $[\alpha]_D^{25} = +25^\circ$ (C=1% in CHCl_3).

EXAMPLE 10

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(2-benzothiazolyl)-butyl)-imino)]-erythromycin melting at 179°–181° C. and having a specific rotation of $[\alpha]_D^{25} = +18^\circ$ (C=1% in CHCl_3).

EXAMPLE 11

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(2-(3-pyridinyl)-4-thiazolyl)-butyl)-imino)]-erythromycin melting at 150°–152° C. and having a specific rotation of $[\alpha]_D^{25} = +17^\circ$ (C=0.9% in CHCl_3).

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EXAMPLE 12

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-(3-pyridinyl)-5-thiazolyl)-butyl)-imino))-erythromycin melting at 155°-159° C. and having a specific rotation of $[\alpha]_D^{20}=+12^\circ$ (C=1% in CHCl_3).

EXAMPLE 13

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(9H-purin-9-yl)-butyl)-imino))-erythromycin.

EXAMPLE 14

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1H-imidazo(4,5-c)-pyridin-1-yl)-butyl)-imino))-erythromycin with a $R_f=0.42$ (CHCl_3 +8% of MeOH with 8% of NH_4OH).

EXAMPLE 15

11,12-dideoxy-3-de-((2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((5-(1H-benzimidazol-1-yl)-pentyl)-imino))-erythromycin. Prepared from 2-(4-bromophenyl)1H-iso-indole 1,3 (2H)-dione.

EXAMPLE 16

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((5-chloro-1H-benzimidazol-1-yl)-butyl)-imino))-erythromycin melting at 145°-148° C.

EXAMPLE 17

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-12,11-(oxycarbonyl-((4-(1H-indol-1-yl)-butyl)-imino))-erythromycin.

EXAMPLE 18

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-12,11-(oxycarbonyl-((4-(1-methyl-1H-indol-4-yl)-butyl)-imino))-erythromycin and having a specific rotation of $[\alpha]_D^{20}=20^\circ$, (c=1% in CHCl_3).

EXAMPLE 19

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-phenyl-4-quinolinyl)-butyl)-imino))-erythromycin melting at 195°-197° C.

EXAMPLE 20

11,12-dideoxy-3-de-((2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1H-benzotriazole-1-yl)-butyl)-imino))-erythromycin melting at 200°-202° C.

EXAMPLE 21

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2H-benzotriazol-2-yl)-butyl)-imino))-erythromycin melting at 164°-166° C.

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EXAMPLE 22

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(5,6-dimethyl-1H-benzimidazol-1-yl)-butyl)-imino))-erythromycin melting at 174°-176° C.

EXAMPLE 23

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-quinolinyl)-butyl)-imino))-erythromycin melting at 195°-197° C.

EXAMPLE 24

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-quinolinyl)-butyl)-imino))-erythromycin melting at 179°-181° C.

EXAMPLE 25

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-methyl-1H-benzimidazol-1-yl)-butyl)-imino))-erythromycin melting at 128°-132° C.

EXAMPLE 26

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(6-chloro-1H-benzimidazol-1-yl)-butyl)-imino))-erythromycin melting at 192°-194° C.

EXAMPLE 27

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1-methyl-1H-benzimidazol-2-yl)-butyl)-imino))-erythromycin

EXAMPLE 28

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(5H-imidazo(4,5-c)pyridin-5-yl)-imino))-erythromycin with a specific rotation of $[\alpha]_D^{20}=12.20^\circ$ (C=1% in CHCl_3).

EXAMPLE 29

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-chlorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin

1 g of 11-deoxy-10,11-didehydro-3-de-(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy)-12-O-((1H-imidazol-1-yl)-carbonyl)-6-O-methyl-3-oxo-erythromycin 2'-acetate prepared as in Example 1C of the European Patent Application EP 0,596,802 was heated for 7 hours at 75° C. in 4 ml of acetonitrile with 10% water with 1.4 g of 4-(4-(4-chlorophenyl)-1H-imidazol)-butanamine. The reaction medium was allowed to return to ambient temperature and was diluted with water. Extraction was carried out with ethyl acetate, followed by drying. The solvent was evaporated to obtain 2.3 g of product acetylated in position 2'. 60 ml of methanol were added and the mixture was stirred for 16 hours. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH_2Cl_2 -

MeOH-NH₄OH 95-5-0.4), followed by concentration. The residue was crystallized from ether and the crystallized product was dried under reduced pressure at 80° C. to obtain 381 mg of the expected product melting at 192°-194° C. NMR CDCl₃ ppm

0.83 (t): CH₃-CH₂; 1.00 (d)-1.16 (d)-1.24 (d)-1.30 (d)-1.38 (d): the CH₃-CH's; 1.33 (s)-1.47 (s): 6 and 12 Me; 2.26 (s): N(Me)₂; 2.44 (m): H'₃; 2.61 (s): 6-OMe; 2.60 (m): H₈; 3.00 to 3.21: H₄, H₁₀ and H'₂; 3.55 (m): H'₅; 3.56 (s): H₁₁; 3.60 to 3.80 2H-3.99 (t) 2H: CH₂NC=; 3.87 (q): H₂; 4.23 (d): H₅; 4.28 (d): H'₁; 4.93 (dd): H₁₃; 7.26 (d): H₅ imidazole; 7.50 (d): H₂ imidazole; 7.32-7.70: aromatics; 3.51: OH.

Preparation of 4-(4-chlorophenyl)-1H-imidazole-1-butanamine

Stage A: 4-(4-chlorophenyl)-1H-imidazole.

EXAMPLE 30

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino)]-erythromycin

706 mg of the starting compound of Example 29 (obtained as in Example 1C of the European Patent Application EP 0,596,802) in 3 ml of acetonitrile and 908 mg of 4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butanamine were heated at 80° C. for 8 hours and then the reaction medium was allowed to return to ambient temperature and was poured into a solution of sodium hydrogen phosphate (0.5M). Extraction was carried out with ethyl acetate and the extracts were washed with water and dried. The solvent was evaporated to obtain 1.6 g of product acetylated in position 2'. 50 ml of methanol were added and the mixture was stirred for 16 hours. The solvent was evaporated and the residue was chromatographed on silica (eluant: AcOEt-TEA at 4%) and crystallized from ether to obtain 194 mg of the expected product melting at 143°-145° C.

NMR CDCl₃ ppm

0.85 (t): CH₃-CH₂; 1.01 (d)-1.16 (d)-1.24 (d)-1.30 (d)-1.37 (d): the CH₃-CH's; 1.34 (s)-1.47 (s): 6 and 12 Me; 2.26 (s): N(Me)₂; 2.44 (m): H'₃; 2.60 (m): H₈; 2.64 (s): 6-OMe; 3.08 (m): H₄; 3.12 (wq): H₁₀; 3.17 (dd): H'₂; 3.54 (m): H'₅; 3.57 (s): H₁₁; 3.66 (m)-3.74 (m):



3.85 (q): H₂; 3.95 (s): Φ-OMe; 3.99 (wq): CH₂-N-C=; 4.24 (d): H₅; 4.27 (d): H'₁; 4.93 (dd): H₁₃; 6.97 (wd): H₆; 7.51 (s): the imidazole H's; 7.02: phenyl H₆; 7.19 (ddd) phenyl H₄ and H₅; 8.19 (dd): H₂.

Preparation of 4-(2-methoxyphenyl)-1H-imidazol-1-butanamine

Stage A: 4-(2-methoxyphenyl)-1H-imidazole.

936 g of 2-bromo-2'-methoxyacetophenone in 50 ml of formamide were refluxed and then the reaction medium was washed with a 2N hydrochloric acid solution, followed by filtration and alkalizing to pH 8-9 using 2N sodium hydroxide. Extraction was effected with dichloromethane and the extracts were washed with water, dried and evaporated to dryness. The residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 95-5-0.4) to obtain 6.15 g of the expected product.

Stage B: 2-(4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-1H-iso indol-1,3(2H)-dione.

Using the procedure of Stage A of Example 1, 6 g of the product of Stage A, 1.99 g of sodium hydride and 9.93 g of N-4-bromobutyl phthalimide were reacted to obtain 6.15 g of the expected product.

Stage C: 4-(2-methoxyphenyl)-1H-imidazol-1-butanamine(fumarate).

Using the procedure of Stage B of Example 1, 5.65 g of the product of Stage B and 1.45 ml of hydrazine hydrate in 75 ml of ethanol were reacted to obtain 3.8 g of crude product which was dissolved in 4 ml of tetrahydrofuran. Then, 1.87 g of fumaric acid in solution in 20 ml of methanol were added and 10 ml of ether were added. The crystals formed were separated and dried at 80° C. under

23.34 g of bromo 4-chloro acetophenone in 150 ml of formamide was refluxed for one hour and the reaction medium was allowed to cool and alkalized with a sodium hydroxide solution. Extraction was carried out with dichloromethane and the extracts were washed with water and dried. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 8-2-0.04) to obtain 13.4 g of the expected product melting at 146°-148° C.

Stage B: 2-(4-(4-(4-chlorophenyl)-1H-imidazol-1-yl)-butyl)-1H-iso indol-1,3(2H)-dione.

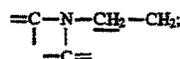
Using the procedure of Stage A of Example 1, 12.2 g of the product of Stage A, 4.96 g of sodium hydride and 23.83 g of N-4-bromobutyl-phthalamide were reacted to obtain 9.7 g of the expected product.

Stage C: 4-(4-chlorophenyl)-1H-imidazol-1-butanamine.

Using the procedure of Stage B of Example 1, 14.2 g of product of Stage B and 3.6 ml of hydrazine hydrate in 200 ml of ethanol were reacted to obtain 12 g of crude product which was chromatographed on silica (eluant CH₂Cl₂-MeOH-NH₄OH 8-2-0.04) to obtain the expected product, which is used as is for the synthesis.

NMR (CDCl₃) ppm

1.22 (ws): mobile 2H's; 1.47 (m)-1.88 (m): 2 central CH₂'s; 2.74 (m): CH₂-CH₂-N; 3.98 (m):



7.19 (d, J=1.5)-7.50 (d, J=1.5): H₂ and H₅; 7.33 and 7.70: aromatics, reduced pressure to obtain 3.77 g of the fumarate of the expected product melting at 160°-162° C.

NMR (CDCl₃) ppm

1.48 (m) 2H-1.87 (m) 2H: the central CH₂'s; 3.46: NH₂; 2.73 (t): CH₂N; 3.94 (s): Φ-OMe; 3.97 (t):



6.94 (dd): H₆; 7.04 (dt)-7.21 (ddd): H₅ and H₄; 7.51: H'₂ and H'₅; 8.19 (dd): H₂.

EXAMPLE 31

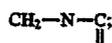
11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-((4-(4-(4-fluorophenyl)-1H-imidazol-1-yl)-butyl) imino)]-erythromycin

2.11 g of the starting compound of Example 29 (obtained as in Example 1C of the European Patent Application EP 0,596,802) in 9 ml of acetonitrile and 2.8 g of 4-(4-(4-

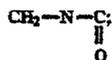
fluorophenyl)-1H-imidazol-1-yl)-butanamine were heated at 60° C. for 4 hours 30 minutes. The reaction medium was allowed to return to ambient temperature and was poured into water. Extraction was carried out with ethyl acetate and the extracts are washed with water and dried. The solvent was evaporated to obtain 5.2 g of product acetylated in position 2'. 20 ml of methanol were added to it and the mixture was stirred for 3 hours 30 minutes. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 95-5-0.3). Crystallization from ether was carried out to obtain 1.34 g of the expected product melting at 190°-192° C.

NMR CDCl₃ ppm

1.33 (s)-1.47 (s): 6 and 12 Me; 2.27 (s): N(Me)₂; 2.61 (s): 6-OMe; 3.0 to 3.18: H₄ and H₁₀; 3.56 (s): H₁₁; 3.59 to 3.81:



3.98 (t):



approx. 7.05—approx. 7.73: fluorophenyl; 7.21 (d): H₂ imidazole; 7.49 (d): imidazole H₃.

Preparation of 4-(4-fluorophenyl)-1H-imidazol-1-butanamine

Stage A: 4-(4-fluorophenyl)-1H-imidazole.

10.85 g of 4-fluorophenacyl bromide in 60 ml of formamide were refluxed for 2 hours and the reaction medium was allowed to return to ambient temperature and was acidified to pH 2 using N hydrochloric acid, followed by filtration. After neutralizing by the addition of ammonium hydroxide, extraction with dichloromethane was effected and the organic phase was washed with water and dried. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 95-5-0.4) to obtain 5.8 g of the expected product melting at 130°-132° C.

Stage B: 2-(4-(4-fluorophenyl)-1H-imidazol-1-yl)-butyl-1H-iso indol-1,3(2H)-dione.

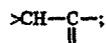
Using the procedure of Stage A of Example 1, 10 g of the product of Stage A, 1.95 g of sodium hydride and 11.80 g of N-4-bromobutyl-phthalimide were reacted to obtain 7.53 g of the expected product melting at 138°-140° C.

Stage c: 4-(4-fluorophenyl)-1H-imidazol-1-butanamine.

Using the procedure of Stage B of Example 1, 3.64 g of the product of Stage B and 1 ml of hydrazine hydrate in 80 ml of ethanol were reacted to obtain 2.4 g of crude product which was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 8-2-0.03) to obtain the desired product which was used as is for the synthesis.

NMR (CDCl₃) ppm

1.48 (m)-1.81 (m): the central CH₂'s; 2.74 (t): N-CH₃; 3.98 (t): >N-CH₂-CH₂; 7.06 (t): >CH-F; 7.22 (m):



7.49 (s): imidazole H₂; 7.15 (s): imidazole H₃.

EXAMPLE 32

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-oxycarbonyl-[(4-(7-methoxy-(4-quinolinyl)-butyl)-imino)]-erythromycin

706 mg of the starting compound of Example 29 (obtained as in Example 1C of the European Patent Appli-

cation EP 0,596,802) in 4 ml of acetonitrile and 1.43 g of 4-(4-7-methoxy-4-quinolinyl)-butanamine were heated at 50° C. for 53 hours. The reaction medium was allowed to return to ambient temperature and was poured into a solution of sodium hydrogen phosphate (0.5M). Extraction was carried out with dichloromethane and the extracts were washed with water and dried. The solvent was evaporated to obtain 1.09 g of product acetylated in position 2'. 10 ml of methanol were added to it and the mixture was stirred for 16 hours. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH 95-5). Crystallization from ether was carried out to obtain 295 mg of the expected product melting at 110° C.

NMR CDCl₃ ppm

3.06 (m): -(CH₂)₂-CH<; 3.70 (m): -N-CH₂-; 3.95 (s): -OCH₃; 7.12 (d)-7.19 (dd)-7.42 (d)-7.94 (d)-8.70 (d): pyridine.

Preparation of 7-methoxy-quinoline-4-butanamine

Stage A: triphenyl phosphonium salt of N-(3-bromopropyl)-phthalimide.

13.4 g of N-bromopropyl-phthalimide and 13.15 g of triphenylphosphine suspended in 75 ml of xylene were refluxed for 44 hours and the reaction medium was allowed to return to ambient temperature. The precipitate was separated, washed with ethyl ether and dried under reduced pressure at 60° C. to obtain 24.88 g of the expected product melting at 220°-222° C.

Stage B: Z-(2-(4-(7-methoxyquinolinyl)-3-butenyl)-1H-isoindol-1,3(2H)-dione.

4 g of 7-methoxy-4-quinolinylcarboxaldehyde were added to a suspension of 12.47 g of the triphenylphosphonium salt of 3-bromopropyl-phthalimide in 200 ml of tetrahydrofuran and after the reaction medium was cooled to -50° C., 2.72 g of potassium tertbutylate were added. The temperature was allowed to rise slowly to -6° C., followed by filtration. The filtrate was concentrated, the residue is taken up in ethyl acetate, washed with water and dried. The solvent was evaporated to obtain 9.26 g of crude product which was chromatographed on silica (eluant: CHCl₃-AcOEt 80-20, then 70-30) to obtain 3.575 g of the expected product.

Stage C: 2-(4-(7-methoxy-4-quinolinyl)-butyl)-1H-isoindol-1,3(2H)-dione.

3.50 g of the product of Stage B were dissolved in 50 ml of methanol and 0.36 g of palladium on activated charcoal were added. The mixture was hydrogenated for 3 hours under 600 mbars. Filtration was carried out and the solvent was evaporated to obtain 3.48 g of the expected product.

Stage D: 7-methoxy-quinolin-4-butanamine. 3.46 g of the product of Stage C were dissolved in 70 ml of hot ethanol and 1.86 ml of hydrazine hydrate were added. The reaction medium was refluxed for 17 hours and the precipitate was eliminated by filtration. The solvent was evaporated and the residue was taken up in 70 ml of dichloromethane. Filtration was carried out and the solvent was evaporated to obtain 2.19 g of the expected product.

NMR (CDCl₃) ppm

1.6 (m)-1.79 (m): central CH₂'s; 2.75 (t): >-CH₂-(CH₂)₃; 3.05 (t): CH₂-NH₂; 3.95 (s): O-CH₃; 7.10 (d, J=4.5)-7.21 (dd)-7.92 (d)-8.71 (d, J=4.5): quinoline.

EXAMPLE 33

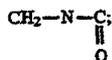
11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-oxycarbonyl-[(4-(2-(2-pyridinyl)-4-thiazolyl)-butyl)-imino)]-erythromycin

705 mg of the starting compound of Example 29 (obtained as in Example 1C of the European Patent Appli-

cation EP 0,596,802) in 3 ml of acetonitrile and 0.705 g of 4-(2-(2-pyridinyl-4-thiazolyl)-butanamine were heated at 60° C. for 5 hours and the reaction mixture was allowed to return to ambient temperature and was poured into water. Extraction was carried out with ethyl acetate and the extracts were washed with water and dried. The solvent was evaporated to obtain 1.8 g of product acetylated in position 2'. 15 ml of methanol were added to it and the mixture was refluxed for 2 hours and the solvent was then evaporated. The residue was chromatographed on silica (eluant: CH₂Cl₂—MeOH—NH₄OH 95-5-0.3 then AcOEt—TEA 9-1) and crystallization from ether was carried out to obtain 194 mg of the expected product melting at 157°–159° C.

NMR (CDCl₃) ppm

1.33 and 1.47: 6 and 12 Me; 2.26 (s): N(CH₃)₂; 2.86 (t): CH₂—C; 3.12 (wq): H₁₀; 3.60 (s): H₁₁; 3.66 (m):



7.03 (s): thiazole H₂; 7.27 (ddd): pyridine H₅; 7.77 (dt): pyridine H₄; 8.18 (dd) pyridine H₃; 8.53 (ddd): pyridine H₆.

Preparation of 2-(2-pyridinyl)-thiazol-4-butanamine

Stage A: 2-aminocarbonyl-pyridine

50 ml of a diazomethane solution (0.4M/l) were added dropwise to a solution of 2 g of picolinic acid, 20 ml of dichloromethane and 5 ml of methanol and after stirring for 30 minutes at ambient temperature, the solvent was evaporated under reduced pressure. The residue was chromatographed on silica (petroleum ether (60-80)-AcOEt 5-5) to obtain 1.48 g of methyl ester. 1.42 g of the ester were heated at 50° C. for 4 hours in 5 ml of ammonium hydroxide and the reaction mixture was allowed to return to ambient temperature. Extraction was carried out with ether and the extracts were washed with water and dried. The solvent was evaporated to obtain 1.05 g of the expected product melting at 105° C.

Stage B: 2-pyridine-carbothioamide

43 g of phosphorus pentasulfide were added slowly to 46.8 g of the amide of Stage A in 700 ml of tetrahydrofuran and the mixture was stirred for 4 hours at ambient temperature. The reaction mixture was poured into water and extracted with ether. The extracts were dried and the solvent was evaporated under reduced pressure. After chromatography on silica (eluant: CH₂Cl₂—AcOEt 8-2), 10 g of expected product melting at 137° C. were obtained.

Stage C: ethyl 2-(2-pyridinyl)-4-thiazole-carboxylate

16.3 ml of ethyl bromopyruvate were added dropwise to 15.9 g of the product of Stage B in 250 ml of ethanol and the mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica (eluant: hexane—AcOEt 1-1) to obtain 10.2 g of the expected product melting at 69.1° C.

Stage D: 2-(2-pyridinyl)-4-thiazole-methanol

40 ml of methanol were added slowly to a mixture of 9.3 g of the ester of Stage C and 4.1 g of sodium borohydride in 100 ml of tetrahydrofuran and the mixture was refluxed for 2 hours. The reaction medium was allowed to return to ambient temperature and was poured into water and neutralized using N hydrochloric acid. Extraction was carried out with dichloromethane and the organic phase was dried. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica (eluant: AcOEt—CH₂Cl₂ 1-1) to obtain 5.8 g of the expected product melting at 100° C.

Stage E: 2-(2-pyridinyl)-4-thiazole-carboxaldehyde

5.8 g of the product of Stage D in 60 ml of toluene were refluxed for 2 hours in the presence of 13 g of manganese oxide and filtration was carried out. The solvent was evaporated under reduced pressure to obtain 5 g of the expected product melting at 131° C.

Stage F: (Z) 2-(4-(2-(2-pyridinyl)-4-thiazolyl)-3-butenyl)-1H-isoindole-1,3(2H)-dione

Using the procedure of Stage A of Preparation 32, 5.70 g of the aldehyde of Stage E and 15.9 g of the triphenylphosphonium salt of 3-bromopropyl-phosphonium and 3.70 g of potassium *tert*-butylate were reacted to obtain 8.73 g of the expected product melting at 139°–141° C.

Stage G: (2-(4-(2-(2-pyridinyl)-4-thiazolyl)-butyl)-1H-isoindol-1,3(2H)-dione

Using the procedure of Stage B of Preparation 32, 7.22 g of the product of Stage F and 1.5 g of palladium on activated charcoal were hydrogenated for 2 hours under 1800 mbars to obtain 6.33 g of the expected product melting at 119°–121° C.

Stage H: 2-(2-pyridinyl)-thiazol-4-butanamine

Using the procedure of Stage C of Preparation 32, 5.45 g of the product of Stage G and 1.6 ml of hydrazine hydrate were refluxed for 6 hours. The solvent was evaporated and the residue was taken up in ethyl acetate and washed with water and dried. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂—MeOH—NH₄OH 9-1-0.03) to obtain 1.65 g of the expected product.

NMR (CDCl₃) ppm

1.50 (m)—1.82 (m): central CH₂'s; 2.76 (t)—2.85 (t): CH₂—C= and CH₂—NH₂; 7.85 (s): thiazole H₂; 7.31 (m): H'₅; 7.78 (dt): H'₄; 8.18 (dt): H'₃; 8.61 (ddd): H'₆; 1.40 (s): NH₂.

EXAMPLE 34

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl 3-0-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl)-{(4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino}]-erythromycin

1 g of the starting compound of Example 29 (obtained as in Example 1C of the European Patent application EP 0,596,802) in 4 ml of acetonitrile and 936 mg of 4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butanamine were heated at 70° C. for 20 hours and the reaction medium was allowed to return to ambient temperature and was poured into water. Extraction was carried out with ethyl acetate and the extracts were washed with water and dried. The solvent was evaporated to obtain 1.34 g of product acetylated in position 2'. 40 ml of methanol were added to it and the mixture was stirred for 2 hours. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂—MeOH—NH₄OH 95-5-0.4). Crystallization from ether yielded 310 mg of the expected product melting at 187°–188° C.

NMR (CDCl₃) ppm

0.83 (t): CH₃—CH₂; 1.01 (d)—1.17 (d)—1.25 (d)—1.31 (d)—1.38 (d): the CH₃—CH's; 1.34 (s)—1.47 (s): 6 and 12 Me; 2.27 (s): N(Me)₂; 2.45 (m): H'₃; 2.62 (s): 6-OMe; 2.60 (m): H₈; 2.85 to 3.25: H₄ and H₁₀, H'₂; 3.52 (m): H₅; 3.56 (s): H₁₁; 3.60 to 3.85 (m):



4.23 (d): H₅; 4.27 (d): H'₁; 4.93 (dd): H₁₃; 7.29 (ddd): pyridine H₅; 8.08 (dt): pyridine H₄; 8.45 (dd): pyridine

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H₅; 8.97 (dd): pyridine H₂; 7.35 (d) and 7.53 (d): imidazole H₂ and H₅.

Preparation of 4-(3-pyridinyl)-1H-imidazol-1-butanamine

Stage A: 2-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl-1H-iso-indol-1,3(2H)-dione

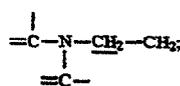
Using the procedure of Stage A of Example 1, 290 mg of 3-pyridinyl-1H-imidazole [prepared as in J. Chem. Soc., pp. 753-5 (1938)], 115 mg of sodium hydride and 633 mg of N-bromoethyl phthalimide were reacted to obtain 277 mg of the expected product melting at 150°-152° C.

Stage B: 4-(3-pyridinyl)-1H-imidazol-1-butanamine

Using the procedure of Stage B of Example 1, 1.66 g of the product of Stage A and 0.46 ml of hydrazine hydrate in 30 ml of ethanol were reacted to obtain 936 mg of the desired product which was used as is for the synthesis.

NMR (CDCl₃) ppm

1.49 (m)-1.89 (m): the central CH₂'s; 2.75 (t): CH₂-CH₂-N; 4.01 (t):



7.29 (d, J=1)-7.55 (d, J=1): H₂ and H₅; 7.30 (partly masked): H₃; 8.09 (dt, J=8 and 2): H₄; 8.47 (dd, J=5 and 2): H₆; 8.96 (d, J=2): H₇; 1.49 (ws): approx. mobile 2H's.

EXAMPLE 35

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butyl)-imino))-erythromycin

1g of the starting compound of Example 29 (obtained as in Example 1C of the European Patent Application EP 0.596.802) in 4 ml of acetonitrile and 1.21 g of 4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butanamine were heated at 75° C. for 8 hours and then the reaction medium was allowed to return to ambient temperature and was poured into water. Extraction was carried out with ethyl acetate and the extracts were washed with water and dried. The solvent was evaporated to obtain 2 g of product acetylated in position 2'. 40 ml of methanol were added to it and the mixture was stirred for 16 hours. The solvent was evaporated and the residue was chromatographed on silica (eluant: CH₂Cl₂-MeOH-NH₄OH 90-10-0.04). Crystallization from ether yielded 292 mg of the expected product melting at 190°-192° C.

NMR (CDCl₃) ppm

0.84 (t): CH₃-CH₂; 1.01 (d): OMe; 1.16 (d): 8Me; 1.25 (d): 5Me; 1.30 (d): 4Me; 1.34 (d): 2Me; 1.33 (s) and 1.47 (s): 6 and 12 Me; 1.67 (m)-1.99 (m): the central CH₂'s; 2.26 (s): N(Me)₂; 2.44 (m): H₃; 2.58 (m): H₈; 2.61 (s): 6-OMe; 3.06 (m): H₄; 3.12 (q): H₁₀; 3.17 (dd): H₂; 3.52 (m): H₅; 3.56 (s): H₁₁; 3.64 to 3.75 (-):



3.85 (q): H₂; approx. 4.25: H₁, H₅ and



4.91 (dd): H₁₃; 8.15 (s): triazole H; 7.35 (dd): pyridine H₅; 8.34 (dt): pyridine H₄; 8.62 (dd): pyridine H₆; 9.31 (wd): pyridine H₂.

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Preparation of 3-(3-pyridinyl)-1H-1,2,4-triazol-1-butanamine

Stage A: 2-(4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butyl)-1H-isoindol-1,3(2H)-dione

Using the procedure of Stage A of Example 1, 2.1 g of 3-pyridinyl-1H-1,2,4-triazole prepared as in J. Org. Chem., Vol. (44) No. 33, pp. 4160-4164 (1979), 1.02 g of sodium hydride and 4.13 g of N-4-bromobutyl phthalimide were reacted to obtain 2.4 g of the expected product melting at 150°-152° C.

Stage B: 3-(3-pyridinyl)-1H-1,2,4-triazol-1-butanamine (fumarate)

Using the procedure of Stage B of Example 1, 3.46 g of the product of Stage A and 1 ml of hydrazine hydrate in 50 ml of ethanol were reacted to obtain 2.1 g of crude product which was converted into the fumarate as in Preparation 30 to obtain 1.13 g of the fumarate of the expected product is obtained melting at approx. 190°-192° C.

NMR (CDCl₃) ppm

1.50 (m)-2.01 (m): the central CH₂'s; 2.76 (t): NH₂-CH₂; 4.24: =N-N-CH₂; 7.37 (ddd): H₅; 8.35 (dt): H₄; 8.63 (dd): H₆; 9.32 (dd): H₂; 8.12 (s): triazole =CH. Operating as previously using the appropriate amines, the following products were prepared:

EXAMPLE 36

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-quinolinyl)-butyl)-imino))-erythromycin melting at 190°-192° C.

EXAMPLE 37

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin melting at 152°-154° C.

EXAMPLE 38

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-phenyl-4-thiazolyl)-butyl)-imino))-erythromycin melting at 141°-143° C.

EXAMPLE 39

11,12-dideoxy 3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(3-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin melting at 144°-146° C.

EXAMPLE 40

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4,5-diphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin melting at 180°-182° C.

EXAMPLE 41

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-quinazolinyl)-butyl)-imino))-erythromycin melting at 212°-214° C.

EXAMPLE 42

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-

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12,11-(oxycarbonyl-((4-(2-(4-pyridinyl)-4-thiazolyl)-butyl)-imino))-erythromycin melting at 192°-194° C.

EXAMPLE 43

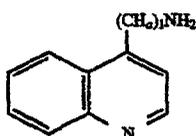
11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)-butyl)-imino))-erythromycin melting at 251°-253° C.

EXAMPLE 44

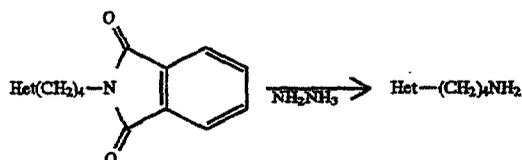
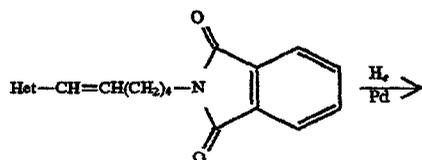
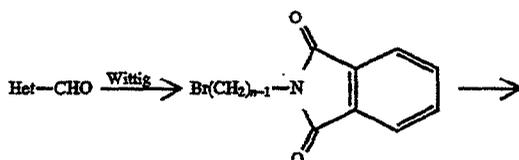
11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-trifluoromethoxy)-phenyl)-1H-imidazol-4-yl)butyl)-imino))-erythromycin melting at 168°-170° C.

The amines used as starting products were prepared by the following methods:

A—When the chain is attached to a carbon such as



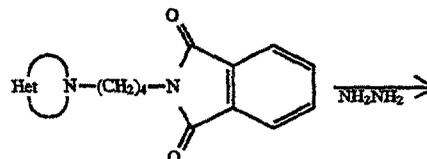
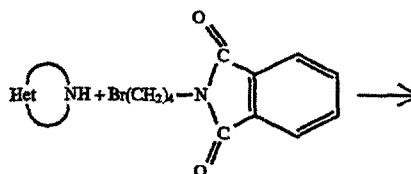
one can start with the corresponding aldehydes in the following equation



The amines used for the preparation of the products of Examples 4, 8, 11, 12, 18, 19, 23 and 24 were prepared in this way.

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B—When the chain is attached to a nitrogen, the amines can be prepared in the following way:



The amines used for the preparation of the products of Examples 1, 2, 3, 5, 9, 13, 14, 15, 16, 17, 20, 21, 22, 25, 26 and 28 were prepared in this way.

C—Certain amines were prepared in a particular way with the heterocycle constructed and the chain introduced at the same time (Example 6, 7, 10 and 27).

Examples of Pharmaceutical Compositions

Compositions were prepared containing 150 mg of the Product of Example 1 or 2 or 3 and sufficient excipient of starch, talc and magnesium stearate for 1 g.

Pharmacological Study of the Products of the Invention

Method of Dilutions in Liquid Medium

A series of tubes were prepared into which an equal quantity of sterile nutritive medium was divided. Increasing quantities of the product to be studied were distributed into each tube and then each tube was seeded with a bacterial strain. After incubation for twenty-four hours in an oven at 37° C., the growth inhibition was evaluated by transillumination which permitted the minimal inhibiting concentrations (M.I.C.) to be determined expressed in micrograms/ml. The following results were obtained:

Products	GRAM ⁺ bacterial strains							
	Ex. 1	Ex. 2	Ex. 3	Ex. 29	Ex. 31	Ex. 32	Ex. 34	Ex. 35
<i>Staphylococcus aureus</i> 011UC4	0,04	0,04	0,08	0,04	0,04	0,08	0,04	0,08
<i>Staphylococcus aureus</i> 011G025I	0,08	0,15	0,15	0,15	0,08	0,15	0,08	0,6
<i>Staphylococcus epidermidis</i> 012G011I	0,08	0,04	0,15	0,04	0,4	0,08	0,04	—

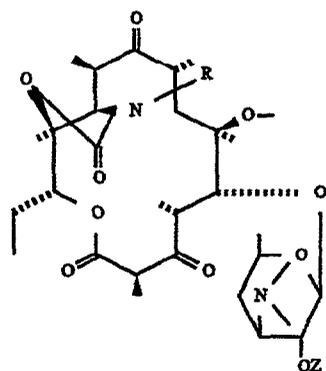
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Products	GRAM ⁺ bacterial strains							
	Ex. 1	Ex. 2	Ex. 3	Ex. 29	Ex. 31	Ex. 32	Ex. 34	Ex. 35
<i>Streptococcus pyogenes</i> group A 02A1UC1	0,04	≤0,02	0,04	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02
<i>Streptococcus agalactiae</i> group B 02B1HT1	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02
<i>Streptococcus faecalis</i> group D 02D2UC1	0,04	≤0,02	0,04	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02
<i>Streptococcus faecium</i> group D 02D3HT1	≤0,02	≤0,02	0,04	≤0,02	≤0,02	≤0,02	0,3	≤0,02
<i>Streptococcus</i> sp group G 02G0GR5	0,04	≤0,02	0,04	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02
<i>Streptococcus mitis</i> 02mitCB1	≤0,02	≤0,02	0,02	≤0,02	≤0,02	≤0,02	≤0,02	≤0,02
<i>Streptococcus mitis</i> 02mitGR1G1	≤0,02	0,15	0,04	≤0,02	≤0,02	≤0,02	≤0,02	0,02
<i>Streptococcus agalactiae</i> group B 02B1ST1	0,08	0,08	0,04	—	0,08	0,04	0,04	0,08
<i>Streptococcus pneumoniae</i> 030SI5	0,04	0,04	0,15	0,04	0,15	0,15	≤0,02	≤0,02

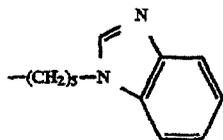
Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

What we claim is:

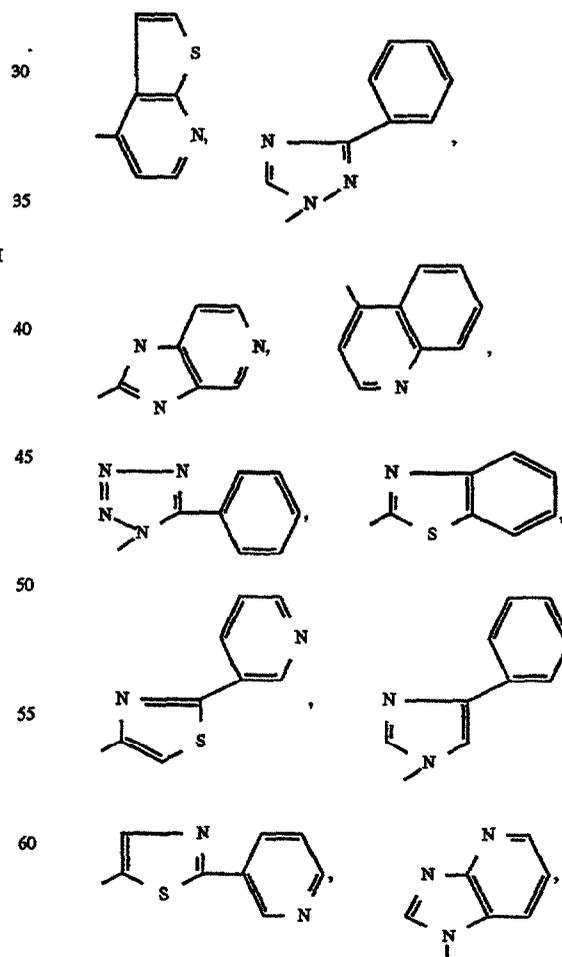
1. A compound of the formula



wherein R is

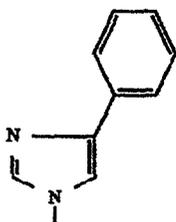


or $-(CH_2)_n-Ar$, n is an integer from 3 to 5, Ar is an optionally substituted heterocyclic selected from the group consisting of



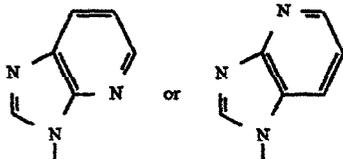
29

4. A compound of claim 1 wherein Ar is



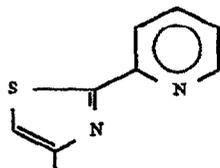
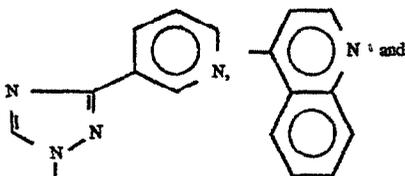
optionally substituted.

5. A compound of claim 1 wherein Ar is



optionally substituted.

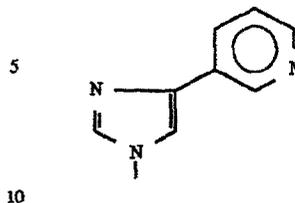
6. A compound of claim 1 wherein Ar is selected from the group consisting of



optionally substituted.

30

7. A compound of claim 1 wherein Ar is



optionally substituted.

8. A compound of claim 1 selected from the group consisting of

15 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-phenyl-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

20 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3H-imidazo(4,5-b)pyridin-3-yl)-butyl)-imino))-erythromycin,

25 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1H-imidazo(4,5-b)pyridin-1-yl)-butyl)-imino))-erythromycin,

30 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-chlorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

35 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

40 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-fluorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

45 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(7-methoxy-4-quinoleinyl)-butyl)-imino))-erythromycin,

50 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-(2-pyridinyl)-4-thiazolyl)-butyl)-imino))-erythromycin,

55 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butyl)-imino))-erythromycin,

and their non-toxic, pharmaceutically acceptable acid addition salts.

9. A compound of claim 1 which is 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin.

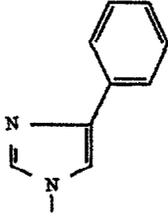
60 10. An antibacterial composition comprising an antibiologically effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

11. A method of treating bacterial infections in warm-blooded animals comprising administering to warm-blooded animals having a bacterial infection an antibiologically effective amount of a compound of claim 1.

12. A method of claim 11 wherein Z is hydrogen.

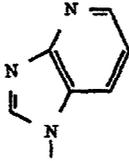
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13. A method of claim 11 wherein n is 4.
14. A method of claim 11 wherein Ar is

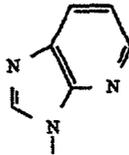


optionally substituted.

15. A method of claim 11 wherein Ar is

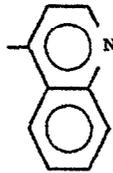
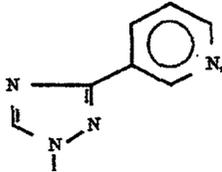


or

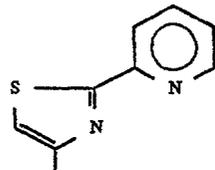


optionally substituted.

16. A method of claim 11 wherein Ar is selected from the group consisting of



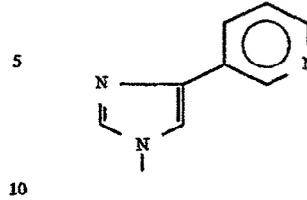
and



optionally substituted.

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17. A method of claim 11 wherein Ar is



optionally substituted.

18. A method of claim 11 wherein the compound is selected from the group consisting of

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-phenyl-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3H-imidazo(4,5-b)pyridin-3-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(1H-imidazo(4,5-b)pyridin-1-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-chlorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(2-methoxyphenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(4-fluorophenyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(7-methoxy-4-quinoleinyl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(2-(2-pyridinyl)-4-thiazolyl)-butyl)-imino))-erythromycin,

11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(3-(3-pyridinyl)-1H-1,2,4-triazol-1-yl)-butyl)-imino))-erythromycin,

and their non-toxic, pharmaceutically acceptable acid addition salts.

19. A method of claim 11 wherein the compound is 11,12-dideoxy-3-de-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-oxy]-6-O-methyl-3-oxo-12,11-(oxycarbonyl-((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)-butyl)-imino))-erythromycin.

* * * * *

EXHIBIT B



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Patent Assignment Abstract of Title

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Total Assignments: 3

Patent #: 5635485 Issue Dt: 06/03/1997 Application #: 08425067 Filing Dt: 04/21/1995

Inventors: CONSTANTIN AGOURIDAS, JEAN-FRANCOIS CHANTOT, ALEXIS DENIS, SOLANGE G. D'AMBRIERES et al

Title: ERYTHROMYCIN COMPOUNDS

Assignment: 1

Reel/Framc: 007586/0264 Recorded: 06/28/1995 Pages: 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: <u>AGOURIDAS, CONSTANTIN</u>	Exec Dt: 06/19/1995
<u>CHANTOT, JEAN-FRANCOIS</u>	Exec Dt: 06/19/1995
<u>DENIS, ALEXIS</u>	Exec Dt: 06/19/1995
<u>D'AMBRIERES, S. GOUIN</u>	Exec Dt: 06/19/1995
<u>LE MATRET, ODILE</u>	Exec Dt: 06/19/1995

Assignee: ROUSSEL UCLAF
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ROMAINVILLE, FRANCE 93235

Correspondent: BIERMAN AND MUSERLIAN
CHARLES A. MUSERLIAN
600 THIRD AVENUE
NEW YORK, NY 10016

Assignment: 2

Reel/Framc: 009168/0986 Recorded: 04/23/1998 Pages: 11

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: ROUSSEL UCLAF Exec Dt: 11/19/1997

Assignee: HOECHST MARION ROUSSEL
102, ROUTE DE NOISY
93230 ROMAINVILLE, CEDEX, FRANCE

Correspondent: BIERMAN, MUSERLIAN AND LUCAS
CHARLES A. MUSERLIAN
600 THIRD AVENUE
NEW YORK, NY 10016

Assignment: 3

Reel/Framc: 011497/0001 Recorded: 02/01/2001 Pages: 12

Conveyance: MERGER (SEE DOCUMENT FOR DETAILS).

Assignor: ROUSSEL, HOECHST MARION Exec Dt: 01/02/2001

Assignee: AVENTIS PHARMA S.A.

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 G, 011, 142
 G, 584, 028
 U, 679, 788
 U, 788, 980
 U, 986, 103
 G, 143, 774
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 U, 834, 452
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Patent No.:

Issued:

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-8-

It is also requested that the same be recorded against the following patent applications:

Serial No.:Filed:

696,647	08/14/96
101,027	12/19/96
117,628	01/30/97
142,288	03/03/97
155,063	03/20/97
171,347	04/17/97
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103,460	06/24/98
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463,705	07/21/98
133,162	08/12/98
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296,325	04/22/99
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733,377	12/08/00
734,162	12/11/00
746,245	12/22/00

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PCT No.:

PCT Date:

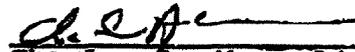
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PCT/FR99/01491

12/10/97
12/22/97
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05/22/99

Also submitted herewith is PTO Form-1619A as well as PTO Form-2038 authorizing the fee of \$13,680.00 for the recording of 342 documents.

Respectfully submitted,
Bierman, Muserlian and Lucas

By:


Charles A. Muserlian #19,683
Attorney for Applicants
Tel.# (212) 661-8000

CAM:ds
Enclosures



Aventis Pharma S.A.



CERTIFICATE OF MERGER

I, undersigned,

Jean-Pierre LABROUE, acting as Vice President, General Counsel and Corporate Secretary of Aventis Pharma S.A., a company having its registered office at 20, Avenue Raymond Aron, 92160 Antony (France), registered in the Commercial and Company Register of Nanterre under the number 304 463 284,

Do hereby certify that

- (i) by virtue of a merger Agreement dated November 27, 2000, unanimously approved by the Extraordinary Shareholders meeting held on December 29, 2000, and effective as of the date of December 31st, 2000, Hoechst Marion Roussel, a company having its registered office at 1, Terrasse Bellini, 92800 Puteaux (France), registered in the Commercial and Company Register of Nanterre under the number 552 081 473 has been merged into Aventis Pharma S.A.,
- (ii) according to the French Company Law, Aventis Pharma S.A. is the successor of Hoechst Marion Roussel in the entirety of all its rights and obligations.

Made in Antony, on January 2nd, 2001.

Jean-Pierre LABROUE
Vice President, General Counsel and
Corporate Secretary

Aventis Pharma S.A., 20 avenue Raymond Aron • F-92160 Antony • www.aventis.com
Téléphone + 33 (0)1 55 71 71 71 • Fax + 33 (0)1 47 02 50 14

Société Anonyme au capital de 4.069.384.915 F • R.C.S Nanterre B 304 463 284

RECORDED: 02/01/2001

PATENT
FEE: 011497 FRAME: 0012

EXHIBIT C

Aventis Pharmaceuticals Inc.



Patent Department

Gerald V. Dahling
Senior Vice President, Head of Global Patents
Aventis

May 21, 2004

Re: Application for Patent Term Extension Pursuant to 35 U.S.C. §156

Dear Mr. Dahling:

As Aventis Senior Vice President, Head of Global Patents (including patents assigned to Aventis S.A.), it is hereby brought to your attention that Aventis SA, owner of all right, title and interest in U.S. Patent No. 5,635,485 is authorized to rely on Aventis Pharmaceutical, Inc.'s approval from the Food and Drug Administration of New Drug Application No. 21-144 to market Ketek (telithromycin) in support of its application for patent term extension.

Best,

A handwritten signature in black ink, appearing to read "Louis J. Wille".

Louis J. Wille
Vice-President, Global Patent Litigation
Aventis Pharmaceuticals Inc.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals, Inc.
Attention: Steve Caffé, MD
Senior Vice President and Head
US Regulatory Affairs
200 Crossing Boulevard
P. O. Box 6800
Bridgewater, NJ 08807-0800

Dear Dr. Caffé:

Please refer to your new drug application (NDA) dated February 28, 2000, received March 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketek™ (telithromycin) Tablets, 400 mg.

We acknowledge receipt of your submissions dated:

October 17, 2003	October 27, 2003	October 31, 2003
November 18, 2003	November 26, 2003	December 11, 2003
December 22, 2003	January 8, 2004	January 13, 2004
January 23, 2004	January 26, 2004	January 27, 2004
January 30, 2004	February 2, 2004	February 3, 2004
February 4, 2004	February 5, 2004	February 10, 2004
February 13, 2004	February 16, 2004	February 27, 2004
March 1, 2004	March 4, 2004	March 16, 2004
March 19, 2004	March 23, 2004	March 24, 2004
March 25, 2004	March 26, 2004	March 31, 2004
April 1, 2004		

The October 17, 2003, submission constituted a complete response to our January 24, 2003, action letter.

This new drug application provides for the use of Ketek™ (telithromycin) Tablets for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below, for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*,
Haemophilus influenzae, or *Moraxella catarrhalis*.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* or *Staphylococcus aureus*.

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae* (including multi-drug resistant *Streptococcus pneumoniae* [MDRSP] strains), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomyphila pneumoniae*, or *Mycoplasma pneumoniae*.

We completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text included with this letter.

The final printed labeling (FPL) must be identical to enclosed labeling (text for the package insert, patient package insert, and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-144." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirements for acute exacerbation of chronic bronchitis for all pediatric ages. We are deferring submission of your pediatric studies for ages less than 18 years for acute bacterial sinusitis and community-acquired pneumonia until March 31, 2008.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post-marketing commitments. The status of post-marketing commitments shall be reported annually according to 21 CFR 314.81. These commitments are listed below:

1. Information to support the pediatric use of telithromycin for the treatment of acute bacterial sinusitis in pediatric patients ages less than 18 years of age.

Final Report Submission: March 31, 2008

2. Information to support the pediatric use of telithromycin for the treatment of community-acquired pneumonia in pediatric patients ages less than 18 years of age.

Final Report Submission: March 31, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric post-marketing commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

In addition, we remind you of your post-marketing commitment in your submission dated April 1, 2004. This commitment is listed below

3. Submit an updated assessment of all post-marketing visual adverse events that are reported globally for the first eighteen months after U.S. launch. This assessment will include detailed information regarding the nature of the visual adverse event, duration, resulting sequelae, if any, and description of any formal diagnostic evaluations to assess this event. Particular attention will be paid to patients whose symptoms did not resolve promptly. Information on the patients in question including but not limited to underlying diseases and concomitant medications will also be submitted.

Final Report Submission: March 31, 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

The Agency emphasizes the importance of describing the visual adverse effects of telithromycin in promotional materials to provide fair balance to promotional claims.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Judit Milstein, Regulatory Project Manager at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, MD, MPH
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Package Insert
Patient Package Insert
Carton and Container Labeling

Rev. March 2004

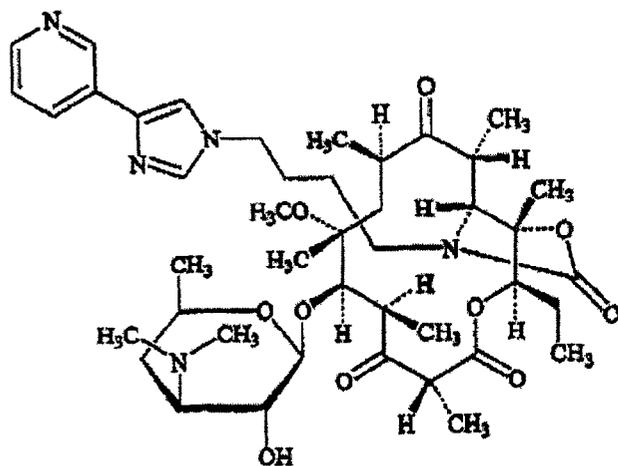
KETEK™
(telithromycin) Tablets

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 light-orange, oval, film-coated tablets, each containing 400 mg telithromycin, plus the following inactive ingredients: cornstarch, croscarmellose sodium, hypromellose, lactose

monohydrate, 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

Parameter	Mean (SD)	
	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/Plasma Ratio
		Tissue or fluid	Plasma	
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 (0-24)_{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.

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.

At present, no dose has been established in severely renal-impaired patients including those who need dialysis. (See **DOSAGE AND ADMINISTRATION**.)

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), no dose has been established.

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, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin in healthy subjects.

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 antiovolatory 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 decreased 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

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

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

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Viridans group streptococci

Anaerobic bacteria*Prevotella bivia**Prevotella intermedia**Peptostreptococcus* spp.**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

<u>Pathogen</u>	<u>Minimal Inhibitory Concentrations (µg/mL)</u>			<u>Disk Diffusion (zone diameters in mm)</u>		
	<u>S</u>	<u>I</u>	<u>R^a</u>	<u>S</u>	<u>I</u>	<u>R^a</u>
<i>Staphylococcus aureus</i>	≤ 0.25			≥ 22		
<i>Streptococcus pneumoniae</i>	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15

INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, or *Mycoplasma pneumoniae*.

*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 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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including telithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agents.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin-producing strains of *Clostridium difficile* are the primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes,

protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

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.

No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical efficacy trials, including 204 patients having a prolonged QTc at baseline.

Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for respiratory tract infections with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored. Patients must be advised that if they experience exacerbation of their symptoms, they should discontinue treatment of KETEK and immediately seek medical attention. Supportive measures should be instituted as medically necessary.

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.

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. Patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities. (See **ADVERSE REACTIONS, CLINICAL STUDIES**.)

Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible. Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. (See **ADVERSE REACTIONS, Liver and biliary system**.)

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), the dose of KETEK has not been established. (See **DOSAGE AND ADMINISTRATION**.)

Information for patients

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 **PRECAUTIONS, General** and **ADVERSE REACTIONS**.)

If visual difficulties occur:

- patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.
- avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.
- patients should contact their physician if these visual difficulties interfere with their daily activities.

Patients should also be advised:

- that 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.
- that KETEK has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.
- that 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.
- that telithromycin is not recommended in patients with myasthenia gravis. Patients should inform their physician if they have myasthenia gravis.
- that 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.

- that 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.**)

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 ($900 \text{ mg}/\text{m}^2$) and 0.49 times ($240 \text{ mg}/\text{m}^2$) the daily human dose of 800 mg ($492 \text{ mg}/\text{m}^2$) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the $900 \text{ mg}/\text{m}^2$ and $240 \text{ mg}/\text{m}^2$ 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 ($750 \text{ mg}/\text{m}^2/\text{d}$) 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 \geq 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 \geq 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	Comparato r† n= 2139	KETEK n= 2702	Comparato r† 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 \geq 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 ($\geq 0.2\%$ 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 **PRECAUTIONS, General** 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

Liver and biliary system: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with telithromycin. This hepatic dysfunction may be severe and is usually reversible.

Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See WARNINGS.)

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 taken orally once every 24 hours. The duration of therapy depends on the infection type and is described below. KETEK tablets can be administered with or without food.

Table 6

Infection	Daily dose and route of administration	Frequency of administration	Duration of treatment
Acute bacterial exacerbation of chronic bronchitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Acute bacterial sinusitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Community-acquired pneumonia	800 mg oral (2 tablets of 400 mg)	once daily	7-10 days

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 of KETEK has not been established.

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)

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/mm³. Total number of clinically evaluable patients in the telithromycin group included 2016 patients.

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

Controlled Studies	Patients (n)		Clinical cure rate	
	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 8.

Table 8. CAP: Clinical cure rate by pathogen at post-therapy follow-up (17-24 days)

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

Acute bacterial sinusitis

KETEK was studied in two randomized, double-blind, comparative studies for the treatment of acute sinusitis. Clinical cure rates with KETEK given for 5 days and comparator drug are shown in Table 10.

Table 10. Acute Sinusitis: Clinical cure rate at post-therapy follow-up (17-24 days)

Controlled Studies	Patients (n)		Clinical cure rate	
	KETEK (5 day treatment)	Comparator (10 day treatment)	KETEK (5 day treatment)	Comparator (10 day treatment)
KETEK vs. amoxicillin/clavulanic acid 500/125 mg TID	146	137	75.3%	74.5%
KETEK vs. cefuroxime axetil 250 mg BID	189	89	85.2%	82.0%

A third study compared 5 days with 10 days of KETEK for the treatment of acute bacterial sinusitis, clinical cure rates for the two treatments were similar (91.1% vs. 91.0% respectively).

Clinical cure rates in microbiologically evaluable patients for KETEK against the most common pathogens from the two acute sinusitis controlled clinical trials are displayed in Table 11.

Table 11. Acute Sinusitis: Clinical cure rate by pathogen

Pathogen	KETEK 5 days	Comparator 10-days
<i>Streptococcus pneumoniae</i>	27/31 (87.1%)	14/16 (87.5%)
<i>Haemophilus influenzae</i>	28/34 (82.4%)	13/15 (86.7%)
<i>Moraxella catarrhalis</i>	7/7 (100%)	7/7 (100%)
<i>Staphylococcus aureus</i>	8/8 (100%)	2/3 (66.7%)

Acute bacterial exacerbation of chronic bronchitis (AECB)

KETEK was studied in three randomized, double-blind, controlled studies for the treatment of acute exacerbation of chronic bronchitis. Clinical cure rates are displayed in Table 12.

Table 12. AECB: Clinical cure rate at post-therapy follow-up (17-24 days)

Controlled Studies	Patients (n)		Clinical cure rate	
	KETEK	Comparator	KETEK	Comparator
KETEK (5 day therapy) vs. cefuroxime axetil 500mg BID (10 day therapy)	140	142	86.4%	83.1%
KETEK (5 day therapy) vs. amoxicillin/clavulanic acid 500/125 mg TID (10 day therapy)	115	112	86.1%	82.1%
KETEK (5 day therapy) vs. clarithromycin 500mg BID (10 day therapy)	225	231	85.8%	89.2%

Clinical cure rates in microbiologically evaluable patients treated with KETEK against the most common pathogens from the three acute exacerbation of chronic bronchitis clinical trials are displayed in Table 13.

Table 13. AECB: Clinical cure rate by pathogen at post-therapy follow-up (17-24 days)

Pathogen	KETEK	Comparator
<i>Streptococcus pneumoniae</i>	22/27 (81.5%)	15/19 (78.9%)
<i>Haemophilus influenzae</i>	44/60 (73.3%)	45/53 (84.9%)
<i>Moraxella catarrhalis</i>	27/29 (93.1%)	29/34 (85.3%)

Visual Adverse Events

Table 14 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 14. 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/m²/day (1.8x the human dose) or more for 1 month, and 300 mg/m²/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/m²/day (6.1x the human dose) or more for 1 month and 1000 mg/m²/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. March 2004

Aventis Pharmaceuticals Inc.
Kansas City, MO 64137

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US Patent Nos.: 5,527,780; 5,969,161; and 6,022,965

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www.aventispharma-us.com

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: Fourteenth Informational Supplement; Approved Standard, NCCLS Document M2-A8 and M7-A6, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2004.

Rx only

**Patient Information About:
KETEK™
(telithromycin)
400mg Tablets**

Before beginning your treatment, please read this section to learn important information about KETEK™ (telithromycin). Although the information presented here will be useful during your therapy, not all the benefits and risks of treatment with KETEK are discussed in this document. This section is not intended to take the place of conversations with your doctor or healthcare provider about your treatment or medical condition. The medicine described here can only be prescribed by a licensed healthcare provider. With this in mind, be sure to talk to your healthcare provider if you have any questions. It's important to note that only a doctor or healthcare provider can determine if KETEK is right for you.

What is KETEK?

KETEK (*KEE tek*) is an antibiotic used to treat adults 18 years of age and older with certain respiratory (lung and sinus) infections caused by certain germs called bacteria. KETEK kills many of the types of bacteria that can infect the lungs and sinuses, and has been found to treat these infections safely and effectively in clinical trials.

Not all respiratory infections are caused by bacteria. For example, common colds are caused by viruses. KETEK, like other antibiotics, does not kill viruses.

KETEK Tablets are light orange, oval, film-coated tablets, imprinted with "H3647" on one side and "400" on the other side, and each containing 400 mg of active drug.

How and when should I take KETEK?

The usual dose is two KETEK Tablets taken at the same time once daily for 5 to 10 days. KETEK tablets should be swallowed whole and may be taken with or without food. Try to take your tablets at the same time every day, unless your healthcare provider tells you otherwise.

Follow the dosing instructions carefully, and do not take more than the prescribed amount. If you miss a dose, take it as soon as you remember. Do not take more than one dose (e.g., two tablets) of KETEK in a 24-hour period. If you have any questions, talk to your healthcare provider.

To make sure that all bacteria are killed, take all of the medicine that was prescribed for you even if you begin to feel better, unless instructed otherwise. You should contact your healthcare provider if your condition is not improving while taking KETEK.

Who should not take KETEK?

You must not take KETEK if:

- You have ever had a severe allergic reaction to KETEK or to any of the group of antibiotics known as “macrolides” such as erythromycin, azithromycin (Zithromax[®]), clarithromycin (Biaxin[®]) or dirithromycin (Dynabac[®]).
- You are currently taking cisapride (Propulsid[®]) or pimozide (Orap[®]).

You should be sure to talk to your healthcare provider before taking KETEK if any of the following are true, so he/she can determine if KETEK is right for you:

- If you have, or if a relative has, a rare heart condition known as congenital prolongation of the QT interval.
- If you are being treated for heart rhythm disturbances with certain medicines known as antiarrhythmics (such as quinidine, procainamide, or dofetilide) or if you have low blood potassium (hypokalemia), or low blood magnesium (hypomagnesemia).
- If you have a disease known as myasthenia gravis.
- If you are pregnant, planning to become pregnant, or are nursing.
- If you have ever experienced jaundice (yellow color of the skin and/or eyes) while taking KETEK.
- If you have any other serious medical conditions, including heart, liver, or kidney disease.

What about other medications I am taking?

It is important to let your healthcare provider know about all of the medicines you are taking, including those obtained without a prescription. Also see section “**Who should not take KETEK?**”

It is important to tell your healthcare provider if you are taking:

- Simvastatin, lovastatin, or atorvastatin (used for lowering cholesterol). You should stop treatment with these medications while you are taking KETEK.
- Medicines that correct heart rhythm called “antiarrhythmics” (such as quinidine, procainamide, or dofetilide).
- Any of the following medicines: itraconazole, ketoconazole, midazolam, digoxin, ergot alkaloid derivatives, cyclosporine, carbamazepine, hexobarbital, phenytoin, tacrolimus, sirolimus, metoprolol, theophylline or rifampin.
- Medicines called diuretics (also sometimes called water pills) such as furosemide or hydrochlorothiazide.

What are the possible side effects of KETEK?

KETEK is generally well tolerated. Most side effects are mild to moderate.

The most common side effects are nausea, headache, dizziness, vomiting, and diarrhea. If diarrhea persists call your healthcare provider.

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 sometimes came back with the next dose.

If visual difficulties occur:

- You should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.
- Avoiding quickly looking between objects in the distance and objects nearby may help you to decrease these visual difficulties.
- You should contact your physician if these visual difficulties interfere with your daily activities.

There have been reports of side effects on the liver. If you develop jaundice (yellow color of the skin and/or eyes), stop your medication and contact your healthcare provider.

KETEK has the potential to affect the heart, as seen on an electrocardiogram (EKG) test. In very rare cases, this condition may result in a serious abnormal heartbeat. Contact your healthcare provider if you have a fainting spell.

There have been reports of worsening of myasthenia gravis symptoms in patients with myasthenia gravis. If you have myasthenia gravis and experience any worsening of your symptoms (such as muscle weakness, difficulty breathing) during treatment with KETEK, you should stop taking KETEK and seek immediate medical attention.

If you have other side effects not mentioned in this section or have concerns about side effects, be sure to talk to your healthcare provider.

How can I find out more about KETEK?

This is a summary of selected key points about KETEK. If you'd like more information or if you have concerns, talk to your healthcare provider. You can also visit the KETEK website at www.KETEK.com. But remember, neither this Patient Information nor the website can replace discussions with your doctor or healthcare provider.

Other key points to remember:

- Take your prescribed dose of KETEK once a day at the same time each day.
- Complete the course of medication (take all the tablets prescribed), even if you start to feel better, unless instructed otherwise.
- As with all other medications, do not use KETEK for other conditions or give tablets to others.
- Store KETEK tablets at room temperature.
- Keep this medication out of the reach of children.
- Do not take your tablets after the expiration date noted.
- Talk to your healthcare provider if you have questions or concerns.

BIAXIN[®] (clarithromycin) is a registered trademark of Abbott Laboratories.
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Aventis Pharmaceuticals Inc,
Kansas City, MO 64137
US Patent Nos.: 5,527,780; 5,969,161; and 6,022,965
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ID number:	50066796	
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Minimum point size of text: 5 pt.		
Colors Used:		
Reflex Blue	 PMS 138	 PMS 186

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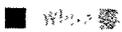
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 R/R: X = 180.5001, Y = 160.0000
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 01/03/29

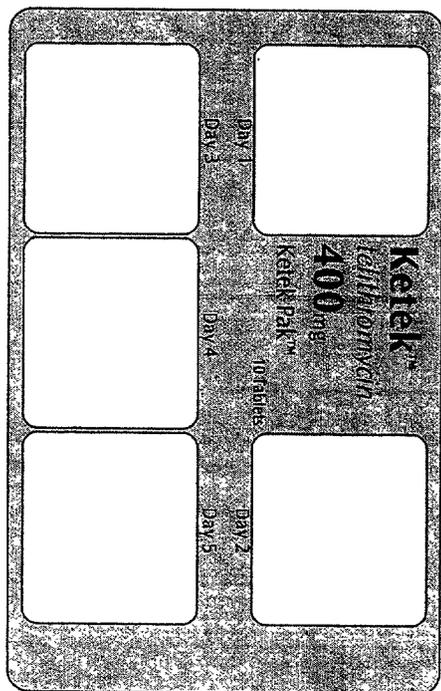


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Colors Used:		
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Signature: _____

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Signature: _____



NDC 0088-2225-07 

Ketek™
telithromycin

Each KETEK™ Tablet contains 400mg telithromycin.

Usual Dosage: Take two Ketek™ Tablets (at the same time) once a day. Tablets may be taken with or without food. See package insert for full prescribing information.

WARNING: Keep out of reach of children.

Important: This package is not child resistant.

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

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Kansas City, MO 64137 USA ©2002
www.aventispharma-us.com
50066805

Aventis Pharma (Kansas)
 REF: Ketek Display 3's ctn#1
 69 x 68 x 104
 R/R: 11.258 x 12.789
 PGM #: Im02404
 02/05/16

Three 10 Tablet Cartons
 Aventis

Ketek Pak™
 telithromycin
Ketek™ 400mg
 NDC 0088-2225-07

Three 10 Tablet Cartons
 Aventis

Ketek Pak™
 telithromycin
Ketek™ 400mg
 NDC 0088-2225-07

Three 10 Tablet Cartons
 Aventis

Ketek™ 400mg
 telithromycin
 Ketek Pak™
 Three 10 Tablet Cartons

ID number:	50066802	
Version:	J	
Country:	USA	
Date:	7-16-02	
Operator:	DM	
Logo version:	AZ	
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Supplier:	Margo	
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Minimum point size of text: 5 pt.		
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Reflex Blue	PMS 186	PMS 138

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Functional: Date: _____
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IM02404

Ketek™ telithromycin **Rx ONLY**

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U.S. Patents 5,527,780; 5,969,161; 6,022,965

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NDC 0088-2225-07

Ketek™
 telithromycin
400mg
 Ketek Pak™
 Three 10 Tablet Cartons

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NDC 0088-2225-07

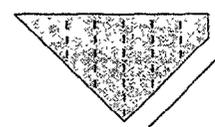
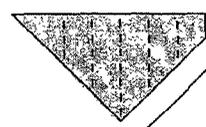
Ketek™
 telithromycin
400mg
 Ketek Pak™
 Three 10 Tablet Cartons

Aventis

NDC 0088-2225-07

Ketek™
 telithromycin
400mg
 Ketek Pak™
 Three 10 Tablet Cartons

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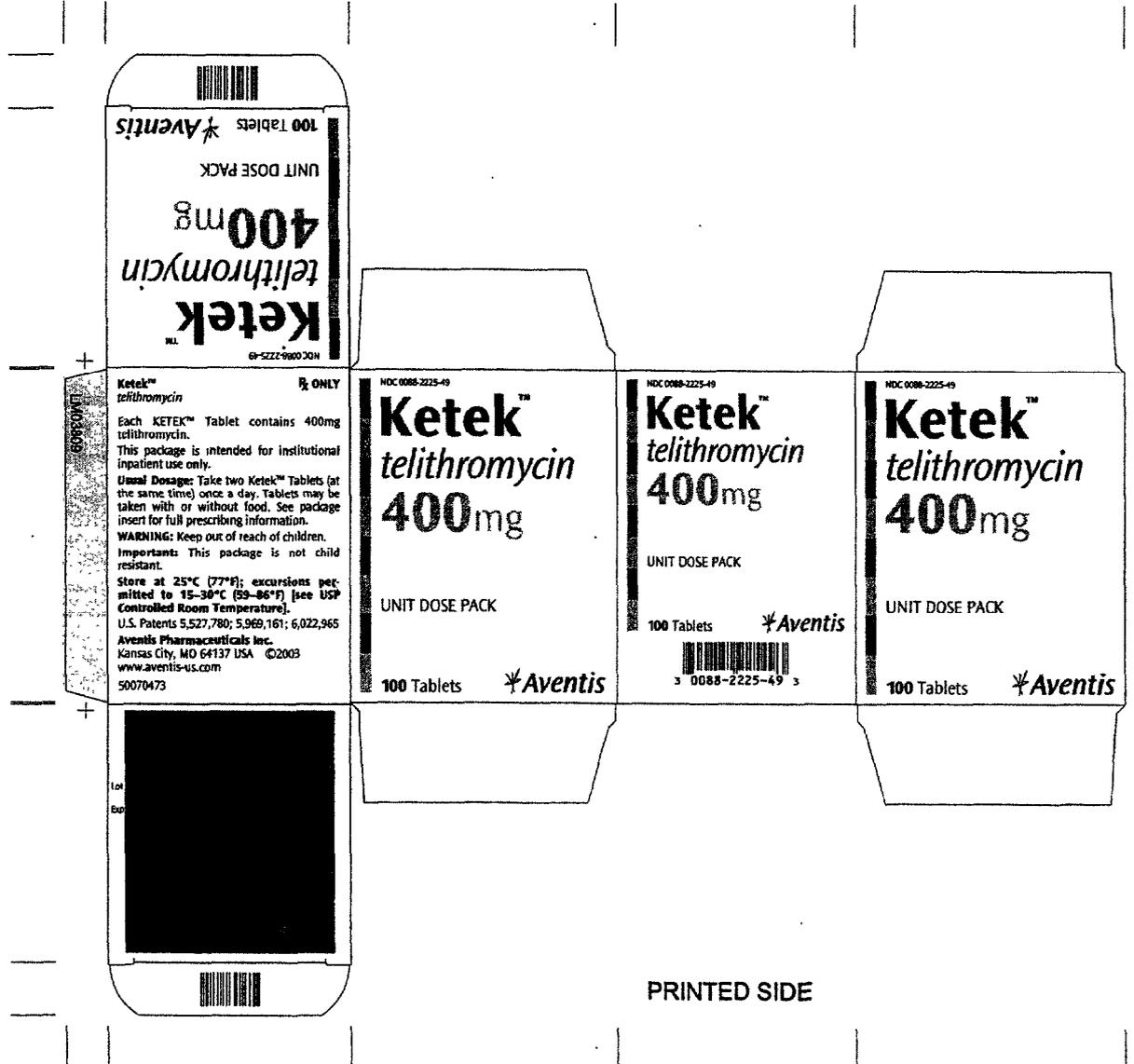


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2 Tablets 50070474 Aventis Pharmaceuticals Inc.	NDC 0088-2225-01 KETEK™ <i>telithromycin</i> 400mg	10-57272-2225-01 KETEK™ <i>telithromycin</i> 400mg	2 Tablets 50070474 Aventis Pharmaceuticals Inc.
R ONLY 50070474 Aventis Pharmaceuticals Inc.	NDC 0088-2225-01 KETEK™ <i>telithromycin</i> 400mg	10-57272-2225-01 KETEK™ <i>telithromycin</i> 400mg	2 Tablets 50070474 Aventis Pharmaceuticals Inc.
2 Tablets 50070474 Aventis Pharmaceuticals Inc.	NDC 0088-2225-01 KETEK™ <i>telithromycin</i> 400mg	10-57272-2225-01 KETEK™ <i>telithromycin</i> 400mg	2 Tablets 50070474 Aventis Pharmaceuticals Inc.

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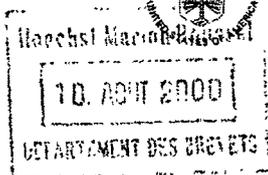
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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT"

Now.
 If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT	STAT
	5,635,485	183	830	----	08/426,067	06/03/97	04/21/95	04 NO	PAID

2407 US

ITM NBR	ATTY DKT NUMBER
1	146.1235

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB 04-424)

In re Application of:)
)
Constantin Agouridas et al.)
)
U.S. Patent No.: 5,635,485) Examiner: Elli Peselev
)
Issued: June 3, 1997) Group Art Unit: 1623
)
For: ERYTHROMYCIN COMPOUNDS)
)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

In regard to the above-identified patent application:

1. We are transmitting herewith the attached:
 - a. Request for Certificate of Correction
 - b. Postcard

2. With respect to additional fees:

___ A. No additional fee is required.

___ B. Attached is a check in the amount of _____

3. Please charge any additional fees or credit over-payments to the Deposit Account No.13-2490.

4. CERTIFICATE UNDER 37 CFR 1.10 (EXPRESS MAIL): The undersigned hereby certifies that this Transmittal Letter and this paper, as described in paragraph 1 hereinabove, are being deposited with the United States Postal Service, as Express Mail, in an envelope addressed to: Commissioner of Patents, Alexandria, VA 22313-1450, on this 26th day of May 2004.

Dated: May 26, 2004

By: _____

Kevin E. Noonan
Reg. No. 35,303

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB 04-424)

In re Application of:)	
)	
Constantin Agouridas et al.)	
)	
U.S. Patent No.: 5,635,485)	Examiner: Elli Peselev
)	
Issued: June 3, 1997)	Group Art Unit: 1623
)	
For: ERYTHROMYCIN COMPOUNDS)	
)	

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner for Patents
Washington, D.C. 20231

Attn: Certificate of Corrections Branch

Sir:

This is a request for issuance of the accompanying Certificate of Correction pursuant to 35 U.S.C. §§ 254 and 255 as well as 37 C.F.R. §§ 1.322(a). The Assignee (Aventis SA) seeks to correct mistakes of a clerical nature, a typographical nature or of minor character in the above-identified Patent. No fee is due. Applicants also attaching a copy of the Certificate of Correction.

The correction is as follows:
In claim 3, column 28, line 67, delete "Z" and insert --n--.