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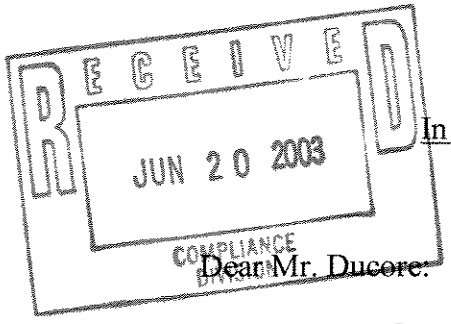


June 19, 2003

In the Matter of Bristol-Myers Squibb Company

Docket No. C-4076

Dear Mr. Ducore:

In compliance with Paragraph XVII of the Decision and Order (the "Order") in In the Matter of Bristol-Myers Squibb Company, Docket No. C-4076, enclosed please find a verified written report setting forth in detail the manner and form in which BMS intends to comply, is complying, and has complied with this Order. I have also forwarded a copy directly to Anne Schenof.

Very truly yours,

Lee S. Bickley

Lee S. Bickley

Mr. Daniel P. Ducore
Bureau of Competition
Federal Trade Commission
600 Pennsylvania Avenue, N.W.
Washington, DC 20580

Encl.

406A

BY FAX AND FEDERAL EXPRESS

001 0221
011 0046
021 0181

UNITED STATES OF AMERICA
BEFORE FEDERAL TRADE COMMISSION

COMMISSIONERS: Timothy J. Muris, Chairman
Sheila F. Anthony
Mozelle W. Thompson
Orson Swindle
Thomas B. Leary

In the Matter of

BRISTOL-MYERS SQUIBB COMPANY,
a corporation.

Docket No. C-4076

Bristol-Myers Squibb Company ("BMS") submits this report in compliance with Paragraph XVII of the Decision and Order served on April 21, 2003 (the "Order").

1. General

To ensure compliance with the Order, BMS has taken three actions: (1) implementation of a training program for inside counsel and executives to educate them as to the requirements of the Order; (2) review of existing agreements and Orange Book listings for possible issues; and (3) ongoing review of proposed new agreements and Orange Book listings for compliance with the Order.

The training program was designed by outside counsel, Richard Stark of Cravath, Swaine & Moore LLP, in conjunction with inside counsel. Two training sessions for inside counsel were held in April 2003 and were attended by over 30 inside

attorneys. Substantially all the inside attorneys responsible for patents, patent litigation and licensing attended the training sessions, each of which was approximately two hours in duration. All attendees were provided with a copy of the Order and the FTC's Analysis to Aid Public Comment, as well as a PowerPoint presentation and Frequently Asked Questions prepared by outside counsel. Attorneys from the areas of patents and licensing who were unable to attend either training session were provided with the written materials. A training session for the company's Corporate Policy Committee was conducted by Linda Willett, Vice President and Deputy General Counsel. Charles Linzner, Vice President and Senior Counsel-PRI, provided a training session for executives in the Corporate Development, Business Development, Licensing and External Science and Technology areas.

For the purposes of reviewing existing agreements and Orange Book listings and proposed new agreements and Orange Book listings, BMS has formed a compliance team, consisting of:

- Linda Willett, Vice President and Deputy General Counsel [senior managing attorney]
- Matthew Blischak, Senior Counsel [responsible for patent litigation]
- David Bonk, Vice President and Associate General Counsel [counsel for R&D, intellectual property, government affairs]
- Thomas Costa, Vice President and Deputy General Counsel [senior managing attorney]
- Charles Linzner, Vice President and Senior Counsel [counsel for licensing and business development]
- Jonathan Provoost, Associate Counsel [counsel for non-patent exclusivity]
- Richard Stark, Outside Counsel

The results of the compliance reviews are discussed in the appropriate sections below.

2. Specific Provisions of the Order

a. Paragraph II

BMS has not sought, maintained, certified to or taken any other action in furtherance of the listing or continued listing in the Orange Book of U.S. Patent No. 6,150,365.

b. Paragraph III

Since the effective date of the Order, BMS has not made any Patent Infringement Claim[1] that a Taxol Patent is infringed by any Drug Product or the use of any Drug Product where the subject of the Patent Infringement Claim is the making, using, selling, offering to sell, or importing of Taxol. BMS had one royalty-bearing license of a Taxol Patent in effect as of the effective date of the Order. BMS informed the licensees (Ben Venue Laboratories, Bedford Laboratories and Boehringer Ingelheim Corp.) that, as of April 21, 2003, it waived any further royalties that would have been payable under the license. (Exhibit 1, attached hereto.)

c. Paragraph IV

As of the effective date of the Order, BMS did not have any 30-Month Stay in effect as to any ANDA referencing NDA No. 018731 or NDA No. 020262. No new 30-Month Stay as to any ANDA referencing either NDA has been obtained since the effective date of the Order.

d. Paragraph V

Since the effective date of the Order, BMS has not made any Patent Infringement Claim regarding U.S. Patent 6,150,365.

[1] Capitalized terms not otherwise defined herein have the meaning assigned to them in the Order.

e. Paragraph VI

BMS conducted a review of the patents listed in the Orange Book for its NDAs as of the effective date of the Order. As a result of this review, BMS asked the FDA to remove from the Orange Book a number of patents, for various reasons (Exhibit 2):

NDA	Patent	Reason
20-152 Serzone (nefazodone)	U.S. Patent No. 5,256,664	Relates to a metabolite of nefazodone.
18-731 BuSpar (buspirone)	U.S. Patent No. 5,015,646	Relates to BuSpar.
18-057 Platinol (cisplatin)	U.S. Patent No. 5,562,925	Invalidated in litigation.
12-142 lyophilized cytoxan (lyophilized cyclophosphamide)	U.S. Patent No. 4,537,883	Expired.
20-262 Taxol (paclitaxel)	U.S. Patent No. 5,496,804 U.S. Patent No. 5,670,537 U.S. Patent No. 6,150,398	Relate to Taxol.

After the effective date of the Order, the following patent was listed in the Orange Book:

NDA	Patent	Date of Listing
20-972 Sustiva (efavirenz) capsules	U.S. Patent No. 6,555,133 (Exhibit 3). Methods of using the FDA-approved formulation of efavirenz capsules.	May 26, 2003

f. Paragraph VII

Since the effective date of the Order, BMS has not, in connection with any patent listed in the Orange Book under any NDA for which BMS is the NDA Holder, taken any action, or Encouraged any other person to take any action, that initiates,

maintains, or causes to be initiated or maintained, a 30-Month Stay of FDA approval of any ANDA referencing such NDA under any of the circumstances specified in Paragraph VII.A-F of the Order.

The following litigations where BMS is the "NDA Holder" (as defined in the Order) and a 30-Month Stay of FDA approval of an ANDA is in effect are pending:

Action	NDA	ANDA	Patents in Suit
Bristol-Myers Squibb Company and E.R. Squibb & Sons, LLC v. Teva Pharmaceuticals USA, Inc., C.A. 01-CV-5572 (SHS) (S.D.N.Y.)	19-915 Monopril (fosinopril sodium)	76-139	U.S. Patent No. 5,006,344
Bristol-Myers Squibb Company and E.R. Squibb & Sons, LLC v. Andrx Pharmaceuticals, LLC and Andrx Pharmaceuticals, Inc., C.A. 03-CV-2503 (S.D.N.Y.)	19-915 Monopril (fosinopril sodium)	76-620	U.S. Patent No. 5,006,344
Bristol-Myers Squibb Company and E.R. Squibb & Sons, LLC v. Andrx Pharmaceuticals, LLC and Andrx Pharmaceuticals, Inc., C.A. 03-60703 (S.D. Florida)	19-915 Monopril (fosinopril sodium)	76-620	U.S. Patent No. 5,006,344
Bristol-Myers Squibb Company and E.R. Squibb & Sons, LLC v. Andrx Pharmaceuticals, LLC and Andrx Pharmaceuticals, Inc., C.A. 03-CV-2503 (S.D.N.Y.)	20-286 Monopril HCT (fosinopril sodium/ hydrochlorothiazide combination product)	76-608	U.S. Patent No. 5,006,344
Bristol-Myers Squibb Company and E.R. Squibb & Sons, LLC v. Andrx Pharmaceuticals, LLC and Andrx Pharmaceuticals, Inc., C.A. 03-CV-60703 (S.D. Florida)	20-286 Monopril HCT (fosinopril sodium/ hydrochlorothiazide combination product)	76-608	U.S. Patent No. 5,006,344
Bristol-Myers Squibb Company and Research Corporation Technologies, Inc. v. Pharmachemie B.V., C.A. No. 01-3751	19-880 Paraplatin (carboplatin)	76-162	U.S. Patent No. 4,657,927
Bristol-Myers Squibb Company and Research Corporation Technologies, Inc. v. Pharmachemie, B.V., C.A. No. 02-1270	19-880 Paraplatin (carboplatin)	76-292	U.S. Patent No. 4,657,927
Sanofi-Synthelabo, Sanofi-	20-839 Plavix	76-274	U.S. Patent Nos. 4,847,265 and

Synthelabo Inc., and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership v. Apotex Inc. and Apotex Corp., C.A. No. 02-2255 (RWS)	(clopidogrel)		5,576,328*
Sanofi-Synthelabo, Sanofi-Synthelabo Inc., and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc., C.A. No. 02-3672 (RWS)	20-839 Plavix (clopidogrel)	76-273	U.S. Patent Nos. 4,847,265 and 5,576,328*

*In the clopidogrel litigation, BMS and Sanofi elected to withdraw the '328 patent from the action.

BMS has reviewed each of the above-listed litigations, and none of the circumstances listed in Paragraph VII.A-F of the Order applies in any of the actions.

g. Paragraph VIII

Since the effective date of the Order, BMS has made no statements to the FDA relating to the approvability of an ANDA referencing an NDA for which BMS is the "NDA Holder" (as defined in the Order), or the sale of any product pursuant to such ANDA.

h. Paragraph IX

Since the effective date of the Order, BMS has not, in connection with a Patent Infringement Claim, asserted any fraudulent or objectively baseless claim, or otherwise engaged in sham litigation for the purpose of injuring an ANDA Filer rather than to obtain a favorable outcome to the Patent Infringement Claim. Since the effective date of the Order, BMS has not, in connection with a Patent Infringement Claim, enforced or sought to enforce any patent that it knows is invalid, unenforceable, or not

infringed. In the clopidogrel litigation, BMS and Sanofi elected to withdraw the '328 patent from the action.

i. Paragraphs X-XI

The BMS compliance team has reviewed proposed new licensing agreements to ensure compliance with Paragraphs X-XI. Since the effective date of the Order, BMS has not acquired any patents or Exclusive Licenses within the scope of Paragraph X of the Order.[2] Since the effective date of the Order, BMS has not entered into any non-exclusive licenses to patents that are listed or listable in the Orange Book or would otherwise be relevant to the enforcement of Paragraph XI of the Order.

BMS has, since the effective date of the Order, entered into a number of agreements that include patent licensing provisions, but which, BMS respectfully submits, are not covered by Paragraphs X-XI of the Order and are not relevant to enforcement of the Order. However, if additional information is required, the staff is invited to contact Richard J. Stark at Cravath, Swaine & Moore LLP, Worldwide Plaza, 825 Eighth Avenue, New York, NY 10019, (212) 474-1000. These agreements are of the following two types:

(1) From time to time, BMS licenses in research materials and research tools (e.g., compounds, genetic materials, data, assay technology). Such license agreements often include non-exclusive licenses under patents covering such materials and tools and may include options to exclusively

[2] This statement is not intended to cover filings of patent applications by BMS employees or the issuance of new patents to employees or under agreements existing at the time an NDA received FDA approval, which are not within the scope of Paragraph X.

license certain patents (which options would typically be exercised in the event that a commercial product were developed).

(2) From time to time, BMS also enters into "material transfer agreements", under which research materials are provided to outside entities, such as universities. Such agreements typically include provisions that would grant BMS a non-exclusive license in the event that the outside entity's research resulted in a patent and often include provisions that would grant BMS an option to take an exclusive license to such patents.

(3) From time to time, BMS also enters into service, funded research and/or feasibility and similar agreements under which outside parties conduct certain activities (e.g., manufacture materials, evaluate improved manufacturing processes, conduct various types of research activities, etc.). Such agreements typically include provisions that grant BMS exclusive and/or non-exclusive licenses to the outside entity's platform technologies used in performing the services and grant BMS exclusive and/or non-exclusive licenses in the event the outside entity's activities result in a patent or other intellectual property.

j. Paragraphs XII-XV

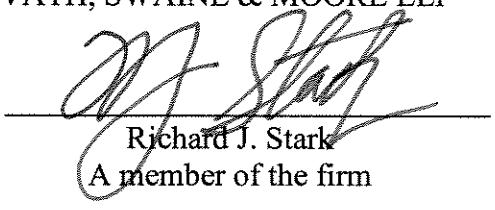
BMS did not have any agreements in effect as of the effective date of the Order of the types that are prohibited by Paragraphs XII-XV of the Order. BMS has not entered any agreements after the effective date of the Order that are prohibited by Paragraphs XII-XV of the Order.

Dated: June 20, 2003

Respectfully submitted,

CRAVATH, SWAINE & MOORE LLP

by

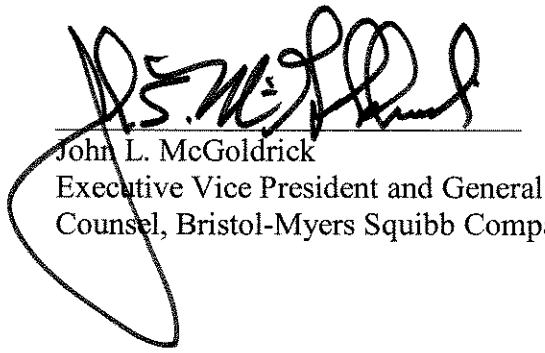


Richard J. Stark
A member of the firm

Worldwide Plaza
825 Eighth Avenue
New York, NY 10019
(212) 474-1000

Verification

The foregoing is true and correct to the best of my knowledge, information and belief.



John L. McGoldrick
Executive Vice President and General
Counsel, Bristol-Myers Squibb Company

Exhibit 1

Matthew P. Blischak
Senior Counsel
Patent Litigation
Legal Division

P.O. Box 4000 Princeton, NJ 08543-4000
Tel 609 252-4814 Fax 609 252-3265
matthew.blischak@bms.com

Bristol-Myers Squibb Company

June 12, 2003

Via: Facsimile and Federal Express

President
Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, OH 44146

RE: Waiver of royalty payments relating to the Settlement Agreement.

Dear Sir or Madam:

This letter officially provides notice to Ben Venue Laboratories, Inc. ("Ben Venue") in accordance with paragraph 23 of the Settlement Agreement between Bristol-Myers Squibb Co. ("Bristol") and Ben Venue dated December 2001 relating to the sale of paclitaxel.

As a result of the Consent Agreement between Bristol and the U.S. Federal Trade Commission, Bristol hereby waives any royalties or other fees from Ben Venue pursuant to that agreement. Accordingly, effective April 21, 2003, Bristol releases Ben Venue from its obligation to make royalty payments to Bristol under the royalty provisions contained in paragraphs 4 and 5 of the Settlement Agreement.

If you have any questions or need additional information, please do not hesitate to contact me.

Best regards,

Matthew P. Blischak

Matthew P. Blischak

cc: Anthony Russ

Exhibit 2

Bristol-Myers Squibb Company

David T. Bonk
Vice President & Associate General Counsel
Legal Division

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-3414 Fax 609-252-6880
david.bonk@bms.com

TIME SENSITIVE PATENT INFORMATION

April 4, 2003

VIA HAND DELIVERY
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Re: Bristol-Myers Squibb Company Products
Amendments to Patent Information

Dear Sir/Madam:

Attached hereto, please find an Appendix listing certain Bristol-Myers Squibb Company (BMS) products, which Appendix identifies the NDA number for these products, and which further identifies certain patents currently listed in connection therewith.

As the NDAs holder, and in accordance with 21 C.F.R.¶ 314.53, BMS wishes to amend the information submitted for listing in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) in connection with the aforementioned products. Specifically, BMS requests that FDA remove from the Orange Book those patents set forth on the attached Appendix (and no others), which patents are currently listed for these products.

An original and a copy of this letter are being submitted. Should there be any questions regarding this submission, please contact the undersigned.

Sincerely,

David T. Bonk

cc: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs/HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773
(Via hand delivery, with accompanying fax to: 301-827-5911)

Appendix

Product *Proprietary Name*	**Product** *Active Ingredient*	**NDA number**	**Currently listed patents for which delisting is requested**
Serzone	nefazodone	20-152	US Patent No. 5,256,664
Buspar	buspirone	18-731	US Patent No. 5,015,646
Platinol	cisplatin	18-057	US Patent No. 5,562,925
Lyophilized Cytoxan	lyophilized cyclophosphamide	12-142	US Patent No. 4,537,883
Taxol	paclitaxel	20-262	US Patent No. 5,496,804 US Patent No. 5,670,537 US Patent No. 6,150,398

Exhibit 3

US006555133B2

(12) **United States Patent**
Makooi-Morehead et al.

(10) **Patent No.: US 6,555,133 B2**
(45) **Date of Patent: Apr. 29, 2003**

(54) **FORMULATION OF FAST-DISSOLVING EFAVIRENZ CAPSULES OR TABLETS USING SUPER-DISINTEGRANTS**

(75) Inventors: **William T. Makooi-Morehead**, Wallingford, PA (US); **John D. Buehler**, Ambler, PA (US); **Brian R. Landmann**, Hoboken, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/824,071**

(22) Filed: **Apr. 2, 2001**

(65) **Prior Publication Data**

US 2001/0012518 A1 Aug. 9, 2001

Related U.S. Application Data

(63) Continuation of application No. 09/286,902, filed on Apr. 6, 1999, now Pat. No. 6,238,695.
(60) Provisional application No. 60/080,925, filed on Apr. 7, 1998.

(51) **Int. Cl.**[7] **A61K 9/20**; A61K 9/48
(52) **U.S. Cl.** **424/451**; 424/452; 424/464; 424/465; 514/772.3; 514/778; 514/781; 514/885
(58) **Field of Search** 424/451, 464, 424/465, 452, 456, 466, 468, 470, 472

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,519,021	A		5/1996	Young et al.
6,238,695	B1	*	5/2001	Makooi-Morehead et al. 424/451

FOREIGN PATENT DOCUMENTS

EP	0301006	2/1987
EP	0394553	10/1990
HU	207950	8/1991
WO	WO 9520389	8/1994
WO	WO 9622955	8/1996
WO	WO 9641634	12/1996
WO	WO 8705804	10/1997
WO	WO 9961026	12/1999

OTHER PUBLICATIONS

John E. Botzolakis and Larry L. Augsburger, 1988, Disintegrating Agents in Hard Gelatin Capsules, Drug Development and Industrial Pharmacy, 14(1), 29–41.
Bolhuis et al., 1997, European Journal of Pharmaceutical Science, 5(2), 63–69.
Te Wiernik, et al., 1992, ACTA Pharm Nord, 4(4), 239–44.
Remington's Pharmaceutical Sciences 19th. Edition, p. 1619 (1995).

* cited by examiner

Primary Examiner—James M. Spear
(74) *Attorney, Agent, or Firm*—Paul D. Golian

(57) **ABSTRACT**

The present invention provides improved oral dosage form formulations of efavirenz that are useful in the inhibition of human immunodeficiency virus (HIV), the prevention or treatment of infection by HIV, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). In particular, the present invention relates to compressed tablets or capsules comprising efavirenz that contain one or more disintegrants that enhance the dissolution rate of the efavirenz in the gastrointestinal tract thereby improving the rate and extent of absorption of efavirenz in the body. The present invention also relates to the process of making such tablets or capsules.

15 Claims, No Drawings

FORMULATION OF FAST-DISSOLVING EFAVIRENZ CAPSULES OR TABLETS USING SUPER-DISINTEGRANTS

This application is a continuation of U.S. patent application Ser. No. 09/286,902, filed Apr. 6, 1999, which is now U.S. Pat. No. 6,238,695, and claims benefit of U.S. provisional application No. 60/080,925, filed Apr. 7, 1998.

FIELD OF THE INVENTION

The present invention provides improved oral dosage form formulations of efavirenz that are useful in the inhibition of human immunodeficiency virus (HIV), the prevention or treatment of infection by HIV, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). In particular, the present invention relates to compressed tablets or capsules comprising efavirenz that contain one or more disintegrants that enhance the dissolution rate of the efavirenz in the gastrointestinal tract thereby improving the rate and extent of absorption of efavirenz in the body. The present invention also relates to the process of making such tablets or capsules.

BACKGROUND OF THE INVENTION

In the dose titration of a patient, the objective is to attain and maintain a blood level of drug substance that exceeds the minimum effective level required for response but does not exceed the minimum toxic level. Absorption of a drug from an oral dosage form such as a tablet or a capsule can be affected by properties of the formulation and its method of manufacture. This is particularly true when the drug has low solubility in water, has a hydrophobic nature, and/or is administered in high therapeutic doses. In such cases, dissolution of the drug from the dosage form in the gastrointestinal tract can be the limiting factor that determines the rate and extent of absorption of drug into the body. Changes in the composition and/or method of manufacture of the dosage form can affect the dissolution rate.

An active area of research is in the discovery of new methods of drug formulation. Drug release from a solid dosage form can be enhanced by addition of materials referred to as disintegrants. Disintegrants are substances or a mixture of substances added to the drug formulation that facilitate the breakup or disintegration of the tablet or capsule contents into smaller particles that dissolve more rapidly than in the absence of the disintegrant (Handbook of Pharmaceutical Excipients, Ainley Wade and Paul J. Weller eds., 2d ed. 1994; The Theory and Practice of Industrial Pharmacy, Leon Lachman, Herbert A. Lieberman, and Joseph L. Kanig eds., 3rd ed. 1986; Disintegrating Agents in Hard Gelatin Capsules, John E. Botzolakis and Larry L. Augsburger, Drug Development and Industrial Pharmacy 14(1), 29–41 1988). Materials that serve as disintegrants include starches, clays, celluloses, algins, gums and cross-linked polymers. A group of disintegrants referred to as "super-disintegrants" are generally used at a low level in the solid dosage form, typically 1 to 10% by weight relative to the total weight of the dosage unit. Examples of super-disintegrants are croscarmellose, crospovidone and sodium starch glycolate, which represent examples of a cross-linked cellulose, a cross-linked polymer and a cross-linked starch, respectively. EP 0,301,006 describes the use of super-disintegrants to enhance the dissolution properties of tablet and capsule formulations containing methylprednisolone, a glucocorticoid steroid.

It is desirable to develop formulations where the tablet or capsule disintegrates rapidly and the pharmaceutical agent dissolves readily. This is especially important where the pharmaceutical agent is highly insoluble and/or must be administered in high-strength dosage forms.

This invention relates to new solid oral dosage form formulations containing the HIV drug efavirenz that enhance the dissolution rate of efavirenz in the gastrointestinal tract in order to improve the rate and extent of absorption into the body, thereby improving its therapeutic effect.

SUMMARY OF THE INVENTION

The present invention provides improved solid dosage forms containing the non-nucleoside HIV reverse transcriptase inhibitor (NNRTI) drug efavirenz that disintegrate and dissolve rapidly thereby enhancing the therapeutic characteristics of the formulation. The present invention also provides processes for the manufacture of capsule and tablet formulations of efavirenz that allow a significantly higher strength of efavirenz to be formulated in a single capsule or tablet.

An embodiment of the present invention includes formulations and processes for manufacturing tablets or capsules containing efavirenz using a high-shear, wet granulation step where a very high level of a super-disintegrant such as sodium starch glycolate is included in the wet granulation step.

Another embodiment of the present invention uses the super-disintegrant sodium starch glycolate in both a wet granulation and a dry blending step in the manufacturing process of tablets and capsules containing efavirenz. In a preferred embodiment of the manufacturing process the quantity of the sodium starch glycolate used in the wet granulation step is in the range from about 20% to about 75% by weight relative to the total dry weight of materials being granulated in the wet granulation step. More preferably the super-disintegrant component in the wet granulation step is in the range from about 20% to about 55% by weight relative to the total dry weight of the materials being granulated in the wet granulation step.

In another embodiment of the present invention the range for the efavirenz in the wet granulation step can vary from about 25% to about 80% by weight relative to the total dry weight of the materials being granulated in the wet granulation step. More preferably the drug substance component will range from about 45% to about 80% by weight relative to total dry weight of the ingredients in the wet granulation step.

In the present invention a surfactant such as sodium lauryl sulfate is preferably used in the wet granulation step of the process for the manufacture of the capsules or tablets of the present invention. The sodium lauryl sulfate is preferably dissolved in the wet granulating fluid. Most preferably the sodium lauryl sulfate will range from about 0.1% to about 5% by weight relative to the total dry weight of the materials being granulated in the wet granulation step.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved oral dosage form formulations of efavirenz that are useful in the inhibition of human immunodeficiency virus (HIV), the prevention or treatment of infection by HIV, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). In particular, the present invention relates to compressed tablets or capsules comprising efavirenz that contain one or more disintegrants that enhance the dissolution rate of the

efavirenz in the gastrointestinal tract thereby improving the rate and extent of absorption of efavirenz in the body. The present invention also relates to the process of making such tablets or capsules.

The active ingredient of the formulation of the present invention is the NNRTI efavirenz, which is present in a therapeutically effective amount. Methods for the manufacture of efavirenz are disclosed in U.S. Pat. No. 5,519,021. The disclosure of U.S. Pat. No. 5,519,021 in its entirety is hereby incorporated by reference. Efavirenz is (s)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

In addition to the active ingredient, solid dosage forms contain a number of additional ingredients referred to as excipients. These excipients include among others diluents, binders, lubricants, glidants and disintegrants. Diluents are used to impart bulk to the formulation to make a tablet a practical size for compression. Examples of diluents are lactose and cellulose. Binders are agents used to impart cohesive qualities to the powered material ensuring the tablet will remain intact after compression, as well as improving the free-flowing qualities of the powder. Examples of typical binders are lactose, starch and various sugars. Lubricants have several functions including preventing the adhesion of the tablets to the compression equipment and improving the flow of the granulation prior to compression or encapsulation. Lubricants are in most cases hydrophobic materials. Excessive use of lubricants can result in a formulation with reduced disintegration and/or delayed dissolution of the drug substance. Glidants are substances that improve the flow characteristics of the granulation material. Examples of glidants include talc and colloidal silicon dioxide. Disintegrants are substances or a mixture of substances added to a formulation to facilitate the breakup or disintegration of the solid dosage form after administration. Materials that serve as disintegrants include starches, clays, celluloses, algins, gums and cross-linked polymers. A group of disintegrants referred to as "super-disintegrants" generally are used at a low level in the solid dosage form, typically 1% to 10% by weight relative to the total weight of the dosage unit. Croscarmellose, crospovidone and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer and a cross-linked starch, respectively. Sodium starch glycolate swells seven- to twelve-fold in less than 30 seconds effectively disintegrating the granulations that contain it. Granulation refers to a mixing technique by which the overall particle size of a formulation is increased through the permanent aggregation of smaller particles. Wet granulation refers to granulation that is accomplished by wetting the smaller particles so they tack to one another. The newly-formed larger particles remain intact after drying. In dry granulation, larger particles are formed as a result of the compaction of the dry ingredients, followed by milling of this compacted material into suitably sized particles.

An embodiment of the present invention is a formulation and a process for manufacturing tablets or capsules using a high-shear, wet granulation step in which a very high level of a super-disintegrant such as sodium starch glycolate is included, followed by a dry blending step that incorporates additional quantities of super-disintegrant. In the present invention the amount of the super-disintegrant in the wet granulation step of the manufacturing process is preferably in the range of about 20% to about 75% by weight relative to the total dry weight of the materials used in the wet granulation step. More preferably the super-disintegrant component will range from about 20% to about 55% by weight relative to the total dry weight of all of the ingredients in the wet granulation step of the manufacturing process. In general, the range for the HIV reverse transcriptase inhibitor in the wet granulation step can vary from about 25% to about 80% by weight relative to the total dry weight of all of the ingredients in the wet granulation step of the manufacturing process. More preferably the drug substance component will range from about 45% to about 80% by weight relative to the total dry weight of all of the ingredients in the wet granulation step of the manufacturing process. Also included in the wet granulation step is a surfactant such as sodium lauryl sulfate, or another material that improves the wettability of the drug. Preferably the surfactant component will range from about 0.1% to about 5% by weight relative to the total weight of ingredients in the formulation. After the wet granulation step, the material is dried, milled, and dry blended with other ingredients such as diluents, glidants, disintegrants, and lubricants. The result of the dry blending step is then filled into gelatin capsule shells or compressed into tablets. Gelatin capsules may contain the active ingredient and powdered carriers such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both capsules and tablets can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and to protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Technology for the formation of solid dosage forms such as capsules and compressed tablets, that utilize conventional pharmaceutical manufacturing equipment for their purpose, is described in detail in Remington's Pharmaceutical Sciences (Alfonso R. Gennaro ed., ch. 89, 18th ed. 1990).

In one aspect of the present invention, it was discovered that the sodium starch glycolate acts as a highly swellable carrier material onto which the efavirenz adheres during the wet granulation step of the process for the manufacture of tablets or capsules containing efavirenz. Granulation refers to a processing technique by which the overall particle size of a formulation is increased through the permanent aggregation of smaller particles. Wet granulation refers to granulation that is accomplished by wetting the smaller particles so they tack to one another. The newly-formed larger particles remain intact after drying. In the dry blending step of the process for the manufacture of tablets or capsules containing efavirenz, extragranular materials are added to the granulation to impart other improved characteristics such as flow and lubricity. The granulation is evenly blended throughout the mixture.

The adherence of the drug efavirenz substance particles to the hydrated disintegrant sodium starch glycolate is accomplished by intimate mixing in the wet granulation step. In an embodiment of the present invention the quantity of sodium starch glycolate used in the wet granulation step is significantly higher than is typically used. In the present invention the wet granulation preferably contains about 20% to about 75% by weight sodium starch glycolate relative to the total dry weight of the ingredients of the wet granulation step, as opposed to the 1–10% that is used in a typical wet granulation step (Handbook of Pharmaceutical Excipients, Ainley Wade and Paul J. Weller eds., 2d ed. 1994; The Theory and Practice of Industrial Pharmacy, Leon Lachman, Herbert A. Lieberman, and Joseph L. Kanig eds., 3rd ed. 1986; Disintegrating Agents in Hard Gelatin Capsules, John E. Botzolakis and Larry L. Augsburger, Drug Development and

Industrial Pharmacy 14(1), 29–41 1988). During the wet granulation, efavirenz drug substance particles are attached to the surface of the sodium starch glycolate particles. When these granules are exposed to the fluid in the gastrointestinal tract following the disintegration of the solid dosage form, the sodium starch glycolate rapidly swells and presents the attached efavirenz drug substance particles to the fluid allowing for rapid dissolution of the efavirenz.

The present invention provides capsule or compressed tablet pharmaceutical dosage forms comprising a therapeutically effective amount of efavirenz and comprising one or more disintegrants in an amount greater than about 10% by weight relative to the total weight of the contents of the capsule or the total weight of the tablet.

The disintegrant used in the present invention is preferably selected from the group comprising modified starches, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone.

The preferred disintegrant in the present invention is a modified starch.

The more preferred disintegrant in the present invention is the modified starch sodium starch glycolate.

In the present invention the capsule formulation contains efavirenz present in an amount from about 5 to about 1000 mg per capsule.

It is preferred in the present invention that the capsule formulation contain from about 5 to about 500 mg of efavirenz per capsule.

It is preferred in the present invention that the capsule formulation contain from about 500 to about 1000 mg of efavirenz per capsule.

It is preferred in the present invention that the capsule formulation contain from about 25 to about 350 mg of efavirenz per capsule.

It is preferred in the present invention that the capsule formulation contain from about 50 to about 200 mg of efavirenz per capsule.

The compressed tablet of the present invention contains efavirenz in an amount from about 5 to about 800 mg per tablet.

The present invention provides for a pharmaceutical dosage form comprising:

(a) a therapeutically effective amount of efavirenz;

(b) a surfactant;

(c) a disintegrant;

(d) a binder;

(e) a diluent;

(f) a lubricant;

(g) a glidant; and

(h) optionally additional pharmaceutically acceptable excipients;

wherein the disintegrant is selected from modified starches, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone and is present in an amount greater than about 10% by weight of the total dry weight of the capsule contents or the compressed tablet.

Another embodiment of the present invention provides a method for manufacturing a solid dosage form comprising the steps of:

(a) wet granulating the efavirenz and the intragranular sodium starch glycolate in a high-shear granulator using an aqueous solution of sodium lauryl sulfate;

(b) drying result of step (a);

(c) milling result of step (b);

(d) dry blending result of step (c) with the extragranular sodium starch glycolate and additional pharmaceutically acceptable excipients; and

(e) encapsulating or compressing into tablets the result of step (d).

As used herein, the following terms and expressions have the indicated meanings.

"Sodium starch glycolate" refers to sodium carboxymethyl starch.

"Efavirenz" refers to the pharmacologically active ingredient (S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. The process for the synthesis of this compound is described in U.S. Pat. No. 5,519,021, which is hereby incorporated by reference.

"Therapeutically effective amount" is intended to mean an amount of a compound sufficient to produce the desired pharmacological effect.

"Modified starch" as used herein means any of several water-soluble polymers derived from a starch (corn, potato, tapioca) by acetylation, chlorination, acid hydrolysis, or enzymatic action.

EXAMPLES

In the following embodiments of the invention, the below-listed quantities of drug substance and additional components are combined using standard pharmaceutical manufacturing techniques. The resulting formulations are used to fill gelatin capsule shells or compressed into tablets utilizing standard pharmaceutical manufacturing techniques.

Example 1

Wet Granulation 100 mg Capsule Formulation

Method of manufacture: The efavirenz and intragranular sodium starch glycolate are mixed and then wet granulated after adding an aqueous solution of sodium lauryl sulfate. This wet mass may then be dried in a fluid bed, tray or other suitable dryer. The dried granulation may then be milled to achieve a suitable particle size distribution and then is blended with the other ingredients. This blend is then filled into two piece hard gelatin capsule shells.

Ingredient	Amount per capsule	%
efavirenz	100 mg	39.06
sodium lauryl sulfate	5 mg	1.95
lactose, hydrous	57 mg	22.26
magnesium stearate	4 mg	1.56
sodium starch glycolate (intragranular)	80 mg	31.25
sodium starch glycolate (extragranular)	10 mg	3.91
Total Capsule Weight	256 mg	

Example 2

Wet Granulation 100 mg Capsule Formulation

Method of manufacture: The efavirenz and intragranular sodium starch glycolate are granulated using an aqueous solution of sodium lauryl sulfate. This wet mass may then be dried in a fluid bed, tray or other suitable dryer. The dried granulation may then be milled to achieve a suitable particle size distribution and then is blended with the other ingredients. This blend is then filled into two piece hard gelatin capsule shells.

Ingredient	Amount per capsule	%
efavirenz	100 mg	21.93
sodium lauryl sulfate	5 mg	1.10
sodium starch glycolate (intragranular)	50 mg	10.96
sodium starch glycolate (extragranular)	10 mg	2.19
lactose, hydrous	277 mg	60.75
talc	8 mg	1.75
colloidal silicon dioxide	4 mg	0.88
stearic acid	2 mg	0.44
Total Capsule Weight	456 mg	

Example 3

Wet Granulation 300 mg Tablet Formulation

Method of manufacture: The efavirenz, sodium starch glycolate and microcrystalline cellulose are granulated using an aqueous solution of sodium lauryl sulfate. This wet mass may then be dried in a fluid bed, tray or other suitable dryer. The dried granulation may then be milled to achieve the desired particle size distribution. This blend is compressed into tablets. These tablets may be coated if desired.

Ingredient	Amount per tablet	%
efavirenz	300 mg	50.00
sodium lauryl sulfate	12 mg	2.00
microcrystalline cellulose	120 mg	20.00
sodium starch glycolate	120 mg	20.00
lactose, hydrous	42 mg	7.00
magnesium stearate	6 mg	1.00
Total Tablet Weight	600 mg	

Assays were performed on capsule and tablet samples taken during the manufacturing processes described above. Analyses of the capsules and tablets utilized USP specified procedures. The dissolution test used USP methodology Apparatus 2 (paddles at 50 RPM, 900 mL of 1% sodium lauryl sulfate-distilled water solution at 37° C.)

TABLE 1

Dissolution Assay of Capsule Formulation
Capsule Formulation of Example 1:

Time (minutes)	% Dissolved
10	82.9
15	94.6
30	98.5
45	99.3
60	99.6

TABLE 2

Dissolution Assay of Tablet Formulation
Tablet Formulation of Example 3:

Time (minutes)	% Dissolved
10	78.0
15	91.5
30	100.0
45	102.1
60	102.9

Assays were performed to determine dosage-form uniformity on capsule and tablet samples taken during the manufacturing processes described above. Capsules and tablets were tested for content uniformity following USP specified guidelines. Results are shown in Table 3. "RSD" as used herein refers to relative standard deviation and is calculated according to USP guidelines.

TABLE 3

Content Uniformity Assay	
Capsules from Example 1: content uniformity	100.2 ± 1.7% (mean ± RSD)
Tablets from Example 3: content uniformity	104.3 ± 0.7% (mean ± RSD)

What is claimed is:

1. A method for treating infection by HIV comprising administering to a patient, in need of such treatment, a capsule or a compressed tablet pharmaceutical dosage form comprising a therapeutically effective amount of efavirenz and greater than about 10% by weight of a disintegrant relative to the total dry weight of the pharmaceutical dosage form.

2. A method for treating infection by HIV according to claim 1, wherein at least one disintegrant is selected from the group consisting of modified starches, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone.

3. A method for treating infection by HIV according to claim 2, wherein the disintegrant is selected from one or more modified starches.

4. A method for treating infection by HIV according to claim 3, wherein the modified starch is sodium starch glycolate.

5. A method for treating infection by HIV according to claim 3 wherein the capsule or compressed tablet pharmaceutical dosage form is prepared using a wet granulation step containing efavirenz and one or more modified starches, wherein the modified starch is present in the wet granulation step in an amount of from about 10% to about 75% by weight relative to the total dry weight of the components of the wet granulation step.

6. A method for treating infection by HIV according to claim 3 wherein the modified starch is present in the wet granulation step of the manufacturing process in an amount of from about 20% to about 55% by weight relative to total dry weight of the components of the wet granulation step.

7. A method for treating infection by HIV according to claim 1 wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from about 5 to about 1000 mg.

8. A method for treating infection by HIV according to claim 1 wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from about 5 to about 500 mg.

9. A method for treating infection by HIV according to claim 1 wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from 500 to about 1000 mg.

10. A method for treating infection by HIV according to claim 1 wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from about 25 to about 350 mg.

11. A method for treating infection by HIV according to claim 1 wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from about 50 to about 200 mg.

12. A method for treating infection by HIV according to claim 5 or 6, wherein the wet granulation step is carried out in the presence of sodium lauryl sulfate.

13. A method for treating infection by HIV according to claim 12, wherein the sodium lauryl sulfate is present in an amount of about 0.1% to about 5% by weight relative to total dry weight of the components of the wet granulation step.

14. A method for treating infection by HIV according to claim 1, wherein the efavirenz is present in the pharmaceutical dosage form in an amount of from about 5 to about 800 mg.

15. A method for treating infection by HIV comprising administering to a patient, in need of such treatment, a pharmaceutical dosage form comprising:

(a) a therapeutically effective amount of efavirenz;

(b) a surfactant;

(c) a disintegrant;

(d) a binder;

(e) a diluent;

(f) a glidant; and

(g) optionally additional pharmaceutically acceptable excipients; wherein at least one disintegrant is selected from the group consisting of modified starches, croscarmellose sodium, carboxymethylcellulose calcium and crospovidone and such disintegrant is present in an amount greater than about 10% by weight of the total dry weight of the capsule contents or the compressed tablet.

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