1103326-0018/0914

#29

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re: | **US 5,674,860** |
| Issued: | **October 7, 1997** |
| To: | **Christer Carl Gustav Carling; Jan William Trofast** |
| For: | **Combination of a Bronchodilator and a Steroidal Anti-Inflammatory Drug for the Treatment of Respiratory Disorders** |

I hereby certify that this paper is being deposited with the United States Patent and Trademark Office via hand delivery on September 19, 2006.

RAMEL CARRINGTON

Name of person depositing the paper and fee

Signature of person depositing the paper and fee

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

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

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**Exhibits**

**APPLICATION FOR EXTENSION OF**
**PATENT TERM UNDER 35 U.S.C. § 156**

Sir:

Applicant, AstraZeneca AB, a corporation organized and existing under the laws of Sweden, the address of which is S-151 85 Södertälje, Sweden, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,674,860 (attached hereto as Exhibit A), granted to Christer Carl Gustav Carling and Jan William Trofast on the 7th day of October, 1997, for "Combination of a Bronchodilator and a Steroidal Anti-Inflammatory Drug for the Treatment of Respiratory Disorders," by virtue of assignment from Christer Carl Gustav Carling and Jan William Trofast to Aktiebolaget Astra, recorded December 17, 1992, at Reel 6378, Frame 0021; and from Aktiebolaget Astra to Astra Aktiebolaget, recorded June 9, 1997, at Reel 008546, Frame 0050. AstraZeneca AB is the successor company to Astra Aktiebolaget after its merger with Zeneca Group PLC in 1999.

The Approved Product that is relevant to this application is Symbicort® Inhalation Aerosol, which was approved in two dosage strengths: Symbicort 80/4.5 [budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg)]; and Symbicort 160/4.5 [budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg)], collectively "Symbicort" or "Approved Product."

The holder of marketing approval for Symbicort is AstraZeneca Pharmaceuticals LP. The NDA holder and patent owner, AstraZeneca Pharmaceuticals LP and AstraZeneca AB, respectively, are both owned by AstraZeneca PLC, headquartered in London, England.

Applicant, through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the statute, 35 U.S.C. §156(d), and by the Rules of Practice in Patent Cases, 37 C.F.R.

§ 1.740. For the convenience of the United States Patent and Trademark Office ("USPTO"), the information in this application is presented in the order set forth in Section 1.740 of the Rules.

**1. Identification of the Approved Product (37 C.F.R. § 1.740(a)(1))**

The Approved Product is Symbicort, a combination of budesonide and formoterol fumarate dihydrate for oral inhalation in two different dosage strengths (approved label attached as Exhibit B). The two dosage strengths of Symbicort each deliver the same amount of formoterol fumarate dihydrate (4.5 mcg) but different amounts of budesonide (80 and 160 mcg, respectively).

Pursuant to 37 C.F.R. § 1.740, the chemical and generic name, physical structure or characteristics of the Approved Product, Symbicort, are as follows:

The chemical name of budesonide is (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity.

The chemical name for formoterol fumarate dihydrate is (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. Formoterol fumarate is a long-acting selective $ß_2$-adrenergic agonist ($ß_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator.

Symbicort is furnished in 10.2 g canisters and is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing 120 actuations. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg (budesonide micronized/ formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the

lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. Symbicort also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

### 2. Identification of Federal Statute Under Which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2))

The Approved Product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

### 3. Identification of Date on Which Approved Product Received Permission for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(3))

The Approved Product received permission for commercial marketing or use in a letter dated July 21, 2006, signed by Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration. A copy of the approval letter is attached as Exhibit C.

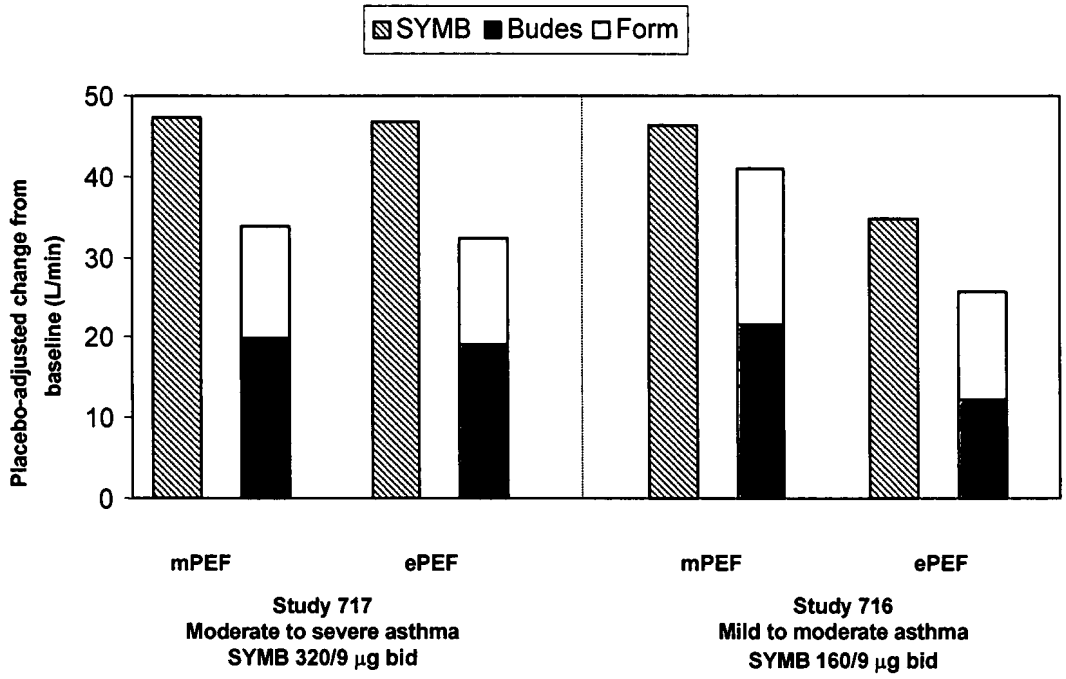
### 4. Identification of Active Ingredient (37 C.F.R. § 1.740(a)(4))

Symbicort has been approved under Section 505(b) of the FFDCA for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Symbicort is the first approved product that contains the combination of budesonide and formoterol fumarate dihydrate, which are shown to have a synergistic effect and a pharmacological interaction, as discussed in Exhibit D attached hereto. Accordingly, consistent with Section 2751 of the Manual of Patent Examining Procedure, Symbicort should be considered to have a new single active ingredient which has not been previously approved for commercial marketing and use.

Clinical evidence of the synergistic effect seen with budesonide and formoterol administered as Symbicort is best illustrated by the results of two pivotal US studies that form the basis of the approval of NDA 21-929 for Symbicort (Figure 1).

**Figure 1** **Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Studies 717 and 716)**




SYMB -SYMBICORT pMDI; Budes - budesonide pMDI (320 µg bid Study 717, 160 µg bid Study 716); Form - formoterol TBH (9 µg bid)
mPEF - Morning peak expiratory flow; ePEF - Evening peak expiratory flow; bid - Twice daily.

Applicant's Studies 716 and 717 were the first studies designed to demonstrate the effects of each separately administered monoproduct, budesonide ("Budes") and formoterol fumarate dihydrate ("Form"), in comparison to the combination product Symbicort ("Symb"), in two different treatment populations. As shown in Figure 1, as measured by the morning and evening Peak Expiratory Flow (PEF) in both studies, the effect of each monoproduct is less than half of the effect seen with Symbicort. Symbicort, therefore, produces in two different treatment populations a synergistic effect that is greater than the additive effect of each compound alone. A more detailed discussion, as well as additional preclinical and clinical data in support of the

synergistic effect of Symbicort, are set forth in Exhibit D and the two Declarations attached thereto that were submitted under 37 CFR § 1.132 by one of the inventors, Dr. Jan William Trofast, during the prosecution of the '860 patent application.

In addition, the two active ingredients in Symbicort are shown to have a pharmacological interaction that produces unexpectedly beneficial results. One example, as discussed further in Exhibit D, is the effect of the administration of budesonide on tolerance to formoterol, as seen in asthmatic patients. Long-term treatment with a formoterol monoproduct, a long-acting $\beta_2$-agonist bronchodilator, can result in tolerance to the drug. Concurrent maintenance treatment with budesonide in conjunction with formoterol has been shown to eliminate this tolerance and, in patients taking chronic formoterol monotherapy, tolerance may be reversed upon administration of budesonide during an acute episode of bronchoconstriction. Such results demonstrate that there is pharmacological interaction between the two administered drugs, formoteral and budesonide, that is observed as a beneficial effect of the combination.

The component active ingredients of the Approved Product have each been separately approved for marketing and use by the U.S. Food and Drug Administration ("FDA"). FDA-approved products containing budesonide include Entocort®, Pulmicort®, and Rhinocort® (all marketed by AstraZeneca). An FDA-approved product containing formoterol is Foradil® (marketed by Novartis). No other combination containing either of these active ingredients has been approved.

**5. Timely Filing of This Application (37 C.F.R. § 1.740(a)(5))**

This application is timely filed, pursuant to 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f), within the permitted sixty-day (60-day) period that began on July 21, 2006, the date

the product received permission under 21 U.S.C. § 355(b), and that will expire on September 19, 2006.

**6. Identification of the Patent for Which an Extension Is Sought (37 C.F.R. § 1.740(a)(6))**

| | |
|---|---|
| Inventors: | **Christer Carl Gustav Carling and Jan William Trofast** |
| Patent No.: | **5,674,860** |
| Issued: | **October 7, 1997** |
| Expiration: | **October 7, 2014** |

**7. Copy of Patent Attached (37 C.F.R. § 1.740(a)(7))**

A copy of US 5,674,860, for which an extension is being sought, is attached in its entirety as Exhibit A. This patent is due to expire on October 7, 2014, based on 35 U.S.C. § 1.54(c)(1), which provides for a 17-year patent term for a patent that issued from an application filed on or before June 8, 1995.

**8. Disclaimers, Certificates of Correction, Receipts of Maintenance Fee Payment or Reexamination Certificate (37 C.F.R. § 1.740(a)(8))**

No Certificates of Correction or Reexamination Certificates have been issued by the USPTO, and no Disclaimers have been filed by Applicant, for the referenced patent. Statements showing payment of the maintenance fee for pay years 04 and 08 are attached as Exhibit E. The maintenance fee payment for pay year 12 is not yet due.

**9. Statement of Patent Claim Coverage of Approved Product (37 C.F.R. § 1.740(a)(9))**

US 5,674,860 claims the Approved Product and methods of using the Approved Product, as shown in Exhibit F. Exhibit F presents a chart showing each applicable patent claim (claims 1, 3-5, 9, 11-13, 17-19, 22, 23, 25-29, 32, 33, 35, and 36) and the manner in which each such

applicable patent claim reads on the Approved Product or method of using the Approved Product.

## 10. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) (37 C.F.R. § 1.740(a)(10))

In accordance with 37 C.F.R. § 1.740(a)(10), the content of this section is provided on a new page.

NDA 21-929 was submitted and approved for Symbicort. The relevant dates are as follows:

a. Effective Date of the Investigational New Drug (IND) Application: November 4, 2001

b. IND Number: 63,394

c. Date on which the NDA was initially submitted: September 23, 2005

d. NDA Number: 21-929

e. Date on which the NDA was approved: July 21, 2006

## 11. Brief Description of Significant Activities Undertaken by Marketing Applicant During Applicable Regulatory Review Period and Respective Dates (37 C.F.R. § 1.740(a)(11))

In accordance with 37 C.F.R. § 1.740(a)(11), the content of this section is provided on a new page.

Attached as Exhibit G is a brief description of the significant activities undertaken by the Applicant with respect to Symbicort during the applicable regulatory review period with respect to the Approved Product from November 4, 2001, to July 21, 2006.

## 12. Statement of Eligibility for Extension (37 C.F.R. § 1.740(a)(12))

In accordance with 37 C.F.R. § 1.740(a)(12), the content of this section is provided on a new page.

Applicant believes that US 5,674,860 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

**a. 35 U.S.C. § 156(a), 37 C.F.R. § 1.720**

US 5,674,860 claims a drug product and a method of using that product.

**b. 35 U.S.C. § 156(a)(1)**

The term of US 5,674,860 will not have expired before submission of this application.

**c. 35 U.S.C. § 156(a)(2)**

The term of US 5,674,860 has never been extended under 35 U.S.C. § 156(e)(1) before submission of this application.

**d. 35 U.S.C. § 156(a)(3)**

This application for extension is submitted by an attorney for the owner of record in accordance with the requirements of 35 U.S.C. § 156(d)(1)-(4) and rules of the U.S. Patent and Trademark Office.

**e. 35 U.S.C. § 156(a)(4)**

The Approved Product, Symbicort, has been subject to a regulatory review period before its commercial marketing or use.

**f. 35 U.S.C. § 156(a)(5)(A)**

The commercial marketing or use of the Approved Product, Symbicort, is the first permitted commercial marketing or use of the product under the FFDCA (21 U.S.C. § 355(b)), pursuant to which such regulatory review period occurred. In this regard, the combination of budesonide and formoterol fumarate dihydrate as a new active ingredient required full scientific review by the FDA. (See Section 4.)

**g. 35 U.S.C. § 156(c)(4)**

No other patent has been extended for the same regulatory review period for the Approved Product, Symbicort.

**13. Statement as to Length of Extension Claimed and the Determination of Such Extension (37 C.F.R. § 1.740(a)(12))**

In the opinion of the Applicant, US 5,674,860 is entitled to an extension of 1011 days, pursuant to 35 U.S.C. § 156 and the implementing regulations, based upon the regulatory review period for Symbicort.

The claimed length of this extension of 1011 days was determined pursuant to 37 C.F.R. § 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. § 156(g)(1)(B), which began on November 4, 2001, and ended on July 21, 2006, and lasted 1721 days, the sum of computations in (a) and (b) below:

(a) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on November 4, 2001, and ended on September 22, 2005, a period of 1419 days (including the last date); and

(b) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on September 23, 2005, and ended on July 21, 2006, a period of 302 days (including the last date);

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 13(1) above (1721 days) less

(a) The number of days in the regulatory review period which were on or before the date on which the patent issued, October 7, 1997, which is zero (0) days, and

(b) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(c) One-half the number of days determined in subparagraph 13(1)(a) (1419 days) after subtracting the number of days determined in subparagraph 13(2)(a) zero (0) and (b) zero (0), or 709 days, which leaves 1011 days (1721 days - 0 days - 0 days - 709 days);

(3) The number of days as determined in subparagraph 13(2) in its entirety (1011 days), when added to the original term of the patent (October 7, 2014), would result in the date July 14, 2017;

(4) Fourteen (14) years when added to the date of approval (July 21, 2006) would result in the date July 21, 2020;

(5) The earlier date as determined in subparagraphs 13(3) and 13(4) is July 14, 2017;

(6) Since the original patent issued after September 24, 1984, five (5) years are added to the original expiration date of the patent (October 7, 2014), resulting in a date of October 7, 2019; and

(7) The earlier of the dates obtained in subparagraph 13(5) and in subparagraph 13(6) is July 14, 2017.

Therefore, the length of extension of patent term claimed by applicant is 1011 days, which is the period of time needed to extend the original expiration of term of October 7, 2014, until July 14, 2017.

**14. Statement of Acknowledgment of Duty to Disclose Material Information (37 C.F.R. § 1.740(a)(13))**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in this application.

**15. Prescribed Fee (37 C.F.R. § 1.740(a)(14))**

Please charge the necessary fee in the amount of $1,120.00, as prescribed in 37 C.F.R. § 1.20(j), and any additional fees which may be required, to Deposit Account 23-1703.

## 16. Contact Information (37 C.F.R. § 1.740(a)(15))

All inquiries and correspondence relating to this application for patent term extension should be directed to:

Leslie Morioka, Esq.
Patent Department
White & Case LLP
1155 Avenue of the Americas
New York, NY 10036-2787
Tel.: (212) 819-8200
Fax: (212) 354-8113
E-Mail: lmorioka@whitecase.com

Dr. Allen Giles, Esq.
Principal Patent Attorney
AstraZeneca Global Intellectual Property
Alderley Park
Macclesfield
Cheshire SK1O 4TG
United Kingdom
Tel: 011-44-625-516573
Fax: 011-46-8553-28820

**17. Copies Enclosed (37 C.F.R. § 1.740(b))**

Five duplicate copies of the present application papers are enclosed. The undersigned patent attorney certifies under penalty of perjury that the attached duplicates of the application papers are true and correct copies of such papers.

Dated: Sept. 19, 2006

Respectfully submitted,

Leslie Morioka
Reg. No. 40,304
Attorney for Applicant

White & Case LLP
1155 Avenue of the Americas
New York, New York 10036
Tel.: (212) 819-8200
Fax: (212) 354-8113
lmorioka@whitecase.com