

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5246
(973) 286-6700
clizza@saul.com

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals, Inc. and
Boehringer Ingelheim International GmbH*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC. and
BOEHRINGER INGELHEIM
INTERNATIONAL GMBH,

Plaintiffs,

v.

APOTEX INC. and APOTEX CORP.,

Defendants.

Civil Action No. _____

(Filed Electronically)

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG (collectively, “Plaintiffs” or “Boehringer Ingelheim”) by their undersigned attorneys, bring this action against Apotex Inc. and Apotex Corp. (collectively, “Apotex”), and hereby allege as follows:

NATURE OF THE ACTION

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. § 1, *et seq.*, and in particular under 35 U.S.C §§ 271 (a–c, e–g), arises

from Apotex's submission of Abbreviated New Drug Application ("ANDA") No. 210725 to the United States Food and Drug Administration ("FDA"). Through this ANDA, Apotex seeks approval to market a generic version of the pharmaceutical product GILOTRIF® (afatinib) tablets prior to the expiration of United States Patent No. 8,426,586 (the "patent-in-suit"). Plaintiffs seek injunctive relief precluding infringement, attorneys' fees, and any other relief the Court deems just and proper.

2. This is also an action under 28 U.S.C. §§ 2201–02 for a declaratory judgment of patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, *et seq.*, and in particular under 35 U.S.C. §§ 271(a–c, e–g).

THE PARTIES

3. Plaintiff Boehringer Ingelheim Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Plaintiff Boehringer Ingelheim International GmbH is a private limited liability company organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

5. On information and belief, defendant Apotex Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9.

6. On information and belief, defendant Apotex Corp. is a corporation organized and existing under the laws of Delaware, having its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

7. On information and belief, Apotex Corp. is a wholly-owned subsidiary of Apotex Inc.

8. On information and belief, Apotex Inc., in collaboration with Apotex Corp., prepared and submitted ANDA No. 210725 (the “Apotex ANDA”) and continues to collaborate in seeking FDA approval of that application.

9. On information and belief, Apotex intends to commercially manufacture, market, offer for sale, and sell the product described in the Apotex ANDA (the “ANDA Product”) throughout the United States, including in the State of New Jersey, in the event the FDA approves the Apotex ANDA.

JURISDICTION AND VENUE

10. This civil action for patent infringement arises under the patent laws of the United States, including 35 U.S.C. § 271, and alleges infringement of United States Patent No. 8,426,586 (“the ’586 Patent”). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

11. This Court has jurisdiction over Apotex Inc. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Plaintiffs’ claims arise under federal law; (b) Apotex Inc. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Apotex Inc. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court’s exercise of jurisdiction over Apotex Inc. satisfies due process.

12. On information and belief, this Court also has jurisdiction over Apotex because, *inter alia*, this action arises from actions of Apotex directed toward New Jersey, and because

Apotex has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with New Jersey.

13. On information and belief, Apotex Corp. is registered with the New Jersey Department of Health as a drug manufacturer and wholesaler under Registration Number 5003192, and regularly and continuously transacts business within the State of New Jersey, including by selling pharmaceutical products in New Jersey, either on its own or through an affiliate. Upon information and belief, Apotex derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within the State of New Jersey. Further, Apotex has committed, or aided, abetted, contributed to and/or participated in the commission of, acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufactures GILOTRIF® for sale and use throughout the United States, including this Judicial District.

14. On information and belief, Apotex Corp. has submitted, caused to be submitted, or aided and abetted in the preparation or submission of the Apotex ANDA. On information and belief, in the event that the FDA approves the Apotex ANDA, Apotex Inc., with the participation of Apotex Corp., intends to commercially manufacture, import, market, offer for sell, and sell the ANDA Product throughout the United States and in this Judicial District.

15. Apotex has previously been sued in this Judicial District without objecting on the basis of lack of personal jurisdiction and has availed itself of the rights, benefits, and privileges of New Jersey by asserting claims or counterclaims involving pharmaceutical drug patent disputes in this Judicial District, including in the following cases: *Patheon Softgels Inc. et al. v. Apotex Inc. et al.*, Civil Action No. 17-13819; *Merck Sharp & Dohme Corp. v. Apotex Inc. et al.*,

Civil Action No. 17-5399; *Dexcel Pharma Technologies Ltd. et al. v. Apotex Corp. et al.*, Civil Action No. 17-2423; and *Takeda GmbH et al. v. Apotex Corp. et al.*, Civil Action No. 15-3379.

16. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1400(b) and 1391(c)(3).

BOEHRINGER INGELHEIM'S APPROVED GILOTRIF® DRUG PRODUCT AND PATENT

17. Boehringer Ingelheim makes and sells GILOTRIF®, a product used in the first-line treatment of metastatic non-small cell lung cancer (“NSCLC”) where the tumors have epidermal growth factor receptor (“EGFR”) exon 19 deletions or exon 21 (L858R substitution mutations). GILOTRIF® is also used to treat metastatic, squamous NSCLC that progresses after platinum-based chemotherapy. The active ingredient in GILOTRIF® is afatinib. A true and correct copy of the prescribing label for GILOTRIF® is attached as Exhibit A.

18. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application (“NDA”) No. 201292 for GILOTRIF® and the licensee of the patents-in-suit. The FDA approved NDA No. 201292 for GILOTRIF® in July 2013, and granted GILOTRIF® five years of regulatory exclusivity for a new chemical entity pursuant to 21 C.F.R. § 314.108, which expires on July 12, 2018. The FDA also granted GILOTRIF® orphan drug exclusivity pursuant to 21 C.F.R. § 316.31.

19. Boehringer Ingelheim International GmbH owns the ’586 Patent, which is listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the “Orange Book”) for GILOTRIF®.

20. The ’586 Patent entitled, “Process for Preparing Amino Crotonyl Compounds,” was duly and lawfully issued by the USPTO on April 23, 2013. A true and correct copy of the ’586 Patent is attached as Exhibit B.

APOTEX'S ANDA

21. On information and belief, Apotex has submitted or caused to be submitted ANDA No. 210725 to the FDA under 21 U.S.C. § 355(j), in order to obtain approval to engage in the commercial manufacture, use, or sale of Afatinib Tablets, as a purported generic version of GILOTRIF®, prior to the expiration of the patents-in-suit.

22. On information and belief, on or about May 25, 2018, Apotex mailed Plaintiffs a letter regarding “Notification of Paragraph IV Certification Regarding U.S. Patent No. 8,426,586 Pursuant to Section 505(j)(2)(B)(i)(ii) of the Federal Food, Drug and Cosmetic Act” (the “Notice Letter”). The Notice Letter represented that Apotex had submitted to the FDA the Apotex ANDA and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Apotex ANDA before the expiration of the patent listed in the Orange Book for GILOTRIF®. Hence, Apotex’s purpose in submitting the Apotex ANDA is to manufacture and market the ANDA Product before the expiration of the patent-in-suit.

23. Apotex’s Notice Letter stated that the Paragraph IV certification in the Apotex ANDA alleges that the ’586 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

24. Apotex’s Notice Letter contained a purported detailed statement of the factual and legal basis for its Paragraph IV certification (“Detailed Statement”).

25. On information and belief, Apotex has participated in the preparation and submission of the Apotex ANDA, has provided material support to the preparation and submission of the Apotex ANDA, and intends to support the further prosecution of the Apotex ANDA.

26. On information and belief, if the FDA approves the Apotex ANDA, Apotex will manufacture, offer for sale, or sell the ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

27. Alternatively, on information and belief, if the FDA approves the Apotex ANDA, Apotex will actively induce or contribute to the manufacture, use, offer for sale, or sale of the ANDA Product.

28. This action is pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), filed on July 2, 2018, which is within forty-five days of Plaintiffs' receipt of the Notice Letter.

COUNT I
INFRINGEMENT OF THE '586 PATENT

29. Plaintiffs incorporate by reference paragraphs 1–28 as if fully set forth herein.

30. On information and belief, Apotex has submitted or caused the submission of the Apotex ANDA to the FDA and continues to seek FDA approval of the Apotex ANDA.

31. Apotex has infringed the '586 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Apotex ANDA with a Paragraph IV certification and seeking FDA approval of the Apotex ANDA prior to the expiration of the '586 Patent.

32. On information and belief, if the Apotex ANDA is approved, Apotex and its affiliates will make, offer for sale, sell, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '586 Patent.

33. Apotex's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '586 Patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 210725, Apotex will make, use, offer to sell, or sell the ANDA Product within the United States,

or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '586 Patent.

34. Apotex had actual and constructive notice of the '586 Patent prior to filing the Apotex ANDA, and was aware that the filing of the Apotex ANDA with the request for FDA approval prior to the expiration of the '586 Patent would constitute an act of infringement of the '586 Patent. Apotex had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the '586 Patent.

35. Apotex's Detailed Statement in the Notice Letter does not contend that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the '586 Patent.

36. In addition, Apotex filed the Apotex ANDA without adequate justification for asserting the '586 Patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Apotex's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '586 Patent renders this case "exceptional" under 35 U.S.C. § 285.

37. Plaintiffs will be irreparably harmed if Apotex is not enjoined from infringing and from actively inducing or contributing to the infringement of the '586 Patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Apotex, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '586 PATENT

38. Plaintiffs incorporate by reference paragraphs 1–37 as if fully set forth herein.

39. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

40. On information and belief, if the Apotex ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Apotex and its affiliates.

41. On information and belief, Apotex knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Apotex ANDA and Apotex will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '586 Patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

42. On information and belief, Apotex's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Apotex ANDA. Any such conduct before the '586 Patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '586 Patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

43. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Apotex concerning liability for the infringement of the '586 Patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

44. Plaintiffs will be substantially and irreparably harmed by Apotex's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

45. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

REQUEST FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

- A. A judgment that Apotex infringes the '586 Patent under 35 U.S.C. § 271(e)(2)(A);
- B. A declaratory judgment that under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g), Apotex's commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of the ANDA Product, or inducing or contributing to such conduct, would constitute infringement of one or more claims of the '586 Patent;
- C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Apotex, its affiliates and subsidiaries, and all persons and entities acting in concert with Apotex from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes the '586 Patent, including the ANDA Product described in ANDA No. 210725;
- D. The entry of an order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of ANDA No. 210725 shall be no earlier than the expiration date of the '586 Patent, or any later expiration of exclusivity for the '586 Patent, including any extensions or regulatory exclusivities;
- E. A declaration under 28 U.S.C. § 2201 that if Apotex, its officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engages in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in

ANDA No. 210725, it will constitute an act of direct and/or indirect infringement of the '586 Patent;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Apotex engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes the '586 Patent, or induces or contributes to such conduct, prior to the expiration of the '586 Patent, or any later expiration of exclusivity for the '586 Patent, including any extensions or regulatory exclusivities;

G. The entry of judgment declaring that Apotex's acts render this case an exceptional case, and awarding Plaintiffs their attorneys' fees pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

H. An award to Plaintiffs of their costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: July 3, 2018

OF COUNSEL:

Christopher N. Sipes
Jeffrey Lerner
Jeremy D. Cobb
Alexander R. Trzeciak
Won Ho ("Daniel") Cho
COVINGTON & BURLING, LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
(202) 662-6000

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5246
(973) 286-6700
clizza@saul.com

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals,
Inc. and Boehringer Ingelheim
International GmbH*

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 17-7887 (MAS)(LHG) (consolidated) is related to the matter in controversy because the matter in controversy involves at least United States Patent No. 8,426,586 and the same drug product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: July 3, 2018

OF COUNSEL:

Christopher N. Sipes
Jeffrey Lerner
Jeremy D. Cobb
Alexander R. Trzeciak
Won Ho (“Daniel”) Cho
COVINGTON & BURLING, LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
(202) 662-6000

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5246
(973) 286-6700
clizza@saul.com

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals,
Inc. and Boehringer Ingelheim
International GmbH*

EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GILOTRIF safely and effectively. See full prescribing information for GILOTRIF.

GILOTRIF® (afatinib) tablets, for oral use

Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1.1) 1/2018
Dosage and Administration (2.1) 1/2018

INDICATIONS AND USAGE

GILOTRIF is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test (1.1)
Limitation of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have resistant EGFR mutations (1.1)
- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (1.2)

DOSAGE AND ADMINISTRATION

- Recommended dose: 40 mg orally, once daily (2.2)
- Renal impairment: 30 mg orally, once daily in patients with severe renal impairment (2.2, 8.6, 12.3)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, 30 mg, and 20 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Diarrhea: Diarrhea may result in dehydration and renal failure. Withhold GILOTRIF for severe and prolonged diarrhea not responsive to anti-diarrheal agents. (2.3, 5.1)

- Bullous and exfoliative skin disorders: Severe bullous, blistering, and exfoliating lesions occurred in 0.2% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)
- Interstitial lung disease (ILD): Occurs in 1.6% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)
- Hepatic toxicity: Fatal hepatic impairment occurs in 0.2% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- Keratitis: Occurs in 0.7% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)
- Embryo-fetal toxicity: Can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) were diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of P-gp inhibitors can increase afatinib exposure. Reduce GILOTRIF by 10 mg per day if not tolerated. Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated. (2.4, 7)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2018

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE**

- 1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer
- 1.2 Previously Treated, Metastatic Squamous NSCLC

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC
- 2.2 Recommended Dose
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Dose Modifications for Drug Interactions

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Diarrhea
- 5.2 Bullous and Exfoliative Skin Disorders
- 5.3 Interstitial Lung Disease (ILD)
- 5.4 Hepatic Toxicity
- 5.5 Keratitis
- 5.6 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer
- 14.2 Previously Treated, Metastatic Squamous NSCLC

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see *Clinical Pharmacology (12.1)* and *Clinical Studies (14.1)*].

Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations [see *Clinical Studies (14.1)*].

1.2 Previously Treated, Metastatic Squamous NSCLC

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC

Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of non-resistant EGFR mutations in tumor specimens [see *Indications and Usage (1.1)* and *Clinical Studies (14.1)*].

Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at:

<http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dose

The recommended dose of GILOTRIF is 40 mg orally, once daily until disease progression or no longer tolerated by the patient.

Severe Renal Impairment

The recommended dose of GILOTRIF in patients with severe renal impairment (estimated glomerular filtration rate [eGFR*] 15 to 29 mL/min /1.73 m²) is 30 mg orally, once daily [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

*Use the Modification of Diet in Renal Disease [MDRD] formula to estimate eGFR.

Take GILOTRIF at least 1 hour before or 2 hours after a meal.

Do not take a missed dose within 12 hours of the next dose.

2.3 Dose Modifications for Adverse Reactions

Withhold GILOTRIF for any adverse reactions of:

- NCI CTCAE* Grade 3 or higher
- Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication [see *Warnings and Precautions (5.1)*]
- Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable [see *Warnings and Precautions (5.2)*]
- Renal impairment of Grade 2 or higher [see *Warnings and Precautions (5.1)*]

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 3.0

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinststitute GILOTRIF at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.

Permanently discontinue GILOTRIF for:

- Life-threatening bullous, blistering, or exfoliative skin lesions [*see Warnings and Precautions (5.2)*]
- Confirmed interstitial lung disease (ILD) [*see Warnings and Precautions (5.3)*]
- Severe drug-induced hepatic impairment [*see Warnings and Precautions (5.4)*]
- Persistent ulcerative keratitis [*see Warnings and Precautions (5.5)*]
- Symptomatic left ventricular dysfunction [*see Adverse Reactions (6.1)*]
- Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

2.4 Dose Modifications for Drug Interactions

P-gp Inhibitors

Reduce GILOTRIF daily dose by 10 mg if not tolerated for patients who require therapy with a P-glycoprotein (P-gp) inhibitor. Resume the previous dose after discontinuation of the P-gp inhibitor as tolerated [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

P-gp Inducers

Increase GILOTRIF daily dose by 10 mg as tolerated for patients who require chronic therapy with a P-gp inducer. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

GILOTRIF is available as:

40 mg tablets: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

30 mg tablets: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

20 mg tablets: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred in 697 (16%) of the 4257 patients who received GILOTRIF across 44 clinical trials. In LUX-Lung 3, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with GILOTRIF, of which 1.3% were Grade 3. In LUX-Lung 8, diarrhea occurred in 75% of patients treated with GILOTRIF (n=392), of which 10% were Grade 3 in severity and 0.8% were Grade 4 in severity. Renal impairment as a consequence of diarrhea occurred in 7% of patients treated with GILOTRIF, of which 2% were Grade 3 [*see Adverse Reactions (6.1)*].

For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [*see Dosage and Administration (2.3)*]. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours.

5.2 Bullous and Exfoliative Skin Disorders

Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In LUX-Lung 3, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. In LUX-Lung 8, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 70%, and the incidence of Grade 3 cutaneous reactions was 7%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 1.5% [see *Adverse Reactions (6.1)*].

Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [see *Dosage and Administration (2.3)*].

Postmarketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. The cases of TEN and SJS bullous skin reactions result from a distinct and separate mechanism of toxicity than the bullous skin lesions secondary to the pharmacologic action of the drug on the epidermal growth factor receptor. Discontinue GILOTRIF if TEN or SJS is suspected [see *Dosage and Administration (2.3)*].

5.3 Interstitial Lung Disease (ILD)

Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in Asian patients (2.3%; 38/1657) as compared to Whites (1.0%; 23/2241). In LUX-Lung 3, the incidence of Grade ≥ 3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In LUX-Lung 8, the incidence of Grade ≥ 3 ILD was 0.9% and resulted in death in 0.8% of GILOTRIF-treated patients.

Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD [see *Dosage and Administration (2.3)*].

5.4 Hepatic Toxicity

In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In LUX-Lung 3, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF, of which 3.5% had Grade 3-4 liver test abnormalities. In LUX-Lung 8, liver test abnormalities of any grade occurred in 6% of the patients treated with GILOTRIF, of which 0.2% had Grade 3-4 liver test abnormalities.

Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function [see *Dosage and Administration (2.3)*]. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

5.5 Keratitis

Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with GILOTRIF among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in LUX-Lung 3, with Grade 3 in 0.4%. In LUX-Lung 8, keratitis was reported in 0.3% patients; there were no patients with \geq Grade 3 keratitis.

Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued [see *Dosage and*

Administration (2.3)]. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye [*see Adverse Reactions (6.1)*]. Contact lens use is also a risk factor for keratitis and ulceration.

5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.1 and 8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Diarrhea [*see Warnings and Precautions (5.1)*]
- Bullous and Exfoliative Skin Disorders [*see Warnings and Precautions (5.2)*]
- Interstitial Lung Disease [*see Warnings and Precautions (5.3)*]
- Hepatic Toxicity [*see Warnings and Precautions (5.4)*]
- Keratitis [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to GILOTRIF for clinically significant adverse reactions in 4257 patients enrolled in LUX-Lung 3 (n=229) and LUX-Lung 8 (n=392), and 3636 patients with cancer enrolled in 42 studies of GILOTRIF administered alone or in combination with other anti-neoplastic drugs at GILOTRIF doses ranging from 10-70 mg daily or at doses 10-160 mg in other regimens. The mean exposure was 5.5 months. The population included patients with various cancers, the most common of which were NSCLC, breast, colorectal, brain, and head and neck.

The data described below reflect exposure to GILOTRIF as a single agent in LUX-Lung 3, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in LUX-Lung 8, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

EGFR Mutation-Positive, Metastatic NSCLC

The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 3). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure was 11 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of

64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%).

Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients in LUX-Lung 3 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In LUX-Lung 3, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

Tables 1 and 2 summarize common adverse reactions and laboratory abnormalities in LUX-Lung 3.

Table 1 Adverse Reactions Reported in $\geq 10\%$ of GILOTRIF-Treated Patients in LUX-Lung 3*

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3 [†] (%)	All Grades (%)	Grade 3 [†] (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis ¹	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis ²	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia ³	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*NCI CTCAE v 3.0

[†]None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration²Includes acne, acne pustular, dermatitis, acneiform dermatitis, dermatosis, drug eruption, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer³Includes paronychia, nail infection, nail bed infection

Other clinically important adverse reactions observed in patients treated with GILOTRIF but that occurred at a higher incidence in pemetrexed/cisplatin-treated patients and not listed elsewhere in section 6 include: decreased appetite (29% Grade 1-4, 4% Grade 3), nausea (25% Grade 1-4, 4% Grade 3), and vomiting (23% Grade 1-4, 4% Grade 3).

Table 2 Laboratory Abnormalities Occurring in $\geq 10\%$ of GILOTRIF Arm and at $\geq 2\%$ Higher Incidence than in Chemotherapy Arm in LUX-Lung 3*

Laboratory Abnormality	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase (ALT)	54	2	27	1
Increased alkaline phosphate	51	3	46	1
Decreased creatinine clearance	49	2	47	1
Increased aspartate aminotransferase (AST)	46	3	22	1
Decreased lymphocytes	38	9	32	14
Decreased potassium	30	8	11	3
Increased bilirubin	16	1	8	0

*NCI CTCAE v 3.0

Previously Treated, Metastatic Squamous NSCLC

The safety of GILOTRIF was evaluated in 392 GILOTRIF-treated patients with metastatic squamous NSCLC enrolled in a randomized, multicenter, open-label trial (LUX-Lung 8). Patients were required to have received at least four cycles of platinum-based chemotherapy, ECOG Performance Status (PS) 0 or 1, and normal left ventricular ejection fraction (LVEF). Patients received GILOTRIF 40 mg once daily (n=392) or erlotinib 150 mg once daily (n=395). Treatment continued until documented disease progression or intolerance to the therapy.

Among the 392 GILOTRIF-treated patients, the median age was 65 years, 53% were 65 years of age or older, 84% were male, 72% were White, 25% were Asian, ECOG PS 0 (32%) or 1 (68%). The median exposure was 2.1 months for patients treated with GILOTRIF, 15% were exposed for at least 6 months, and 5% were exposed for at least 12 months.

Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

Dose reductions due to adverse reactions were required in 27% of GILOTRIF-treated patients and discontinuation of GILOTRIF for adverse reactions was required for 20%. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (15%), rash/acne (5.9%), and stomatitis (3.1%). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%). Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in LUX-Lung 8.

Table 3 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in LUX-Lung 8*

Adverse Reaction	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis ¹	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis ²	70	7	70	11
Pruritus	10	0	13	0
Infections				
Paronychia ³	11	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2

*NCI CTCAE v 3.0

¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

²Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

³Includes paronychia, nail infection, nail bed infection

Table 4 Laboratory Abnormalities Occurring in $\geq 10\%$ of GILOTRIF Arm and at $\geq 2\%$ Higher Incidence than in Erlotinib Arm in LUX-Lung 8*

Laboratory Abnormality	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

*NCI CTCAE v 3.0

Other clinically important laboratory abnormalities observed in patients treated with GILOTRIF that are not listed in Table 4 are: increased alanine aminotransferase (10% Grade 1-4; 1% Grade 3-4), increased aspartate aminotransferase (7% Grade 1-4; 1% Grade 3-4), and increased bilirubin (3% Grade 1-4; 0 Grade 3-4).

Less Common Adverse Reactions

Other adverse reactions reported in patients treated with GILOTRIF in LUX-Lung 3 and LUX-Lung 8 include: *Skin and subcutaneous disorders*: nail disorders occurred in 9.2% and 2.8% of patients, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GILOTRIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Pancreatitis
- Toxic epidermal necrolysis/Stevens Johnson syndrome

7 DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Concomitant taking of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. There are no available data on the use of GILOTRIF in pregnant women. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages [see *Data*]. Advise a pregnant woman of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rabbits, administration of afatinib to pregnant animals at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post-implantation loss, and in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily), there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure based on AUC at the recommended human dose of 40 mg daily).

8.2 Lactation

Risk Summary

There are no data on the presence of afatinib in human milk or its effects on the breastfed infant or on milk production. Afatinib was present in the milk of lactating rats [see *Data*]. Because of the potential for serious adverse reactions in nursing infants from GILOTRIF, advise a lactating woman not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Data

Afatinib was present in the milk of lactating rats at concentrations 80 and 150 times higher than those found in plasma at 1 and 6 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF [see *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*].

Infertility

Based on results from an animal fertility study, GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

8.5 Geriatric Use

LUX-Lung 3 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In LUX-Lung 8, 53% of the 398 patients randomized to receive afatinib were 65 years of age or older and 11% were 75 years or older. In an exploratory subgroup analysis of LUX-Lung 8, the hazard ratio for overall survival (OS) in patients less than 65 years old was 0.68 (95% CI: 0.55, 0.85) and in patients 65 years or older was 0.95 (95% CI: 0.76, 1.19). No overall differences in safety were observed between patients 65 years and older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment. Dosing recommendations for patients with eGFR <15 mL/min/1.73 m² or on dialysis cannot be provided as GILOTRIF has not been studied in these patient populations [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

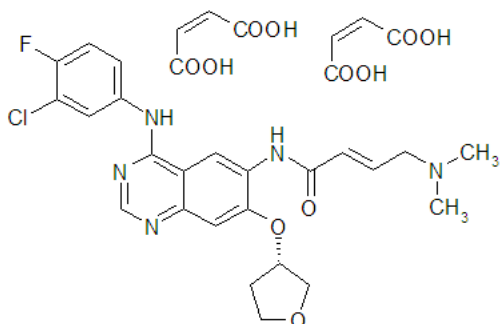
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase [<1.5 times upper limit of normal (ULN)]. Both subjects recovered.

11 DESCRIPTION

GILOTRIF tablets contain afatinib, a tyrosine kinase inhibitor which is a 4-anilinoquinazoline. Afatinib is presented as the dimaleate salt, with the chemical name 2-butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazoliny]-4-(dimethylamino)-, (2*E*)-, (2*Z*)-2-butenedioate (1:2). Its structural formula is:



Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of C₃₂H₃₃ClF₂N₅O₁₁, and a molecular weight of 718.1 g/mol.

GILOTRIF tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively). The inactive ingredients of GILOTRIF are the following: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and Coating: hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling. Certain mutations in EGFR, including non-resistant mutations in its kinase domain, can result in increased autophosphorylation of the receptor, leading to receptor activation, sometimes in the absence of ligand binding,

and can support cell proliferation in NSCLC. Non-resistant mutations are defined as those occurring in exons constituting the kinase domain of EGFR that lead to increased receptor activation and where efficacy is predicted by 1) clinically meaningful tumor shrinkage with the recommended dose of afatinib and/or 2) inhibition of cellular proliferation or EGFR tyrosine kinase phosphorylation at concentrations of afatinib sustainable at the recommended dosage according to validated methods. The most commonly found of these mutations are exon 21 L858R substitutions and exon 19 deletions.

Afatinib demonstrated inhibition of autophosphorylation and/or *in vitro* proliferation of cell lines expressing wild-type EGFR and in those expressing selected EGFR exon 19 deletion mutations, exon 21 L858R mutations, or other less common non-resistant mutations, at afatinib concentrations achieved in patients. In addition, afatinib inhibited *in vitro* proliferation of cell lines overexpressing HER2.

Treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of GILOTRIF (50 mg once daily) on the QTc interval was evaluated in an open-label, single-arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

12.3 Pharmacokinetics

Absorption and Distribution

Following oral administration of GILOTRIF tablets, time to peak afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Maximum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg GILOTRIF tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%.

A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition [*see Dosage and Administration (2.2)*].

Metabolism and Elimination

Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of afatinib is minimal.

In humans, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose.

The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients. Steady-state plasma concentrations are achieved within 8 days of repeat dosing of GILOTRIF resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max} .

Specific Populations

Renal Impairment: A pharmacokinetic study was conducted in 14 subjects with normal (eGFR ≥ 90 mL/min/1.73 m²) renal function, 8 subjects with moderate (eGFR=30 to 59 mL/min/1.73 m²) and 8 subjects with severe (eGFR=15 to 29 mL/min/1.73 m²) renal impairment. All subjects received a single 40 mg oral dose of GILOTRIF. The geometric mean AUC_{inf} for afatinib was 50% higher in subjects with severe renal impairment and was 22% higher in subjects with moderate renal impairment as compared to subjects with normal renal function. Geometric mean C_{max} was 22% higher in subjects with severe renal impairment and was comparable in subjects with moderate renal impairment as compared to subjects with normal renal function [see *Dosage and Administration (2.2) and Use in Specific Populations (8.6)*]. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m² or on dialysis.

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of GILOTRIF. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied [see *Use in Specific Populations (8.7)*].

Body Weight, Gender, Age, and Race: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

Drug Interactions

Effect of P-gp Inhibitors and Inducers on Afatinib: The effect of ritonavir dosing time relative to a single oral dose of GILOTRIF was evaluated in healthy subjects taking 40 mg of GILOTRIF alone as compared to those after ritonavir (200 mg twice daily for 3 days) co-administration at 6 hours after GILOTRIF administration. The relative bioavailability for AUC_{0-∞} and C_{max} of afatinib was 119% and 104% when co-administered with ritonavir, and 111% and 105% when ritonavir was administered 6 hours after taking GILOTRIF. In another study, when ritonavir (200 mg twice daily for 3 days) was administered 1 hour before a 20 mg single dose of GILOTRIF, exposure to afatinib increased by 48% for AUC_{0-∞} and 39% for C_{max} [see *Drug Interactions (7)*].

Pre-treatment with a potent inducer of P-gp, rifampicin (600 mg once daily for 7 days) decreased the plasma exposure to afatinib by 34% (AUC_{0-∞}) and 22% (C_{max}) [see *Drug Interactions (7)*].

P-glycoprotein (P-gp): Based on *in vitro* data, afatinib is a substrate and an inhibitor of P-gp.

Breast Cancer Resistance Protein (BCRP): Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

Effect of CYP450 Enzyme Inducers and Inhibitors on Afatinib: *In vitro* data indicated that drug-drug interactions with GILOTRIF due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. In humans, enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Effect of Afatinib on CYP450 Enzymes: Afatinib is not an inhibitor or an inducer of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4) in cultured primary human hepatocytes. Therefore, afatinib is unlikely to affect the metabolism of other drugs that are substrates of CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with afatinib.

A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. No mutagenic or genotoxic potential was identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as in the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay, and an *in vivo* 4-week oral mutation study in the Muta™ Mouse.

In a dedicated fertility study, male and female rats received afatinib daily by oral administration at doses of 4, 6, or 8 mg/kg. In males at doses of 6 mg/kg (approximately equal to the exposure by AUC in patients at the recommended human dose of 40 mg daily) or greater, there was an increase in the incidence of low or no sperm count, though overall fertility was not affected; decreases in sperm count were supported by findings of increased apoptosis in the testes and atrophy in the seminal vesicles and the prostate in general toxicology studies. In females at the high dose of 8 mg/kg (approximately 0.63 times the exposure by AUC in patients at the recommended human dose of 40 mg daily), there was a mild decrease in the number of corpora lutea along with a mild increase in post-implantation loss due to early resorptions. In a 4-week general toxicology study, female rats had decreases in ovarian weights at all dose levels; organ weight had not fully recovered by the end of a 2-week recovery period.

14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy of GILOTRIF for the first-line treatment of patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) was established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or intravenous pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) once every 21 days for up to 6 cycles (n=115). Randomization was stratified according to EGFR mutation category (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and OS. EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*® EGFR RGQ PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment.

Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were White and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

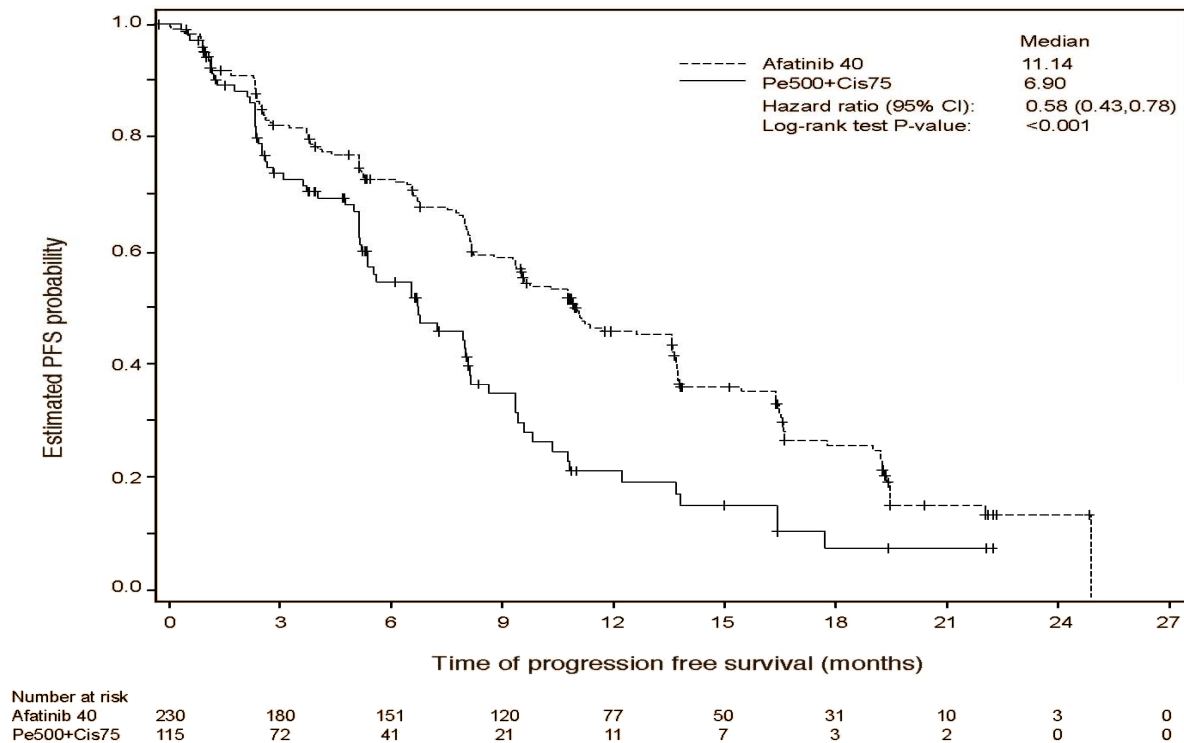
A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 5 and Figure 1. There was no statistically significant difference for OS between the treatment arms at the final pre-planned analysis.

Table 5 Efficacy Results in LUX-Lung 3

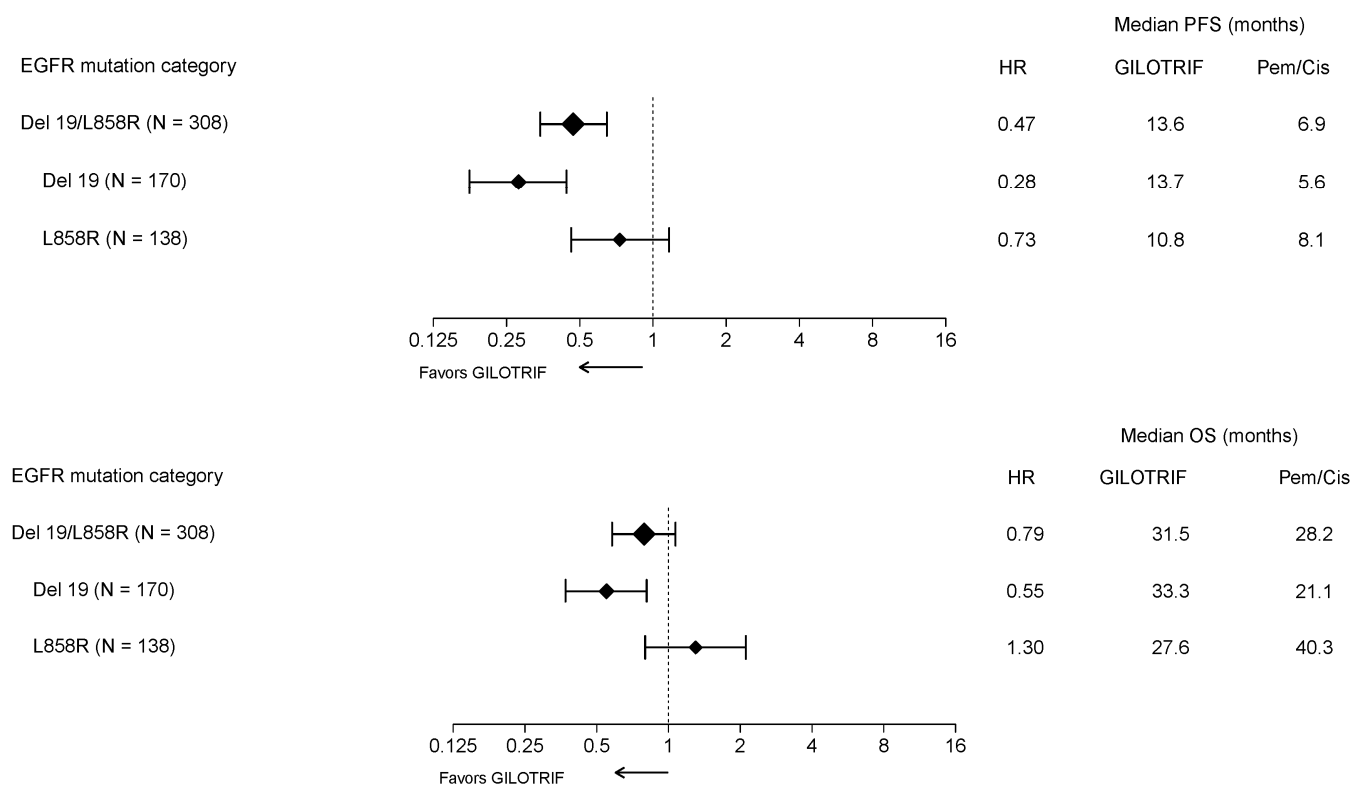
	GILOTRIF (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-Free Survival by IRC		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-Free Survival (months)	11.1	6.9
95% CI	(9.6, 13.6)	(5.4, 8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test p-value*	<0.001	
Overall Survival		
Number of Deaths, N (%)	140 (60.9%)	73 (63.5%)
Median Overall Survival (months)	28.2	28.2
95% CI	(24.6, 33.6)	(20.7, 33.2)
HR (95% CI)	0.88 (0.66, 1.17)	
Stratified Log-Rank Test p-value*	0.39	
Overall Response Rate (CR + PR) by IRC		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

*Stratified by EGFR mutation status and race.

HR=hazard ratio; CR=complete response; PR=partial response

Figure 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group in LUX-Lung 3

Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2.

Figure 2 Forest Plots of PFS and OS by EGFR Mutation Subgroups in LUX-Lung 3

Overall Response Rate In Other EGFR Mutations

The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]).

- LUX-Lung 2 was a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue.
- LUX-Lung 3 was a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m² plus pemetrexed 500 mg/m² every 21 days for up to 6 cycles. EGFR status was determined by the *therascreen*[®] EGFR RGQ PCR Kit.
- LUX-Lung 6 was a randomized, multicenter study comparing treatment with afatinib 40 mg to intravenous gemcitabine 1000 mg/m² on day 1 and day 8 plus cisplatin 75 mg/m² on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the *therascreen*[®] EGFR RGQ PCR Kit.

Among the 75 GILOTRIF treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 66% were female, 97% were Asian, 3% were other races, 38% had an ECOG PS of 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received no prior systemic therapy for advanced or metastatic disease.

The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.

Table 6 IRC-Assessed Responses in Patients with NSCLC Harboring EGFR Mutations G719X, L861Q, and/or S768I from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

EGFR Mutation	Number of GILOTRIF Treated Patients (N=32)	Number of Confirmed Responses (N=21)	Duration of Response (months) (N=21)
S768I	1	1	37.3
S768I and G719X	5	4	4.1, 13.2, 15.2, 29.5+
S768I and L858R	2	1	34.5+
G719X	8	6	5.7+, 8.1, 9.6, 23.5+, 25.2, 31.8+
G719X and L861Q	3	2	2.8+, 6.8
L861Q	12	7	2.8, 4.0, 4.1, 8.3+, 12.9, 15.2, 20.6
L861Q and Del 19	1	0	NA

+ response ongoing at time of censoring

14.2 Previously Treated, Metastatic Squamous NSCLC

The efficacy and safety of GILOTRIF were demonstrated in a randomized, multicenter, open-label, active-controlled study (LUX-Lung 8 [NCT01523587]). Patients were required to have histologically documented, metastatic squamous NSCLC and have experienced disease progression following an adequate course (≥ 4 cycles) of a platinum-based doublet chemotherapy regimen. Patients were randomized (1:1) to receive GILOTRIF 40 mg or erlotinib 150 mg orally once daily until progression. Randomization was stratified by region (Eastern Asia vs other). The major efficacy outcome measure was PFS as assessed by an IRC using RECIST v 1.1. Additional efficacy outcome measures were OS and ORR as assessed by IRC.

Baseline patient demographics of the 795 patients were: median age 64 years (range: 35 to 88); 73% White; 24% Asian; 84% male; 33% ECOG performance status (PS) 0 and 67% ECOG PS 1; and 95% current or former smokers. With regard to tumor characteristics, 96% had squamous cell histology and 3.5% had mixed cell histology. All patients received platinum-based doublet therapy.

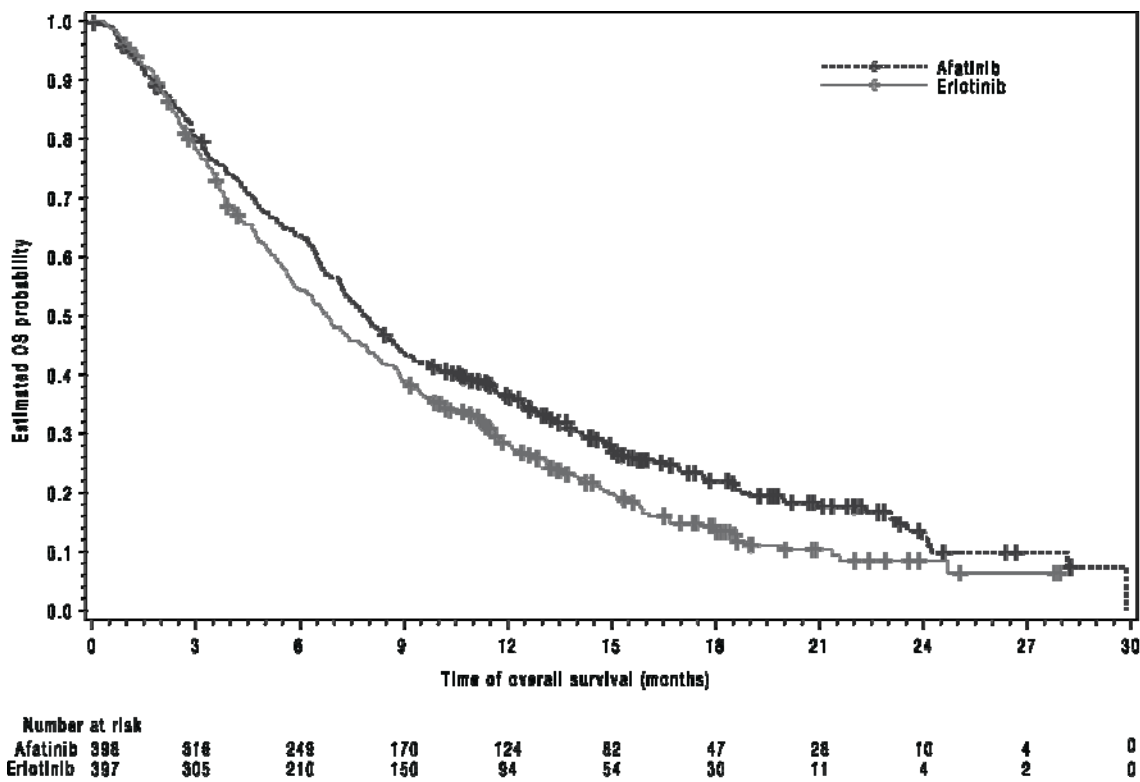
The study demonstrated a statistically significant improvement in PFS and OS for patients randomized to GILOTRIF as compared with erlotinib (see Table 7 and Figure 3).

Table 7 Efficacy Results in LUX-Lung 8

	GILOTRIF	Erlotinib
Overall Survival		
	N=398	N=397
Number of Deaths, N (%)	307 (77%)	325 (82%)
Median overall survival (months)	7.9	6.8
95% CI	(7.2, 8.7)	(5.9, 7.8)
HR (95% CI)	0.81 (0.69, 0.95)	
p-value*	0.008	
Progression-Free Survival (PFS) by IRC		
	N=335	N=334
Number of Events, N (%)	202 (60%)	212 (64%)
Median PFS (months)	2.4	1.9
95% CI	(1.9, 2.9)	(1.9, 2.2)
HR (95% CI)	0.82 (0.68, 0.998)	
p-value*	0.0427	
Overall Response Rate (ORR) by IRC		
	N=335	N=334
ORR	3%	2%
(95% CI)	(1.7, 5.8)	(0.8, 4.3)

*Log-rank test stratified by region.

HR=hazard ratio

Figure 3 Kaplan-Meier Curves of Overall Survival in LUX-Lung 8

16 HOW SUPPLIED/STORAGE AND HANDLING

GILOTRIF tablets are available as follows:

40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0138-30

30 mg: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0137-30

20 mg: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0141-30

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Dispense medication in the original container to protect from exposure to high humidity and light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Diarrhea

Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

Bullous and Exfoliative Skin Disorders

Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF [see *Warnings and Precautions (5.2)*].

Interstitial Lung Disease

Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever [see *Warnings and Precautions (5.3)*].

Hepatic Toxicity

Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem [e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy] [see *Warnings and Precautions (5.4)*].

Keratitis

Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) [see *Warnings and Precautions (5.5)*].

Left Ventricular Dysfunction

Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

Instructions for Taking GILOTRIF

Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating [*see Dosage and Administration (2.2)*]. Advise patients not to take a missed dose within 12 hours of the next dose.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that GILOTRIF can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF and for at least 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.1, 8.3)*].

Lactation

Advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.2)*].

Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from GILOTRIF [*see Use in Specific Populations (8.3)*].

Distributed by:

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Licensed from:

Boehringer Ingelheim International GmbH

GILOTRIF is a registered trademark of and used under license from Boehringer Ingelheim International GmbH.

The other brands listed are trademarks of their respective owners and are not trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.

Copyright © 2018 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

IT5562RA112018

Patient Information
GILOTRIF® (JEE-loh-trif)
(afatinib) tablets

What is GILOTRIF?

GILOTRIF is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that:

- has certain (non-resistant) abnormal epidermal growth factor receptor (EGFR) gene(s). Your healthcare provider will perform a test to make sure that GILOTRIF is right for you.
- has spread to other parts of the body (metastatic), and
- has not been previously treated for metastatic lung cancer

It is not known if GILOTRIF is safe and effective in treating people with lung cancer that has resistant abnormal EGFR genes.

or

is used to treat people with squamous cell lung cancer that:

- has spread to other parts of the body, and
- has been previously treated with chemotherapy that contains platinum.

It is not known if GILOTRIF is safe and effective in children.

Before you take GILOTRIF, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver problems
- have lung or breathing problems other than lung cancer
- have a history of severe dry eye or any other eye problems. Tell your doctor if you wear contact lenses.
- have heart problems
- are pregnant or plan to become pregnant. GILOTRIF can harm your unborn baby. You should not become pregnant while taking GILOTRIF.
 - Women who are able to become pregnant should use effective birth control during treatment with GILOTRIF and for at least 2 weeks after your last dose of GILOTRIF. Talk to your doctor about birth control methods that may be right for you.
 - Tell your doctor right away if you become pregnant or think you are pregnant while taking GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. Do not breastfeed while taking GILOTRIF and for 2 weeks after your last dose of GILOTRIF. Talk to your doctor about the best way to feed your baby if you take GILOTRIF.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GILOTRIF may affect the way other medicines work, and other medicines may affect the way GILOTRIF works.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take GILOTRIF?

- Take GILOTRIF exactly as your doctor tells you to take it.
- Your doctor will tell you how many GILOTRIF tablets to take and when to take them. Do not change your dose or stop GILOTRIF unless your doctor tells you to.
- Take GILOTRIF on an empty stomach at least 1 hour before a meal or 2 hours after a meal.
- If you miss a dose of GILOTRIF, take it as soon as you remember. If it is within 12 hours of your next dose, skip the dose and just take your next dose at your regular time. Do not take 2 doses of GILOTRIF at the same time.
- If you take too much GILOTRIF, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking GILOTRIF?

Limit your time in the sun. GILOTRIF can make your skin sensitive to the sun. You could get or have worsening rash or acne. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin while you are taking GILOTRIF if you have to be in sunlight.

What are the possible side effects of GILOTRIF?

GILOTRIF may cause serious side effects, including:

- **diarrhea.** Diarrhea is common with GILOTRIF and may sometimes be severe. Severe diarrhea can cause loss of too much body fluid (dehydration) and kidney problems that can sometimes lead to death. During your treatment with GILOTRIF, your doctor should prescribe medicines to treat diarrhea. Take this medicine exactly as your doctor tells you to. Tell your doctor if you have diarrhea. Get medical attention right away if your diarrhea does not go away or

becomes severe.

- **skin reactions.** GILOTRIF can cause redness, rash, and acne. It is important to get treatment for skin reactions as soon as you notice them. Take medicines to help skin reactions exactly as your doctor tells you to. Get medical attention right away if you develop severe skin reactions such as peeling or blistering of the skin, or blisters in your mouth.
- **lung or breathing problems.** GILOTRIF may cause inflammation of the lung that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening lung problems, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, or fever.
- **liver problems.** GILOTRIF can cause liver problems that can sometimes lead to death. Tell your doctor right away if you have any symptoms of a liver problem which may include:
 - yellowing of your skin or the white part of your eyes (jaundice)
 - dark or brown (tea colored) urine
 - pain on the upper right side of your stomach area (abdomen)
 - bleeding or bruising more easily than normal
 - feeling very tired

Your doctor will do blood tests to check your liver function during your treatment with GILOTRIF.

- **eye problems.** Tell your doctor right away if you have symptoms of eye problems which may include:
 - eye pain, swelling, redness, or tearing
 - blurred vision
 - sensitivity to light
 - other changes in your vision
- **heart problems.** Tell your doctor right away if you have symptoms of a heart problem which may include:
 - new or worsening shortness of breath while at rest or with activity
 - cough
 - tiredness
 - swelling of your ankles, feet, or legs
 - feeling that your heart is pounding or racing (palpitations)
 - sudden weight gain

The most common side effects of GILOTRIF include:

- diarrhea
- rash
- mouth sores
- nail inflammation
- dry skin
- acne
- decreased appetite
- nausea
- vomiting
- itching

GILOTRIF may cause decreased fertility in females and males. Talk to your doctor if you have concerns about fertility.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GILOTRIF. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GILOTRIF?

- Store GILOTRIF at room temperature 68°F to 77°F (20°C to 25°C).
- Keep GILOTRIF in the original container and keep the container tightly closed.
- Keep GILOTRIF away from moisture and light.
- Safely throw away (discard) any GILOTRIF that is out of date or no longer needed.

Keep GILOTRIF and all medicines out of the reach of children.

General information about GILOTRIF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GILOTRIF for a condition for which it was not prescribed. Do not give GILOTRIF to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about GILOTRIF that is written for health professionals.

What are the ingredients in GILOTRIF?

Active ingredient: afatinib

Inactive ingredients: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate. **Tablet Coating:** hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

Licensed from: Boehringer Ingelheim International GmbH

GILOTRIF is a registered trademark of and used under license from Boehringer Ingelheim International GmbH.

Copyright © 2018 Boehringer Ingelheim International GmbH ALL RIGHTS RESERVED

IT5562RA112018

For more information, go to www.gilotrif.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906, or scan the code to go to www.gilotrif.com.



This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: January 2018

EXHIBIT B

(12) **United States Patent**
Soyka et al.

(10) **Patent No.:** **US 8,426,586 B2**
(45) **Date of Patent:** **Apr. 23, 2013**

(54) **PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS**

(75) Inventors: **Rainer Soyka**, Biberach (DE); **Werner Rall**, Mittelbiberach (DE); **Juergen Schnaubelt**, Oberhoefen/Warthausen (DE); **Peter Sieger**, Mittelbiberach (DE); **Christian Kulinna**, Attenweiler (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1851 days.

(21) Appl. No.: **11/457,622**

(22) Filed: **Jul. 14, 2006**

(65) **Prior Publication Data**

US 2007/0027170 A1 Feb. 1, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/941,116, filed on Sep. 15, 2004, now abandoned.

(60) Provisional application No. 60/517,777, filed on Nov. 6, 2003.

(30) **Foreign Application Priority Data**

Oct. 17, 2003 (DE) 103 49 113

(51) **Int. Cl.**

C07D 239/84 (2006.01)

C07D 215/44 (2006.01)

(52) **U.S. Cl.**

USPC **544/153**; 546/153

(58) **Field of Classification Search** 544/153;
546/153

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,127,374	A	10/2000	Bridges	
6,297,258	B1	10/2001	Wissner et al.	
6,627,634	B2	9/2003	Himmelsbach et al.	
6,972,288	B1	12/2005	Himmelsbach et al.	
7,019,012	B2 *	3/2006	Himmelsbach et al.	514/266.22
7,220,750	B2	5/2007	Himmelsbach et al.	
7,846,936	B2	12/2010	Hilberg et al.	
7,960,546	B2	6/2011	Schroeder et al.	
RE43,431	E	5/2012	Himmelsbach et al.	
8,188,274	B2	5/2012	Schroeder et al.	
2002/0169180	A1	11/2002	Himmelsbach et al.	
2002/0173509	A1	11/2002	Himmelsbach et al.	
2003/0149062	A1	8/2003	Jung et al.	
2003/0158196	A1	8/2003	Jung et al.	
2003/0225079	A1	12/2003	Singer et al.	
2004/0158065	A1	8/2004	Barth et al.	
2005/0043233	A1	2/2005	Stefanic et al.	
2005/0085495	A1	4/2005	Soyka et al.	
2006/0058311	A1	3/2006	Munzert et al.	
2006/0100223	A1	5/2006	Himmelsbach et al.	
2007/0099918	A1	5/2007	Singer et al.	

2007/0185091	A1	8/2007	Himmelsbach et al.
2008/0254040	A1	10/2008	Stefanic et al.
2009/0238828	A1	9/2009	Munzert et al.
2009/0306044	A1	12/2009	Solca et al.
2009/0306101	A1	12/2009	Solca et al.
2009/0306378	A1	12/2009	Schroeder et al.
2009/0318480	A1	12/2009	Solca
2010/0010023	A1	1/2010	Himmelsbach et al.
2010/0069414	A1	3/2010	Himmelsbach et al.
2010/0144639	A1	6/2010	Singer et al.
2011/0039863	A1	2/2011	Hilberg et al.
2011/0046168	A1	2/2011	Himmelsbach et al.
2011/0142929	A1	6/2011	Messerschmid et al.
2011/0171289	A1	7/2011	Stefanic et al.
2011/0207929	A1	8/2011	Schroeder et al.
2011/0207932	A1	8/2011	Schroeder et al.
2012/0107399	A1	5/2012	Barta
2012/0157472	A1	6/2012	Larsen et al.

FOREIGN PATENT DOCUMENTS

DE	19911366	A1	9/2000
EP	0302967	A2	2/1989
EP	0566226	A1	10/1993
WO	9520045	A1	7/1995
WO	9630347	A1	10/1996
WO	9633980	A1	10/1996
WO	9702266	A1	1/1997
WO	9738983	A1	10/1997
WO	9843960	A1	10/1998
WO	9906378	A1	2/1999
WO	9906396	A1	2/1999
WO	9909016	A1	2/1999
WO	9935146	A1	7/1999

(Continued)

OTHER PUBLICATIONS

Abstract in English (2000) for DE19911366 in German cited herein. Fortin, S. et al., "A new Bis (2,2,2,-trifluoroethyl)phosphonate for the Synthesis of Z-Unsaturated N-Methoxy-N-methylamides". Journal Org. Chemistry, 2002, vol. 67, No. 15, p. 5437-5439.

International Search Report for PCT/EP2004/011378 mailed on May 10, 2005.

Meyer, J.K. et al., "Asymmetric Synthesis of B-Amino Acid Derivatives via Catalytic Conjugate Addition of Hydrazoic Acid to Unsaturated Imides". J. Am. Chem. Soc., 1999, 121, p. 8959-8960.

New Experimental Chemistry Course 14, Synthesis and Reaction of Organic Compounds I, Published: Nov. 20, 1977, Edited by: The Chemical Society of Japan. Issued by Shingo Iizumi, Publisher: Maruzen Company, Ltd., English Translation of section referred to by the Examiner, from the middle of p. 238 to entire p. 239.

U.S. Appl. No. 12/706,819 filed Feb. 17, 2010.

Berge, S. M. et al., "Pharmaceutical Salts", Journal of Pharmaceutical Sciences, Jan. 1977, vol. 66, No. 1, pp. 1-19.

Primary Examiner — Paul V. Ward

(74) Attorney, Agent, or Firm — Michael P. Morris; Anthony P. Bottino

(57) **ABSTRACT**

An improved process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and related aminocrotonyl compounds and the preparation of a suitable salt of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline for use as a pharmaceutically active substance.

11 Claims, 2 Drawing Sheets

US 8,426,586 B2

Page 2

FOREIGN PATENT DOCUMENTS

WO	0031068	A1	6/2000
WO	0055141	A1	9/2000
WO	WO0051991		9/2000
WO	0078735	A1	12/2000
WO	WO0250043		6/2002
WO	03094921	A2	11/2003
WO	2004096224	A2	11/2004
WO	2005037824	A2	4/2005

WO	2006018182	A1	2/2006
WO	2007054550	A1	5/2007
WO	2007054551	A1	5/2007
WO	2007085638	A1	8/2007
WO	2008034776	A1	3/2008
WO	2009147238	A1	12/2009
WO	2010081817	A1	7/2010
WO	2011069962	A1	6/2011

* cited by examiner

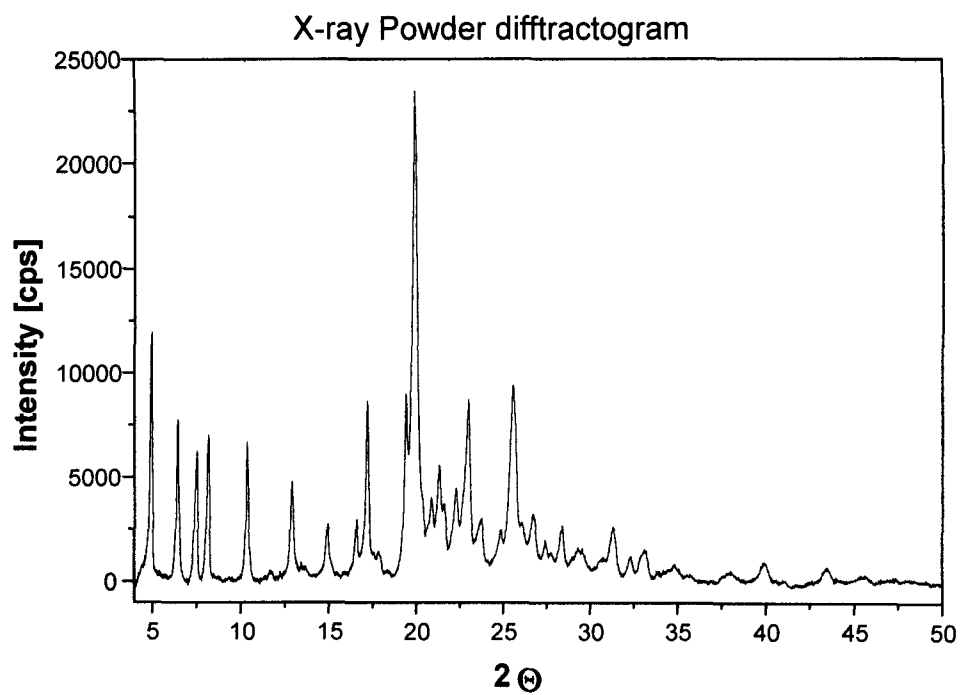


FIG. 1

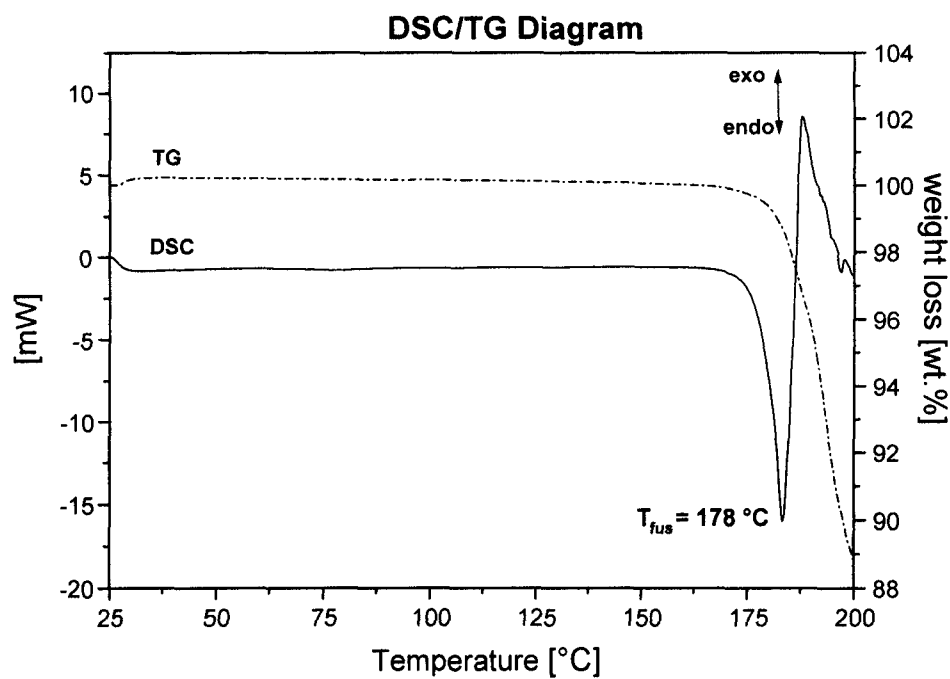


FIG. 2

US 8,426,586 B2

1

PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS

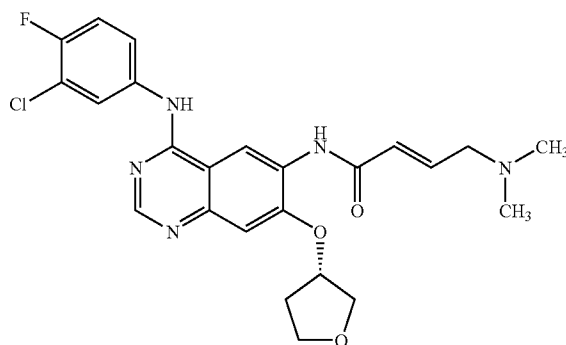
RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 10/941, 116, filed Sep. 15, 2004, which in turn claimed benefit of U.S. Ser. No. 60/517,777, filed Nov. 6, 2003, and priority from German Application No. 103 49 113.9, filed Oct. 17, 2003, each of which related applications is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to an improved process for preparing aminocrotonyl compounds such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and the physiologically acceptable salts thereof, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, as well as 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate and the use thereof for preparing pharmaceutical compositions.

4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline has the following structure:

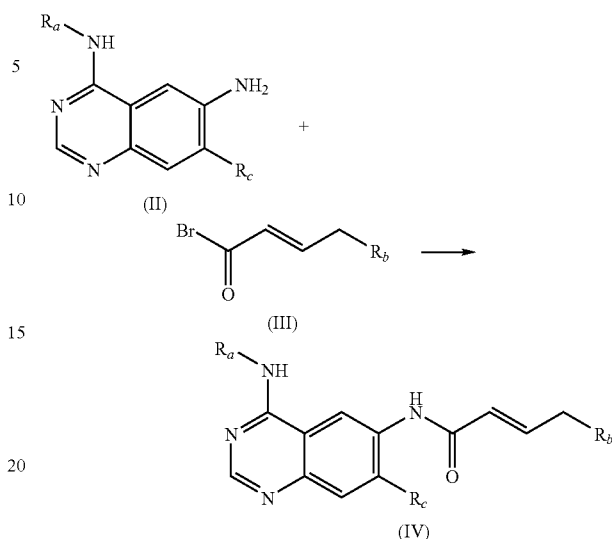


and is already known from WO 02/50043, which describes compounds with valuable pharmacological properties, including in particular an inhibiting effect on signal transduction mediated by tyrosinekinases and an inhibitory effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R). Therefore, compounds of this type are suitable for the treatment of diseases, particularly for the treatment of tumoral diseases, diseases of the lungs and respiratory tract and diseases of the gastrointestinal tract and bile duct and gall bladder.

WO 02/50043 discloses a method of preparation wherein aminocrotonyl compounds (IV) such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline are prepared in a one-pot reaction from the corresponding aniline component (II), bromocrotonic acid (III), oxalyl chloride and a secondary amine (see Diagram 1).

2

Diagram 1:



In this process the yield was at most 50%. In addition, purification was generally carried out by column chromatography. Therefore, the method of preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline was not suitable on an industrial scale. Furthermore, the method had the disadvantage that bromocrotonic acid is not commercially available in large amounts and also the corresponding methyl bromocrotonate is only available in a purity of approx. 80%. These circumstances also militate against the suitability of this process for the industrial production of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline.

In the light of the above disadvantages of the known method of production, the aim of the present invention is to provide a process which allows the production of aminocrotonylarylamides, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, using highly pure starting materials which are readily available and without any great technical expenditure. This new process should therefore also be suitable for synthesis on an industrial scale and hence for commercial application.

This aim is achieved by the process according to the invention for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and other aminocrotonyl compounds. In addition to being industrially practicable with high yields the method of synthesis according to the invention also has the advantages of very good chemical purities and a low cis content of less than 0.1%.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-ray powder diffractogram of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate; and

FIG. 2 is a diagram depicting Thermoanalysis of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

US 8,426,586 B2

3

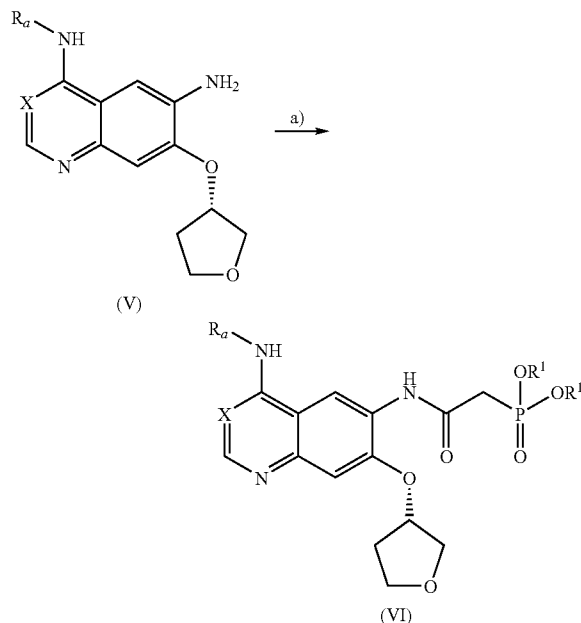
In the process according to the invention the corresponding aminoaryl compound (V) is reacted with a di-(C₁₋₄-alkyl)-phosphonoacetic acid, preferably with diethylphosphonoacetic acid, in suitable solvents, after corresponding activation, preferably with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole or propanephosphonic anhydride, particularly preferably with 1,1-carbonyldiimidazole, according to Diagram 2. The solvent used may be for example tetrahydrofuran (THF), dimethylformamide (DMF) or ethyl acetate.

The activation may be carried out by any possible method of amide linking, i.e. for example with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole, DCC(N,N-dicyclohexylcarbodiimide), EDC (N'-dimethylaminopropyl)-N-ethylcarbodiimide), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), thiazolidine-2-thione or by conversion into the corresponding acid chloride, possibly using thionyl chloride. If desired the activation may be carried out using organic bases such as triethylamine or pyridine, while DMAP (dimethylaminopyridine) may additionally be added. Suitable solvents include DMF, THF, ethyl acetate, toluene, chlorinated hydrocarbons or mixtures thereof.

In the formulae that follow X denotes a methyne group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R¹ denotes a straight-chain or branched C₁₋₄-alkyl group.

The process is preferably used for compounds wherein X denotes a nitrogen atom, R_a denotes a 3-chloro-4-fluorophenyl group and R¹ denotes an ethyl group.

Diagram 2:



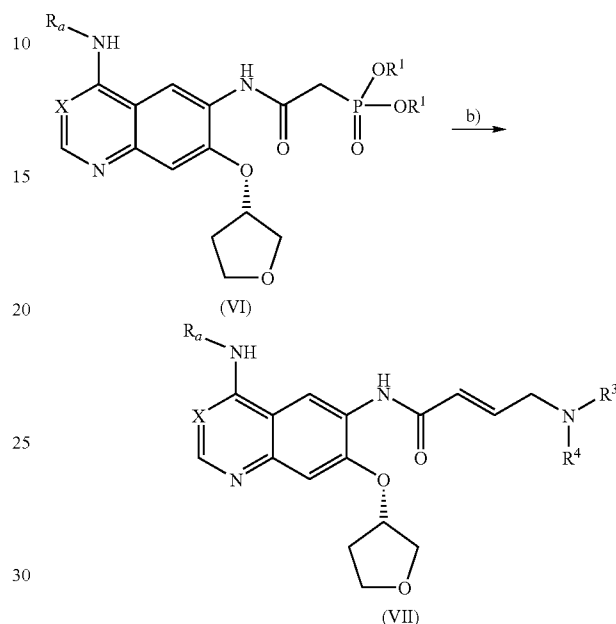
a) di-(C₁₋₄-alkyl)-phosphonoacetic Acid, Activating Agent

The arylamide (VI) thus obtained in a high yield and high purity is reacted with the corresponding 2-aminoacetaldehyde using suitable organic or inorganic bases in the sense of a Wittig-Horner-Emmons reaction (Diagram 3). This reaction may be carried out directly or after isolation of the compound (VI), for example by precipitation by the addition of tert-butylmethyl ether, for example. Suitable bases include for example DBU (1,5-diazabicyclo[4.3.0]non-5-ene), sodium

4

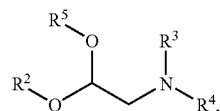
hydroxide and potassium hydroxide, of which sodium hydroxide and potassium hydroxide are preferred and potassium hydroxide is particularly preferred. Instead of the aldehyde a corresponding equivalent, e.g. a hydrate or acetal, may be used, from which the aldehyde is released (beforehand or in situ).

Diagram 3:



b) Aldehyde, Base, THF/Water

The acetals used may be for example compounds of the following general type:



wherein R² to R⁵ in each case represent a straight-chain or branched C₁-C₄-alkyl group, while the groups may be identical or different.

45 Preferably

R³ and R⁴ in each case represent a methyl group and R² and R⁵ in each case represent an ethyl group.

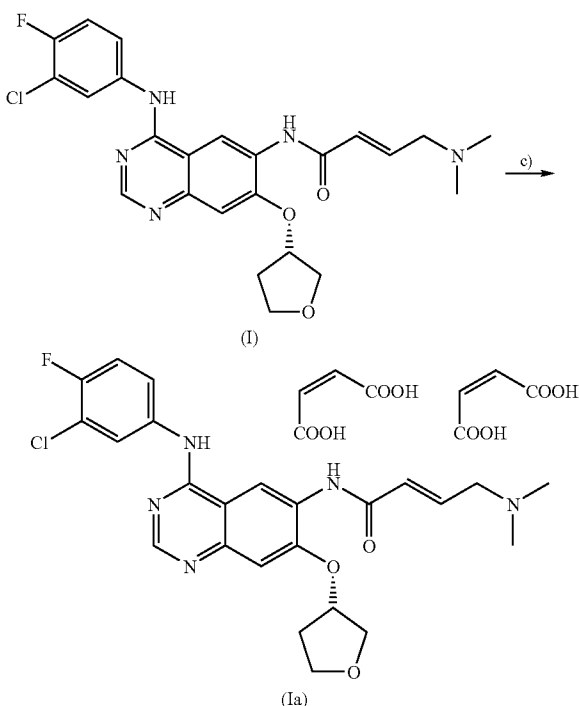
The aminocrotonylarylamide of formula (VII) thus obtained, for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of formula (I), may then be converted into the salts thereof, particularly the physiologically acceptable salts thereof, by methods known per se. Preferably they are converted into fumarates, tartrates or maleates. The dimaleate of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of structural formula (Ia) and the conversion of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into its dimaleate as shown in Diagram 4 are particularly preferred. To do this the compound (I) is dissolved in a suitable solvent, such as for example methanol, isopropanol, n-butanol or ethanol, optionally with the addition of water, preferably ethanol, and combined with crystalline maleic acid or a maleic acid solution, with heating. When ethanol is used as solvent the work is preferably done at a

US 8,426,586 B2

5

temperature of between 60 and 75° C. using an ethanolic maleic acid solution. The reaction conditions are preferably selected so that the desired salt crystallises out as quickly as possible. Preferably approx. 2 equivalents of maleic acid are used. After crystallisation has set in the mixture is cooled to ambient temperature, stirred and the crystals consisting of compound (Ia) are separated off.

Diagram 4:



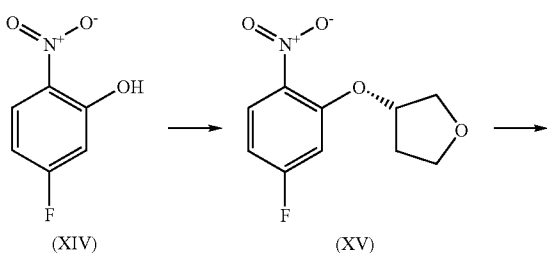
c) Maleic Acid, Ethanol

The starting compound of formula (V) may for example be prepared as follows in accordance with methods known from the literature.

The quinoline components of formula (V), wherein X=CH, may be obtained starting from commercially obtainable 3-fluoro-6-nitrophenol (XIV) by alkylation, exchanging the fluorine atom for an amino group and reacting with ethoxyacrylic acid esters, ethoxymethylene-cyanoacetic acid esters or ethoxymethylene-malonic acid esters (Diagram 5a).

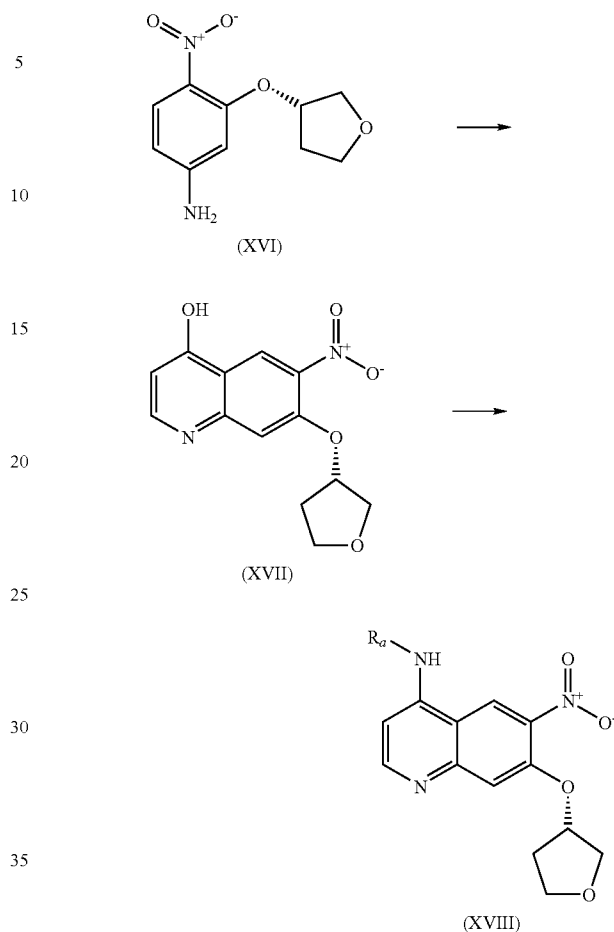
The compound thus obtained (XVII) is then converted into the compound (XVIII) as described in Diagram 6 for the quinazoline analogue

Diagram 5a:



6

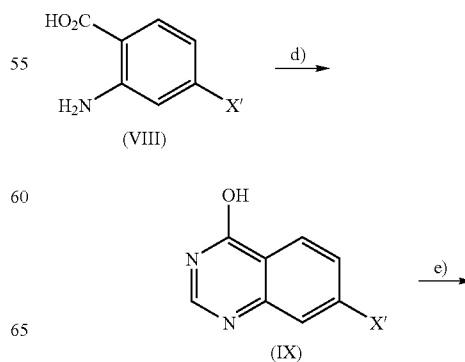
-continued



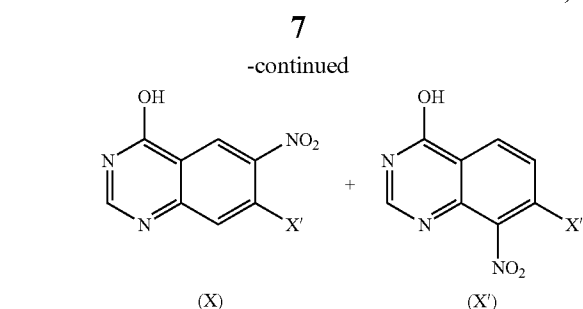
To prepare the compound (V) wherein X=N the following procedure is used:

Starting from commercially obtainable 4-chloro-anthranilic acid (VIII; X'=Cl) the quinazolinone (IX) is obtained by reaction with formamidine-acetate, and is then nitrogenated using sulphuric acid and concentrated nitric acid (Diagram 5b). Alternatively, 4-fluoro-anthranilic acid may also be used as the starting material.

Diagram 5b:



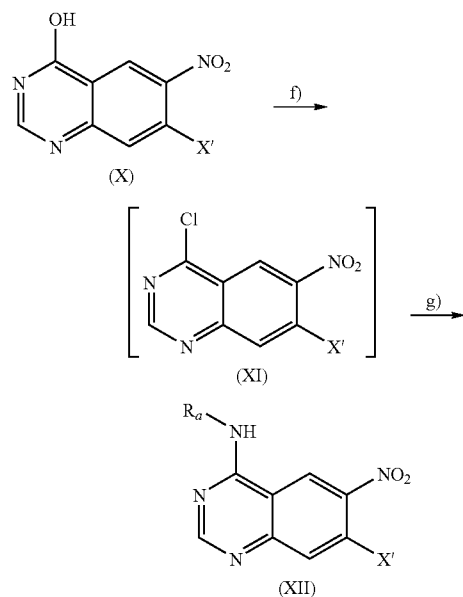
US 8,426,586 B2



a: X' = Cl
b: X' = F
d) formamidine-acetate
e) H₂SO₄, HNO₃ conc.

The desired regioisomer (X) of the nitrogenation products thus obtained is then chlorinated, and the chlorination product (XI) is reacted in situ with the corresponding amine (Diagram 6).

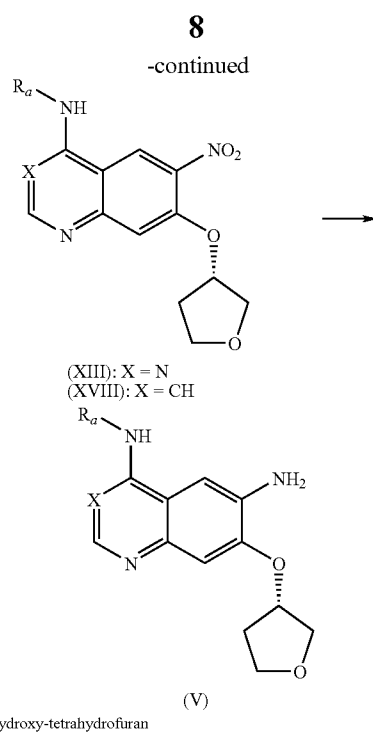
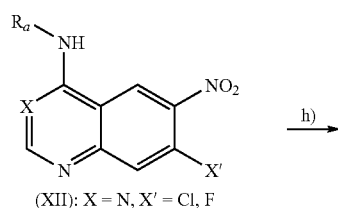
Diagram 6:



f) SOCl₂, acetonitrile
g) R_aNH₂

The compound of formula (XII) thus obtained is reacted with (S)-(+)-3-hydroxytetrahydrofuran to form compound (XIII). Hydrogenation of compound (XIII) or compound (XVIII) from Diagram 5a then yields the starting compound (V) (diagram 7).

Diagram 7:



The invention also relates to 4-[(3-chloro-4-fluorophenyl) amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate. This salt is particularly suitable for pharmaceutical use as it exists in only one crystalline modification, which is moreover anhydrous and very stable.

For pharmaceutical use an active substance not only has to exhibit the desired activity, but must also conform to additional requirements in order to be allowed to be used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the pharmaceutical compositions should therefore have a high stability which must be guaranteed even under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in pharmaceutical formulations might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g. by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way. Preferably a pharmaceutically active substance should therefore have only limited hygroscopicity.

US 8,426,586 B2

9

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible. This problem is solved by 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethyl-amino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate has a melting point of 178° C. (cf. the thermoanalysis shown in FIG. 2). The crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate was investigated further by X-ray powder diffraction. The diagram obtained is shown in FIG. 1.

The following Table lists the data obtained in this analysis:

TABLE

X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate		
2- Θ [°]	d-value [Å]	intensity I/I _o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7

10

TABLE-continued

X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate		
2- Θ [°]	d-value [Å]	intensity I/I _o [%]
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.467	1
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5

In the preceding Table the value “2 Θ [°]” denotes the angle of diffraction in degrees and the value “d_{hkl} [Å]” denotes the specified distances in Å between the lattice planes.

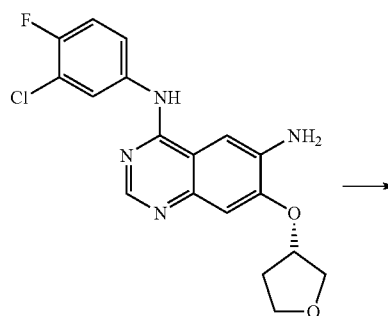
The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a PSD detector and a Cu anode as the x-ray source (CuK_{α1} radiation, λ=1.5418 Å, 40 kV, 40 mA).

The following Examples are intended to illustrate the invention:

EXAMPLES

Example 1

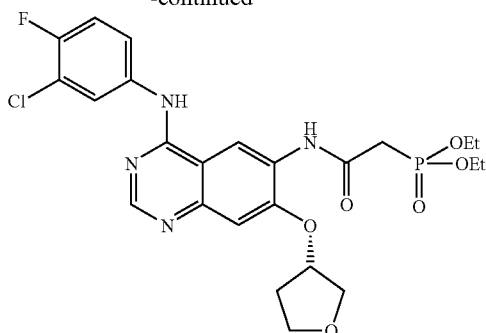
Diethyl {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbonyl]-methyl}-phosphonate



US 8,426,586 B2

11

-continued



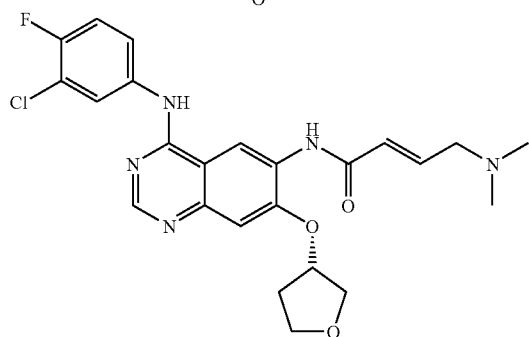
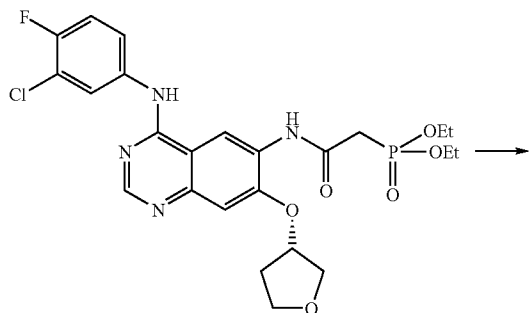
3.58 kg of 1,1-carbonyldiimidazole (22.16 mol) are placed in 12.8 liters of tetrahydrofuran and at 40° C. combined with 4.52 kg (22.16 mol) of diethylphosphonoacetic acid dissolved in 6.5 liters of tetrahydrofuran. The mixture is stirred for 30 minutes at 40° C. The resulting solution is referred to as solution A.

6.39 kg (17.05 mol) of N⁴-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine are placed in 26.5 liters of tetrahydrofuran and at 40° C. combined with solution A and stirred for 2 hours at 30° C. 64 liters of tert.-butylmethylether are added to the suspension and after cooling to 20° C. the precipitate is removed by centrifuging. It is washed with a mixture of 16 liters of tetrahydrofuran and 16 liters of tert.-butylmethylether and then with 32 liters of water and dried at 50° C.

Yield: 6.58 kg (69.8%) of white crystals, content: HPLC 99.1 Fl %

Example 2

(E)-4-dimethylamino-but-2-enoic acid-[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl]-amide



5.6 liters of 30% hydrochloric acid (53.17 mol) are added to 4.4 liters of water. Then 4.28 kg of 95% (dimethylamino)-acetaldehyde-diethylacetal (26.59 mol) are added dropwise

12

within 20 minutes at 30° C. The reaction solution is stirred for 8 hours at 35° C. stirred, cooled to 5° C. and stored under argon. This solution is referred to as solution B.

4.55 kg (68.06 mol) of potassium hydroxide are dissolved in 23.5 liters of water and cooled to -5° C. This solution is referred to as solution C.

5.88 kg (10.63 mol) of diethyl ((4-(3-chloro-4-fluoro-phenylamino)-7-(tetrahydrofuran-3-yloxy)-quinazolin-6-yl-carbamoyl)-methyl)-phosphonate and 0.45 kg of lithium chloride (10.63 mol) are placed in 23.5 liters of tetrahydrofuran and cooled to -7° C. The cold solution C is added within 10 minutes. Then solution B is added at -7° C. within 1 hour. After stirring for a further hour at -5° C. the reaction mixture is heated to 20° C. and combined with 15 liters of water. After cooling to 3° C. the suspension is suction filtered, the precipitate is washed with water and dried. Yield: 5.21 kg of crude product, 100%, water content: 6.7%

The crystallisation of the crude product is carried out with butyl acetate/methylcyclohexane

Yield: 78% purity HPLC 99.4 Fl %, water content 5.4%

Example 3

(E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl)-amide dimaleate

6.0 kg (12.35 mol) of (E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-yl)-amide are placed in 84 litres of ethanol and heated to 70° C. and combined with a solution of 2.94 kg (25.31 mol) of maleic acid in 36 liters of ethanol. After crystallisation has set in, first the mixture is cooled to 20° C. and stirred for 2 hours, then for 3 hours at 0° C. The precipitate is suction filtered, washed with 19 liters of ethanol and dried in vacuo at 40° C.

Yield: 8.11 kg (91.5%)

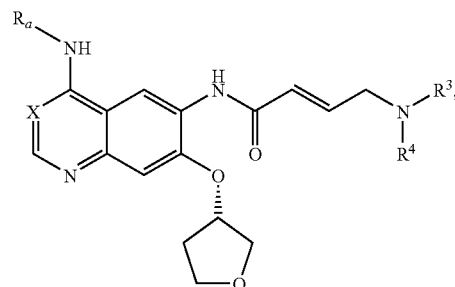
Melting point: 178° C.

¹H-NMR (CD₃OD): δ=2.47+2.27 (m+m, 2H), 2.96 (s, 6H), 4.03 (m, 2H), 4.07+3.92 (m+m, 2H), 4.18+4.03 (m+m, 2H), 5.32 (m, 1H), 6.26 (s, 4H), 6.80 (m, 1H), 6.99 (m, 1H), 7.27(s, 1H), 7.30 (t, 1H), 7.66 (m, 1H), 7.96 (dd, 1H), 8.62 (s, 1H), 9.07 (s, 1H) ppm

What is claimed is:

1. A process for preparing a compound of the formula (VII)

(VII)

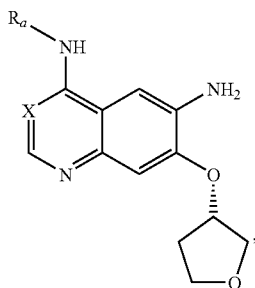


wherein X denotes a methyne group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R³ and R⁴ denote a straight-chain or branched C₁₋₄-alkyl group,

US 8,426,586 B2

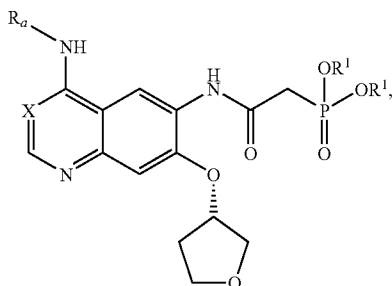
13

comprising the following synthesis steps:
a) reacting a compound of the formula (V)

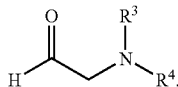


wherein X denotes a methylene group or a nitrogen atom and R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group, in suitable solvents after corresponding activation with di-(C₁₋₄-alkyl)-phosphonoacetic acid and

b) reacting the resulting compound of the formula (VI)



wherein X denotes a methylene group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R¹ denotes a straight-chain or branched C₁₋₄-alkyl group, with the aldehyde of formula



wherein R³ and R⁴ in each case represent a straight-chain or branched C₁-C₄-alkyl group, while the groups may be identical or different, or a corresponding aldehyde equivalent, using suitable organic or inorganic bases.

2. A process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising the following synthesis steps:

- a) reacting N⁴-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine in suitable solvents after corresponding activation with di-(C₁₋₄-alkyl)-phos-phonoacetic acid and
- b) reacting the resulting dialkylester {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate with the aldehyde prepared in situ from the corresponding

14

(dimethylamino)-acetaldehyde-dialkylacetal using suitable organic or inorganic bases.

3. The process according to claim 2, wherein in step a) diethylphosphonoacetic acid is used as reagent.
4. The process according to claim 1, wherein in step b) DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene), sodium hydroxide or potassium hydroxide is used as base.
5. The process according to claim 4, wherein in step b) potassium hydroxide is used as base.
6. A process for preparing the dimaleates of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising steps a and b according to claim 1 as well as the following step c):
- c) converting the resulting 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into the dimaleate by reacting with maleic acid in a suitable solvent, with heating.
7. The process according to claim 6, wherein ethanol or isopropanol is used as solvent, optionally with the addition of water.
8. The process according to claim 6, wherein at least 2 equivalents of maleic acid are used.
9. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using CuK_{α1} radiation, λ=1.5418 Å in the following table:

	2-Θ [°]	intensity I/I ₀ [%]
35	4.91	47
	6.42	33
	7.47	27
	8.13	30
	10.37	30
	17.19	36
	19.43	38
	19.91	100
	21.33	21
	22.94	32
	25.56	37.

10. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using CuK_{α1} radiation, λ=1.5418 Å in the following table:

	2-Θ [°]	intensity I/I ₀ [%]
55	4.91	47
	6.42	33
	7.47	27
	8.13	30
	10.37	30
	12.91	20
	14.94	11
	16.58	12
	17.19	36
	19.43	38
	19.91	100
	20.84	13
	21.33	21

US 8,426,586 B2

15

-continued

2- Θ [°]	intensity I/I _o [%]
21.58	12
22.25	15
22.94	32
25.56	37.

11. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-
 {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-
 ((S))-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, char-
 acterized by 2 Θ [°] values obtained by X-ray powder diffrac-
 tion using CuK $_{\alpha 1}$ radiation, $\lambda=1.5418 \text{ \AA}$ in the following
 table:

2- Θ [°]	d-value [\AA]	intensity I/I _o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12

16

-continued

2- Θ [°]	d-value [\AA]	intensity I/I _o [%]
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.46	71
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5.

* * * * *