

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75-189

CORRESPONDENCE



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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May 1, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT

N / AF
FPL

ANDA #75-189
NABUMETONE TABLETS, 500 mg and 750 mg
LABELING AMENDMENT

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced tentatively approved ANDA as a result of a telephone contact between Jim Braw of the Office of Generic Drugs and Deborah Jaskot, Senior Director of Regulatory Affairs at TEVA Pharmaceuticals USA on April 14, 2000. Mr. Braw requested revision of our package insert labeling such that all reference to Nabumetone Tablets, 750 mg be deleted.

Per Mr. Braw's request, TEVA USA labeling has been revised to delete all reference to the 750 strength, and twelve copies of final print labeling are provided herein. Please note that as TEVA recently acquired Copley Pharmaceuticals, we were also requested to revise the labeling for this product (ANDA # 75-179) to remove all reference to the 500 mg strength. Therefore, revised labeling for ANDA # 75-179 is being submitted today in an amendment under separate cover.

Should you have any further questions or concerns regarding ANDA # 75-189, please contact me by telephone at (215) 256-8400, extension 5249 or by facsimile at (215) 256-8105.

Sincerely,

DAJ/jbp
Enclosures





Deborah A. Jaskot
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February 22, 2000

ANDA 071-189-01-01
N/A M

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
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7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
TELEPHONE AMENDMENT -REVISION OF DRUG SUBSTANCE & DRUG PRODUCT
METHODS

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending application for the purpose of responding to deficiencies presented to us via a telephone conversation with Ms. Ruby Yu of your office. Specifically, the analytical methods for the inclusion of an RSD requirement to the Assay and Related Substances tests for the drug substance as well as to the degradant/impurity test for the finished drug product. The response will be presented such that a summarization of the deficiency will be provided, in bold, followed by our response.

Although all test results were within specification, the method specifies no RSD limits for replicate injections for the drug substance Assay and Related Substances determinations. FDA's analyst did perform six replicate injections and obtained RSDs and respectively. It is recommended that these determinations incorporate an RSD specification with an appropriate value such as '

The chromatographic system used in the Assay and Related Substances determinations are identical. As such, the two tests are typically performed in the same chromatographic run. To this end we propose that, under typical use when the two



tests are performed simultaneously, the *Assay* standard will be used to establish the reproducibility of the system. Specifically, the *Assay* standard will undergo five replicate injections, the results of which must meet an RSD requirement of "NMT

In the event that the *Related Substances* determination were to be performed separate from the *Assay* determination, the *Related Substances* Solution #2 (equivalent in concentration to the *Assay* standard) will be used to ensure acceptable reproducibility of the system. This *Related Substances* Solution will undergo six replicate injections, the results of which must meet the requirement of

A copy of the drug substance method AM-2812, revised to add the RSD requirements, is provided as Attachment 1.

The drug product method for the *Determination of Impurities and Degradation Products* specifies an RSD limit of _____ for replicate injections of Standard Solution C. As FDA's analyst obtained an actual RSD _____ a lower specification, such as "NMT _____", seems appropriate.

Historical data that has been generated during the performance of this test was reviewed to determine the appropriateness of the recommended specification. During this review it became apparent that RSD results that have been obtained in our laboratories have not been as low as that obtained by the FDA analyst. The following are the RSD results obtained from the accelerated stability samples for the two pivotal batches:

RSD results, in %, obtained during <i>Determination of Impurities and Degradation Products</i> testing		
Month	K-22264 (500 mg)	K-22174 (750 mg)
0	2.4	4.6
1	5.6	0.9
2	3.2	1.8
3	1.1	8.5

The variation in the reproducibility of the impurity standard injections observed in these tables demonstrates the real reproducibility of this measurement. The variables that each test station experienced includes different equipment, different time intervals,

and different analysts. As with any test, each of these variables can contribute to the total observed error such that the effects can partially "cancel each other out", or they can be additive. The concentration of Standard Solution C is :

Using a _____ as requested by your laboratory, would correlate to a deviation of approximately _____. This extremely low level would, without doubt, be nearing the sensitivity limit of many _____ systems. While the new, more sophisticated systems may be more sensitive to quantitation at this level, the older, though still acceptable systems, that are prevalent in many QC laboratories may not bode as well.

Based on the above, we propose an RSD requirement, based on six replicate injections of Standard Solution C, _____". It is our opinion that this limit will ensure that the reproducibility of the system will be acceptable for the determination of the impurities and degradation products contained in the finished drug product. Both the release method, AM-41260, and the method used for stability studies, SI-11125, have been revised to contain our proposed RSD requirement. AM-41260 is provided as Attachment 2 and SI-11125 is provided as Attachment 3.

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249 or by facsimile at (215)-256-8105.

Sincerely,



DAJ/rsv
Enclosures



Deborah /
Sr. Director, Regulator

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January 11, 2000

Douglas Sporn, Director
Office of Generic Drugs
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Document Control Room
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MINOR AMENDMENT

ORIG AMENDMENT

N/A

ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
90 DAY AMENDMENT - CHEMISTRY, MANUFACTURING & CONTROLS, AND LABELLING

Dear Mr. Sporn:

As required by our letter of tentative approval on December 24, 1998, we submit herewith an amendment to our above referenced ANDA. Based on Smith-Kline Beecham's receipt of Notice of Non-Infringement, the thirty month stay period provided by the regulations is due to expire on April 10, 2000. This amendment is being provided approximately 90 days prior to this date which corresponds to January 11, 2000.

The intent of this correspondence is to disclose any revisions that have been made to the control documents contained in this application since tentative approval was received. All changes are summarized below.

<u>Document</u>	<u>Date Implemented</u>	<u>Description of Change</u>
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NW
1-11-00

Document

Date Implemented

Description of Change

Twelve copies of final print container labels and insert labelling were provided in our April 28, 1998 Major Amendment. Review of the FDA Labeling Web Site shows that the last approved version of innovator labelling was from 1993. As such, no changes have been made to our product labelling since the submission of the final print material.

This information is submitted for review and retention in your files. If there are any questions regarding information presented in this amendment, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105. We look forward to your continued review and final approval of this pending abbreviated new drug application.

Sincerely,



DAJ/rsv
Enclosures



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March 4, 1999

*Noted.
NAE
Theresa Anderson
application
remains in
TA status
3/31/99*

ADJ CORRESP

NC

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-189
NABUMETONE TABLETS, 500 MG AND 750 MG
CORRESPONDENCE - WITHDRAWAL OF FEBRUARY 9, 1999 AMENDMENT

Dear Mr. Sporn,

We submit herewith a request to withdraw our February 9, 1999 "Gratuitous Amendment" to the above referenced tentatively approved ANDA. It has come to our attention that the testing facilities proposed therein had previously been approved as part of the tentative approval received for this file on December 24, 1998. As such, we wish to withdraw this unnecessary February 9, 1999 amendment. We apologize for any confusion that this submission may have caused. Additionally, we will act on this product's tentative approval as instructed in your letter of December 24, 1998.

Sincerely,

Deborah Jaskot/pe
DAJ/pe

RECEIVED

MAR 06 1999

GENERIC DRUGS



Deborah A. Jaskot
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*Noted -
see subsequent
submissions dated
3/4/99
N/A
Muel Anderson*

February 9, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT

NDA ORIG AMENDMENT

N/A A

ANDA #75-189
NABUMETONE TABLETS, 500 mg and 750 mg
GRATUITOUS AMENDMENT - ADDITION OF ANALYTICAL TESTING FACILITIES

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced tentatively approved ANDA. Specifically, we propose the use of two alternate analytical testing facilities for the stability testing of post approval batches for the above mentioned product in addition to the Kfar Saba, Israel site which was tentatively approved in the original application. The two proposed analytical testing facilities (both owned by TEVA Pharmaceuticals Industries, Ltd.) are as follows:

vim -
RECEIVED
FEB 11 1999

In support of this change, TEVA Pharmaceuticals USA acknowledges the **GENERIC DRUGS**

1. The test method(s) approved in the application will be used.
2. The new testing facilities have the capability of performing the intended testing.
3. The new testing facilities have had satisfactory current good manufacturing practice (cGMP) inspections within the past two years. (Attachment 1)

This information is submitted for your review and approval.

Should you have any questions or concerns regarding this submission, please contact me by telephone at (215) 256-8400, extension 5249 or by facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/pe

Attachments



Deborah A. Jaskot
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February 3, 1999

*Noted:
see T. com of
2/18/99. Consider this piece
to be NC and NAI
Mark Anderson
(Contractors agreement rec. and dated 2/17/99)
PAC-ATLS SPECIAL SUPPLEMENT
CHANGES BEING EFFECTED*

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP,
NC

ANDA #75-189
NABUMETONE TABLETS, 500 mg and 750 mg
SPECIAL SUPPLEMENT - CHANGE IN ANALYTICAL TESTING FACILITIES

Dear Mr. Sporn:

We submit herewith a Special Supplement - Changes Being Effected in accord with PAC-ATLS. Specifically, we propose the use of two alternate analytical testing facilities for the stability testing of post approval batches for the above mentioned product in addition to the Kfar Saba, Israel site which was approved in the original application. The two proposed analytical testing facilities (both owned by TEVA Pharmaceuticals Industries, Ltd.) are as follows:

In support of this change, TEVA Pharmaceuticals USA acknowledges the following:

1. The test method(s) approved in the application or methods that have been implemented under 21 CFR 314.70(d) are used.
2. All post approval commitments relating to the test method(s) have been fulfilled. (Attachment 1)

[Faint stamps and handwritten notes]

3. The new testing facilities have the capability of performing the intended testing.
4. The new testing facilities have had satisfactory current good manufacturing practice (cGMP) inspections within the past two years. (Attachment 2)

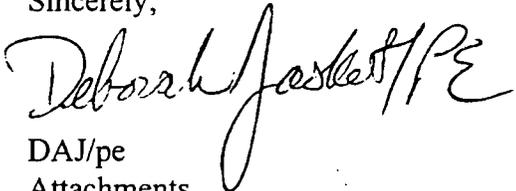
In accord with the Agency's submission guideline dated November 8, 1991, we draw your attention to the essentially identical supplement to the following applications:

<u>ANDA#</u>	<u>PRODUCT NAME</u>
75-147	Isosorbide Mononitrate Tablets, 20 mg
74-989	Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg

This information is submitted for your review and approval.

Should you have any questions or concerns regarding this submission, please contact me by telephone at (215) 256-8400, extension 5249 or by facsimile at (215) 256-8105.

Sincerely,



DAJ/pe
Attachments

Deborah A. Jaskot
Sr. Director, Regulatory Affairs**Corporate Headquarters:**
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FAX: (215) 256-7855**NEW CORRESP**
NC to
FA

November 23, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773**FACSIMILE AMENDMENT**ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
FACSIMILE AMENDMENT -CHEMISTRY, MANUFACTURING, CONTROLS &
BIOEQUIVALENCE

Dear Mr. Sporn:

We submit herewith a facsimile amendment in response to a Bioequivalence review letter dated September 22, 1998 and a Chemistry review letter dated November 3, 1998. The review comments cited in these letters will be addressed in the order in which they were presented, with response to the Bioequivalence letter appearing first.

Bioequivalence

1. The dissolution method and specification indicated in your letter is as follows:

New

This method and its corresponding specification have been incorporated into our release and stability programs for these drug products. The Product Specification Sheets and Finished Product Stability Protocols have been revised to include this requirement and are provided as Attachment 1. The revised dissolution method for stability studies (SI-11069) and the

revised procedures manual for product release (AM-41260) are provided as Attachment 2 for your review.

Notes:

We acknowledge that the bioequivalency comments presented in the aforementioned review letter are preliminary and are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific regulatory issues.

Chemistry

A.

1. Please see response to Bioequivalence #1 above.
2. The requested testing has been performed. However, due to the age of the test batches, testing of 3 month accelerated temperature stability samples was not possible (stability start dates: 750 mg - 3/97; 500 mg - 4/97; Date of request for testing : 11/98). In place of the requested samples, the 20 month controlled room temperature sample for the 750 mg strength product and the 18 month controlled room temperature sample for the 500 mg product were used for the analysis. The results are presented as Attachment 3.

B. Notes & Acknowledgements

We acknowledge that the reporting requirement for the proposed new resin bottle for use in the future commercial manufacturing of the drug products is covered under 21 CFR 314.70(d)(6). As such, this information will be reported in the appropriate annual report for the drug product as required.

It is TEVA Pharmaceuticals USA's opinion that the information presented in this communication provides a complete response to all outstanding deficiencies brought forth by the Office of Generic Drugs. Should there be any questions regarding any of the information provided in this correspondence, please do not hesitate to contact me either by telephone at (215)-256-8400 ext. 5249, or by facsimile at (215)-256-8105.

This information is submitted towards your continued review and approval of this pending Abbreviated New Drug Application.

Sincerely,



DAJ/rsv
Attachments

38. Chemistry Comments to be Provided to the Applicant:ANDA: 75-189 APPLICANT: Teva Pharmaceuticals USADRUG PRODUCT: Nabumetone Tablets, 750 mg and 500 mg

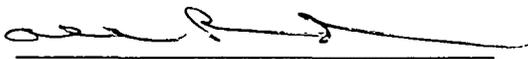
A. The deficiencies presented below represent FACSIMILE deficiencies:

1. Please provide revised method and specifications for Finished Product release and stability to include the method and specifications for dissolution recommended by the Division of Bioequivalence.
2. Please provide dissolution test data for the third month accelerated stability studies for samples of the ANDA exhibit batches packaged in the proposed market container/closure system. The test data should meet the specifications recommended by the Division of Bioequivalence.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Regarding the proposed new resin bottle for use in the future commercial manufacturing of this drug product, please be advised that the change of container is covered under 21 CFR 314.70 (d)(6).

Sincerely yours,


Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-189

APPLICANT: Teva Pharmaceutical

DRUG PRODUCT: 750 mg and 500 mg Nabumetone Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 2% SLS in water at 37° C using USP Apparatus (II) at 50 rpm. The test product should meet the following interim specifications:

Not less _____ of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-189

APPLICANT: Teva Pharmaceutical

DRUG PRODUCT: 750 mg and 500 mg Nabumetone Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 2% SLS in water at 37° C using USP Apparatus (II) at 50 rpm. The test product should meet the following interim specifications:

Not less _____ of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

Page(s) _____

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

4/28/98

8.

9.

number of tablets being coated and taking into account the efficiency of the process, it is possible

10.

In addition to addressing the CMC deficiencies noted in your letter, the following information is supplied for your review. The master production batch records have been revised to correct errors listed in the mixing times and detail has been added to the sampling procedure. The revised records are provided as Attachment 9. The comparative dissolution profiles provided with regards to the hardness verification study were found to contain several typographical errors. These errors have been corrected and a revised profile report is provided as Attachment 10. Typographical errors were also found in the finished product certificates of analysis. The error was located in the reporting of the impurity/degradants. Revised certificates are provided as Attachment 11. Attachment 12 contains a full list of facilities which may be used for the post approval commercial stability testing of this product.

B. NOTES AND ACKNOWLEDGMENTS

1. It is acknowledged that the acceptability of our dissolution method and the corresponding specifications will be determined by the Division of Bioequivalence.

2. The pharmaceutical function of the inactive ingredients contained in our proposed formulation are provided as Attachment 13.
3. TEVA acknowledges that the firms referenced in the ANDA are required to be evaluated for satisfactory cGMP compliance and that evaluations of the referenced firms have been requested from the Division of Manufacturing and Product Quality.
4. It has been TEVA's understanding in past discussions with OGD personnel, that methods validation prior to the approval of the ANDA is preferred but, it should not delay the approval of the ANDA in the absence of any outstanding deficiencies regarding this application.
5. The referenced changes to the monograph requirements for Sodium . . . and Silicon . . . are noted and have been incorporated into the analytical procedures manuals for each ingredient. As stated in our original ANDA submission, TEVA commits to update the analytical test procedures for each of the compendial ingredients contained in the formulation for this product in accord with revisions made to the official compendial monographs.

LABELING

1. Final print labeling, revised in accord with the deficiency comments, is provided as Attachment 14. Please note, comment 2.g.ii. regarding the inclusion of NDC numbers was not added to our insert. It is TEVA's policy not to include the NDC number on the product insert. The omission of this number allows the insert to remain neutral regardless of the possible distributor of the product. Thereby, the potential of mismatching a distributor specific label to a distributor specific insert is avoided. In addition, future revisions to the product insert are guaranteed to be applied for all distributors as all will utilize the same insert.

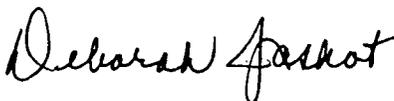
In addition to addressing the reviewer's comments, the statement "Caution: Federal law prohibits dispensing without prescription" has been replaced with "Rx only" on the immediate container label. This revision was made to comply with the Food and Drug Administration Modernization Act of 1997.

BIOEQUIVALENCE

1. Provided as Attachment 15 are the dissolution profiles for our product and the innovator using 2% SLS in water as the media and paddle speeds of 50, 75 and 100 RPM.

This information is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249 or by facsimile at (215)-256-8105.

Sincerely,



DAJ/rsv
Enclosures

FITZPATRICK, CELLA, HARPER & SCINTO

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January 7, 1998

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JOHN A. O'BRIEN
JOHN A. KRAUSE
HENRY J. RENK
DAVID F. RYAN
PETER SAXON
ANTHONY M. ZUPCIC
CHARLES P. BAKER
STEVAN J. BOSSES
EDWARD E. VASSALLO
RONALD A. CLAYTON
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ANNE M. MAHER
MARK J. ITRI *
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TIMOTHY J. KELLY
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MICHAEL P. SANDONATO
JOSEPH M. O'MALLEY, JR.
JOHN D. CARLIN
BRUCE M. WEXLER
JACK M. ARNOLD *
JOSEPH W. RAGUSA
WILLIAM J. ZAK, JR.
DANIEL S. GLUECK *
BRIAN L. KLOCK *
PAUL A. PYSHER *
DOLORES MORO-GROSSMAN
GREGORY B. SEPHTON
DOUGLAS SHARROTT

THOMAS D. PEASE
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GORDON F. SIECKMANN *
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TONY E. PIOTROWSKI
AMR O. ALY
KATHRYN L. SIEBURTH
FLORA W. FENG
LEE B. SHELTON
KENNETH CRIMALDI *
JENNIFER A. REDA
DOROTHY C. ALEVIZATOS *
J. KENNETH JOUNG *
SHU NUK LEE
NATALIE M. DERZKO

NAT
Notification of
Legal action against
Jeva
introduced
1/14/98

* NOT ADMITTED IN NEW YORK

VIA CERTIFIED MAIL --RETURN RECEIPT REQUESTED

Food & Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: SmithKline Beecham Corporation and
Beecham Group p.l.c. v.
Teva Pharmaceuticals, USA.

Gentlemen:

My firm represents SmithKline Beecham Corporation ("SmithKline Beecham") and Beecham Group p.l.c. Teva Pharmaceuticals USA ("Teva") filed ANDA 75-189 directed to 500 mg and 750 mg nabumetone tablets which are generic versions of SmithKline Beecham's Relafen® tablets. Teva's ANDA contains a certification pursuant to the Food, Drug and Cosmetic Act (the "Act") section 505(j)(2)(A)(vii)(IV) asserting that United States Patent No. 4,420,639 owned by Beecham Group p.l.c. ("the '639 patent") will not be infringed by Teva and is not valid. Notice of this certification was received by SmithKline Beecham on or about October 10, 1997. The certification was not provided by Teva to the patent owner, Beecham Group p.l.c.

This letter is to advise the Food and Drug Administration ("FDA") that on November 13, 1997 SmithKline Beecham and Beecham Group p.l.c. filed a lawsuit against Teva in the United States District Court for the District of Massachusetts alleging infringement of the '639 patent. A copy of the Complaint is enclosed.

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JAN 10 9 1998
GENERIC DRUGS

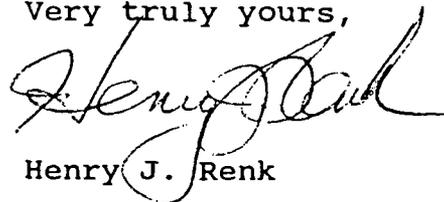
Medline
1-12

Food & Drug Administration
January 7, 1998
Page 2

Because SmithKline Beecham and Beecham Group p.l.c. have filed their action within 45 days of receipt of notice of the certification, pursuant to section 505(j)(4)(B)(iii) of the Act, the FDA cannot approve ANDA 75-189 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice . . . or such shorter or longer period as the court may order"

Should any questions concerning this matter arise, please feel free to contact my firm directly.

Very truly yours,



Henry J. Renk

Enclosure

cc: Stephen Venetianer, Esq. - (w/o encl. - by mail)

HJR:\nj1

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JAN 09 1998

GENERIC DRUGS

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-189

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT:Nabumetone Tablets, 750 mg and 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You should submit dissolution data for your product using 2% SLS in water as the dissolution medium. You should also investigate the dissolution of your product at paddle speeds of 75 and 50 rpms using this medium.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:

TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

December 17, 1997

NDA ORIG AMENDMENT
45

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
SUBMISSION OF REQUESTED BIOEQUIVALENCE CHROMATOGRAMS

Dear Mr. Sporn:

A telephone request was made by Ms. Lizzie Sanchez of your office on December 1, 1997. Ms. Sanchez requested copies of all chromatograms from the analyses of samples contained in the bioequivalence studies that have exhibited the elution of a peak near the 6-methoxy-2-naphthylacetic acid (6-MNA) peak. Subject number 5 was provided as reference to this request. Provided herein are copies of all chromatograms for subject #5 of the fasted study. Please note that this subject was the only study subject exhibiting this phenomena in the fasted study. Also provided are copies of all chromatograms for subjects 1, 2, 10, and 18, who are the only study subjects exhibiting this elution within the post-prandial study. Please also note that in many instances, the peak in question whose elution is near the 6-MNA peak, is below the limit of quantitation for this analytical method. This consideration, combined with the fact that quantitation of the analyte peaks is performed using the peak height parameter, indicates that the likelihood of interference with the quantitation of the 6-MNA peak is slight.

This information is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249.

Sincerely,

DAJ/rsv
Enclosures

RECEIVED

DEC 23 1997

GENERIC DRUGS



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

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*NAB
Nabumetone
12/22/97*

NEW CORRESP

NC

December 16, 1997

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
NOTIFICATION - COMPLETION OF 45 DAY PERIOD PROVIDED UNDER 505(j)(4)(B)(iii)

Dear Mr. Sporn:

In accord with 21 CFR 314.95, Teva Pharmaceuticals USA is hereby providing notice to this ANDA to provide information regarding our claim of non-infringement of U.S. patent # 4,420,639. Notification of our patent certification claiming non-infringement was received by SmithKline Beecham on October 10, 1997. The forty-five day period, as described under section 505(j)(4)(B)(iii) of the Act, has ended as of November 24, 1997. SmithKline Beecham has filed a complaint against Teva Pharmaceuticals USA within the forty-five day period and claims infringement of the above referenced patent. Results of any litigation or settlement will be supplied to this application as it becomes available.

This information is submitted for your review and retention in your files. If there are any questions regarding this information, please do not hesitate to call me at (215)-256-8400 ext. 5249.

Sincerely,

DAJ/rsv
Enclosure

RECEIVED

DEC 18 1997

GENERIC DRUGS

*Madame
12-19-97
1*



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
50 Cathill Road, Sellersville, PA 18960

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Phone: (215) 256 8400
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Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

October 23, 1997

NAI
[Signature]

11/18/97

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-189
NABUMETONE TABLETS, 500 mg and 750 mg
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) AND 21 CFR 314.95

Dear Mr. Sporn:

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby amending this ANDA to provide documentation of the receipt of the Notice of Certification for U.S. Patent No. 4,420,639. The NDA holder, SmithKline Beecham, received the notice on October 10, 1997. This date is evidenced by the attached copy of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is October 11, 1997, the first day after receipt of notice. The 45-day period will therefore end on November 24, 1997.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosure

RECEIVED

OCT 27 1997

GENERIC DRUGS

Madue
11.2.97



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

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FAX: (215) 256 7855

October 8, 1997

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA# 75-189
NABUMETONE TABLETS, 500mg AND 750mg
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Sporn:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 4,420,639 was provided to the holder of NDA 19-583 for Relafen® (Nabumetone Tablets, 500mg and 750mg) and owner of the patent, SmithKline Beecham, in accord with 314.95(b). The notice dated October 8, 1997 contains the information as required under 314.95(c). A copy of the notice is provided herein.

Sincerely,

DAJ/rsv

Enclosures

RECEIVED

OCT 10 1997

GENERIC DRUGS

ANDA 75-189

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

OCT 1 1997

|||||

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Nabumetone Tablets, 500 mg and 750 mg

DATE OF APPLICATION: August 18, 1997

DATE OF RECEIPT: August 25, 1997

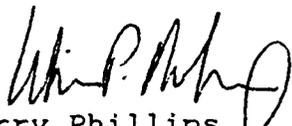
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jim Wilson
Project Manager
(301) 827-5848

Sincerely yours,



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
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Toll Free: (888) TEVA USA
FAX: (215) 256 7855

August 18, 1997

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
NABUMETONE TABLETS, 500 mg and 750 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product **Nabumetone Tablets, 500 mg and 750 mg**.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs April 1997 Guidance for Industry: Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application. These copies are presented in a total of **21** volumes; **10** for the archival copy and **11** for the review copy. The application contains a full report of two *in vivo* bioavailability studies. These studies compared **Nabumetone Tablets, 750 mg** manufactured by TEVA Pharmaceutical Industries Ltd. to the reference listed drug, **Relafen® Tablets 750 mg** under both fasting and post-prandial conditions. The application also contains a request for a waiver of evidence of *in vivo* bioavailability.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should you have any questions or need additional documentation, please do not hesitate to contact me at (215)-256-8400 ext. 5249.

Sincerely,

DAJ/rsv
Enclosures

RECEIVED

AUG 25 1997

GENERIC DRUGS

6. Please provide a specification for disintegration for your in-process test (p. 2706).
7. Please revise the release and stability limit for total impurities/degradation products to be closer to the observed values.
8. Please submit method SI-11127/Ed.02 to the application.
9. Please establish a limit for weight gain in your in-process control for the film coating operation. Alternatively, you may explain how your coating operation ensures that the correct amount of coating material is applied.
10. To our knowledge, as of October 1, 1997, _____ is no longer available. Please provide a commitment that you will incorporate any change of resin into your long term stability program, when your closure system is not made of _____. Also provide a protocol to the application or make a commitment that the USP protocol will be followed in accepting the new closures.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Acceptability of your dissolution method and specifications will be determined by the Division of Bioequivalence.
2. We recommend that you provide the pharmaceutical function of the inactive ingredients used in your formulation.
3. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.
4. We require a satisfactory methods validation prior to approval of the ANDA. We will schedule the validation with the District Office once the test and specification issues are resolved.

5. Pleased be advised that Supplement 7 of NF 18 added Organic Volatile Impurities test for sodium _____, and Supplement 6 of NF 18 contains revisions for Silicon _____. NF. The NF and USP references for each ingredient should be accurate and up to date. Also provide a commitment that the ingredients used in the manufacture of the drug product will meet the current compendian requirements.

Sincerely yours,



sd/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research