BAKER NORTON
PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

March 8, 2000

NDA ORIG AMENDMENT
N/AA

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT
ADDITIONAL INFORMATION

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 6 mg/mL concentration in 30 mg/5 mL, 150 mg/25 mL, and 300 mg/50 mL vial sizes. Reference is also made to the Agency's correspondence of November 8, 1999 (copy attached) and to our Major Amendment dated December 8, 1999, hereafter referred to as the December Amendment.

Hereby, we are submitting a Gratuitous Amendment to the December Amendment. The purpose of this Gratuitous Amendment is to further clarify our responses and corrections to the December Amendment.

For the ease of the review, this Amendment is divided into two sections. Section I contains corrections to our December Amendment on comments 3, 13 and 17 of the November 8, 1999 deficiency letter. With regard to endotoxin limits for the drug substance and drug product (comment 3 of the deficiency letter), we agree with the Agency that lower specification limits of endotoxin level is justified and explained in this Gratuitous Amendment. Please also note that the temperature ranges in our December Amendment on the response to Comment 13 were incorrectly stated and the actual condition is provided in this submission. Furthermore, revision has been made to the master batch record to include a formula to be used to calculate the amount of active drug substance required after correcting for the potency and moisture content. This modification intends to further clarify the Agency's comment 17 of the November 8, 1999 deficiency letter.

Section II includes additional information and clarifications to seven questions which were responded to in the December Amendment and we request this to be reviewed in conjunction with that amendment.

In order to simplify the reviewer's process and alleviate any confusion that may arise in reviewing both amendments simultaneously, we are attaching to this letter a table that lists the question numbers in the Agency's correspondence of November 8, 1999. The table indicates which response should be reviewed: that of the December amendment, that of the attached amendment, or both responses in conjunction with each other.

As required by 21 CFR 314.96(b), we provide a Field Copy Certification of this Gratuitous Amendment. Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

cc: District Office

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

April 21, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT RESPONSE

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

N/A

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. This submission is the response to the deficiencies noted in the Agency's facsimile correspondence dated April 17, 2000 (copy attached).

Attached to this letter, please find the Baker Norton contact report dated April 18, 2000 which documents the conversation with Elaine Hu, the Project Manager and with Dr. Liang Lii Huang, the Chemistry Reviewer to clarify the comments contained in the Deficiency Letter. The agreements from this teleconference form the basis of the Chemistry section response.

The responses to the Chemistry, Environmental Assessment and Labeling comments are attached in the same order as in the deficiency letter. The FDA comments are restated in **bold** print followed by the response in regular print. We understand this response is considered a Minor Amendment.

As required by 21 CFR 314.96(b), we are providing a Field Copy Certification of this Amendment. Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

cc: District Office

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

April 27, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. This submission is a gratuitous amendment to the Minor Amendment submitted on April 21, 2000 in response to the Agency's facsimile correspondence dated April 17, 2000 (copy attached).

Attached to this letter, please find the Baker Norton contact report dated April 18, 2000 which documents the conversation with Nancy Sager (Office of Pharmaceutical Science), to clarify Comment 4 contained in the Deficiency Letter. While our April 21 response was specific to one species, Nancy indicated that our response should be general in nature but include at least one specific example. Based on this clarification, we have reworded our response as requested. In addition, we have also changed the wording in Section 6.2.c from "renewable biomass sources" to "non-endangered wild species or cultivated yew" as had already been changed in Section 8 in response to comment 6, part 2.

These two changes are incorporated into the revised Environmental Assessment included in Appendix 1 of this amendment. Because the appendices of the Environmental Assessment have not changed, they are not included in this update in accordance with the Agency facsimile of April 17, 2000.

As required by 21 CFR 314.96(b), we are providing a Field Copy Certification of this Amendment. Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

cc: District Office

BAKER NORTON
PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

ANDA 75-184
GRATUITOUS AMENDMENT - LABELING

NDA ORIG AMENDMENT
N/AF

May 10, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Paclitaxel Injection, 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL Multi-Dose Vials

Dear Mr Buehler,

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. On April 21, 2000, Baker Norton responded with a Minor Amendment to the Agency's facsimile correspondence received April 21, 2000. Reference is also made to a Gratuitous Labeling Amendment submitted January 26, 2000.

Baker Norton is amending its April 21, 2000 Minor Amendment by submitting this Gratuitous Amendment. This amendment provides for a change in reference to the name of the finished product as it appears on the labeling (cartons, vial labels and insert/patient leaflet). The difference between this revised labeling and previous labeling (04/21/00) is only in reference to the brand name of the drug. No other changes have been incorporated. The BNP revised insert/patient leaflet, carton and vial labeling now refer to the product by another BNP brand name - **Onxol™ (paclitaxel) Injection** instead of Paxene® (paclitaxel) Injection. On the package insert/patient leaflet, the name paclitaxel is retained in areas where the drug is cited in reference to clinical studies.

The reason for the brand name change from Paxene® to **Onxol™** is that the name Paxene® is assigned to the paclitaxel product which has been tentatively approved under our NDA for treatment of patients with AIDS related Kaposi's sarcoma. As the paclitaxel product subject of ANDA 75-184 is indicated for second line treatment of breast and ovarian cancer, a different name is required to avoid any confusion between these two distinct products.

CENTER FOR DRUG
RECD
MAY 11 2000
OGD

It is our intention for the labeling to be reviewed in conjunction with our Minor Amendment dated April 21, 2000, and be treated as one complete Amendment. Included in this submission are 12 copies of the revised package insert/patient leaflet, carton and vial labeling for the 30 mg/5mL, 150 mg/25 mL and the 300 mg/50 mL strengths. Also included is an enlarged version of the package insert/patient leaflet.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to call me at (305) 575-6336.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs
Baker Norton Pharmaceuticals, Inc.

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

May 23, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC

PATENT INFRINGEMENT LITIGATION INFORMATION

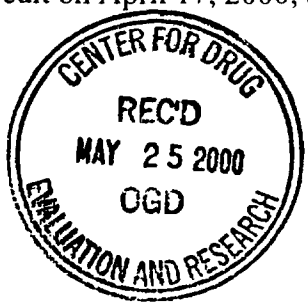
Re: ANDA 75-184: ONXOL™, Paclitaxel Injection, 30 mg/5mL, 150 gm/25 mL And 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to a teleconference on May 11, 2000 with Elaine Hu, Project Manager, OGD, in which Elaine reminded us that it was our responsibility to provide OGD with documentation concerning the outcome of any patent challenges pertaining to this application.

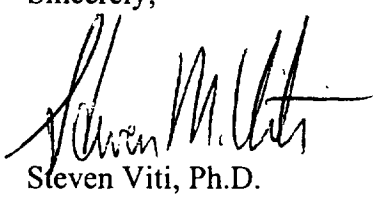
This communication relates to patent infringement litigation between the sponsor of the above-referenced ANDA, Baker Norton Pharmaceuticals Co. (BNP), and Bristol-Myers Squibb Company (BMS), the NDA holder. This litigation was filed by BMS against Immunex Corporation based on the Paragraph IV certification contained in the above-referenced ANDA, which was subsequently transferred to BNP. The lawsuit was filed in the United States District Court for the District of New Jersey as Civil Action No. 97-6050. BMS also sued other companies that had filed ANDAs for injectible paclitaxel containing Paragraph IV certifications, and these actions were consolidated.

Federal Judge William Walls entered a judgment of invalidity on April 7, 2000 (see attachment). This judgment was based on a grant of partial summary judgment in defendants' favor, followed by BMS' permanent abandonment of all patent claims not found invalid on summary judgment, and the Court ruled that this judgment was immediately appealable under Fed. R. Civ. P. 54(b). BMS filed a notice of appeal to the Court of Appeals for the Third Circuit on April 17, 2000, and the appellate proceeding remains pending.



At this time OGD is reviewing our minor amendment submitted April 21, 2000, and we believe the application to be approvable. Since the appeal will not be decided before June 2, 2000, when the 30-month stay under 21 U.S.C.A. §355(j)(5)(B)(iii) expires, we hereby request that final approval be granted for this application on June 2, 2000. If there are any other questions that must be resolved before June 2, 2000, please contact me at 305-575-6336 or via fax at 305-575-6339 as soon as possible.

Sincerely,



Steven Viti, Ph.D.
Director, Regulatory Affairs

BAKER NORTON
PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

May 26, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/Am

Telephone Amendment

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. This submission is a response to a telephone call received on 5/25/00 from Nancy Sager of the FDA regarding additional questions for our Environmental Assessment. The T-con Record of this conversation sent by facsimile is attached to the letter. Below you will find responses to each issue discussed in the teleconference.

1. Section 6.2a - Endangered Species and Yew

Please identify the specific state laws in California, Oregon and Washington for protecting endangered or threatened species.

The identity of the specific state laws have been incorporated into the third paragraph of *Section 6.2.a – Endangered Species and Yew* as shown below:

> *Idaho had no specific state or local laws pertaining to protection of endangered or threatened species. Montana had an endangered species act that was superseded by the federal law. Within these states, the Federal Endangered Species Act formed the basis of the restrictions on harvesting to protect endangered or threatened species. California (California Endangered Species Act), Oregon (ORS 564 and ORS 496.171-192) and Washington (Washington Endangered, Threatened, Sensitive Wildlife Species Classification) have specific state laws pertaining to identification and protection of endangered or threatened species. These state laws, in combination with the Federal Endangered Species Act, formed the basis of the restrictions on harvesting to protect the endangered or threatened species.*

2. The last version of the EA included a statement that "The Pacific Yew is not listed under the Federal Endangered Species Act (ESA), or under the Convention on International Trade in Endangered Species (CITES) as endangered or threatened." This statement was not included in this version of the EA. It should be put back in.

The statement above has been added back in to the first paragraph of *Section 6.2.a – Endangered Species and Yew* as shown below:

> ***Endangered Species And Yew:***
> *The Pacific yew is not listed under the Federal Endangered Species Act (ESA), or under the Convention on International Trade in Endangered Species (CITES) as endangered or threatened. The Pacific yew does comprise a component of habitat for several federally listed threatened or endangered animal species. This list appears in Appendix J of the Pacific Yew DEIS (USDA Forest Service et al. 1993). The list has also been reproduced in Appendix G of this document. As previously described in this section, Pacific Yew trees were harvested from lands in Oregon, Washington, Idaho, Montana and California. Within each of these states it was necessary for the harvesters to abide by all federal, state and local regulations and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting Pacific Yew.*

3. Section 8 - Alternatives

The use of non-endangered wild species (other than Pacific Yew) and cultivated yew need to be listed as separate alternatives. The specific species that are being investigated, the status of your investigation, and the factors, including environmental that will be considered in deciding whether or not to use the alternative should be discussed.

The requested information has been added to *Section 8 –Alternatives* as Alternatives 2 and 3 as shown below:

> *Alternative 2: It is possible to extract paclitaxel from non-endangered wild species such as Taxus yunnanensis, Taxus baccata and Taxus cuspidata. We have not selected any non-endangered wild species as an alternate source at this time. Several environmental and business factors will be considered before proposing this route as a commercial alternative. Environmental factors include confirmation that harvesting will be done within local, state and federal forestry and endangered species laws and that any other effects from the harvesting of these trees on the local ground and water habitats will be limited. Those business factors to be considered are price, quality and reliability of future supplies.*

> *Alternative 3: It is possible to extract paclitaxel from cultivated yew species such as Taxus Hicksii, Taxus media and Taxus X media Hicksii. We have evaluated Taxus X media Hicksii and found it acceptable for use on a chemical basis. Exhibit batches have been manufactured and may be submitted to this application in the future to support this alternate source. Several environmental and business factors will be considered before proposing this route as a commercial alternative. Environmentally, this alternative is attractive, as the cultivated species are harvested from privately controlled plantations, thus assuring that no local, state and federal endangered species laws will be violated. The environmental impact on the l ·al ground and water habitats is also easier to monitor and control. From an environmental standpoint, the use of cultivated yew species is preferable to harvesting of non-endangered wild yew species. Business factors including price, purity and reliability of future supplies have still to be evaluated.*

4. The second sentence in section 8 says that they "propose" that no further Pacific Yew will be collected. This should be clarified to state that there will not be any further harvesting.

The second sentence in Section 8 has been changed to state that there will not be any further harvesting of Pacific Yew as shown below:

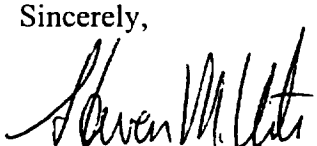
> *The proposed action in this application includes the use of a supply of Pacific Yew bark that has previously been collected for the manufacturing process. No further Pacific Yew will be collected for this product. Any future supplies of paclitaxel will either come from non-endangered wild species or from cultivated yew. At this time we have not selected a future alternate source. Once that selection is made we will notify the FDA in accordance with 21 CFR 314.96 or 314.70 and additional EA information will be provided to FDA if required.*

These four changes are incorporated into the revised Environmental Assessment included in Appendix 1 of this amendment. Because the appendices of the Environmental Assessment have not changed, they are not included in this update in accordance with the Agency facsimile of April 17, 2000.

As required by 21 CFR 314.96(b), we are providing a Field Copy Certification of this Amendment. Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,



Steven M. Viti, Ph.D.
Director, Regulatory Affairs

cc: District Office
Nancy Sager, WOC2

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

May 31, 2000

NEW CORRESP
NC

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Gratuitous Amendment – Labeling Information

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL, our Minor Amendment of April 21, 2000 introducing the brand name Paxene® and our Gratuitous Amendment of May 10, 2000 requesting a change in the brand name from Paxene to Onxol™. Reference is also made to a discussion with Elaine Hu today about withdrawal of the brand name Onxol.

We hereby withdraw, without prejudice, our Gratuitous Amendment of May 10, 2000. We elect to have the product approved as Paclitaxel Injection without any associated brand name. All other labeling changes submitted in the April 21, 2000 Minor Amendment, with the exception of the brand name, Paxene, remain in effect.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

BAKER NORTON
PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

NEW CORRESP

To: Dr. Allen Rudman, Deputy Director
Dr. Paul Schwartz, Chemistry Team Leader
Dr. Liang-Lii Huang, Chemistry Reviewer
Elaine Hu, Project Manager
Division of Chemistry
Office of Generic Drugs

From: Jane Hsiao, Ph.D.
Vice President
Baker Norton Pharmaceuticals, Inc.

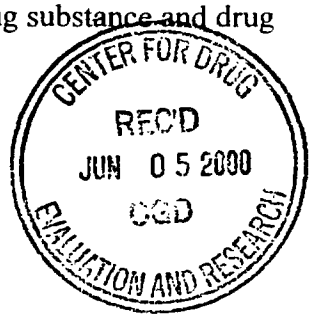
Date: June 2, 2000

Subject: **Additional Information as Requested on June 2, 2000**
ANDA 75-184
Paclitaxel Injection, 30mg/5ml, 150mg/25ml, & 300mg/50ml

Reference is made to the telephone conference call earlier today among Drs. Allen Rudman, Paul Schwartz, Liang-Lii Huang and you from the Agency and representatives from Baker Norton Pharmaceutical. Enclosed please find copies of the investigation reports referred to and requested by the Agency during that telephone call.

You will note the two reports, #99-36 and #99-37 are related to the investigations initiated due to problems experienced during the assay testing of the drug substance, Paclitaxel. Out-of-specification test results were generated for several lots of the Paclitaxel when the analysis was performed by a gradient system. The problem was found to be equipment related. Investigation of the low assay result for Paclitaxel drug substance started in July, 1999 when the analyst encountered failed system suitability check. In the report #99-36 the laboratory chemists reported experiencing temperature fluctuations, observations of higher than normal variability and low test results pointing to a specific unit when method was used. A General Investigation, as described in the Report #99-37 was then initiated to further assess the instrument reproducibility and to compare the results obtained using test methods

During the investigation period, an independent consultant, was invited to review and assist in this task. New equipment were purchased and qualified. Furthermore a comprehensive GMP audit to assess and improve the operation in the analytical laboratory was performed before any testing on Paclitaxel drug substance and drug products were resumed in March of 2000.



It is noted that these two investigation reports document the problems experienced and the steps taken to identify the cause of the out-of-specification potency assay for Paclitaxel drug substance. Several stability samples for the drug products, 150mg/25ml and 300mg/50ml pulled for testing were held in the laboratory while the investigations were in progress. These samples were due for testing, from July 1999 to January 2000, but not tested until March 2000 while the above investigation was in progress. When the analyst first reported the out-specification result of % for the 150mg/25ml 6-month sample on March 22, 1999, the Standard Operating Procedure 0150.022, Procedure for Re-Test, was enacted. The first result was confirmed by a repeat testing of a second set of sample that gave a result of %. The final reported value of % was the average of these two values. All these were documented in the analyst's laboratory notebooks (MD-693 p. 93-100 & MD-912 p.1-9).

Should you require further information please contact me directly at 305-575-6004 by phone. Thank you.

Sincerely,

Jane Hsiao

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

ANDA 75-184
LABELING AMENDMENT

June 5, 2000

ORIG AMENDMENT
NIAT

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Paclitaxel Injection, 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL Multi-Dose Vials

Dear Mr Buehler,

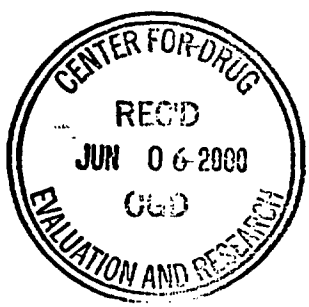
Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL, our Minor Amendment of April 21, 2000 introducing the brand name Paxene® and our Gratuitous Amendment of May 10, 2000 requesting a change in the brand name from Paxene® to Onxol™ and our Gratuitous Amendment–Labeling Information of May 31, 2000 withdrawing the Onxol brand name. A copy of the agency's letter of June 2, 2000 requesting additional changes can be found following this letter.

This amendment responses to the agency's letter of June 2 and also changes the name of the product from Onxol™ (paclitaxel) Injection to the generic name **Paclitaxel Injection** as described in the Gratuitous Amendment of May 31. Included in this submission are 12 copies of the revised package insert/patient leaflet, carton and vial labeling for the 30 mg/5mL, 150 mg/25 mL and the 300 mg/50 mL strengths. Also included is an enlarged version of the package insert/patient leaflet.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to call me at (305) 575-6336.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs
Baker Norton Pharmaceuticals, Inc.



BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

June 15, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

N/NC

TELEPHONE AMENDMENT - ADDITIONAL INFORMATION

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. Reference is also made to a telephone call from Theresa Watkins on June 15, 2000.

Ms. Watkins requested that we submit, to ANDA #75-184, a copy of the FDA's approval letter of the Fujisawa USA suitability petition for Paclitaxel Injection Concentrate, 6 mg/mL, 150 mg/25 mL vials, Docket Number 97P-0058/CP1. This document is referenced on page 100010 of our June 15, 1999 Amendment for ANDA # 75-184.

Attached to this letter you will find the requested document, which was also sent by facsimile to Ms. Watkins at 301-443-3847.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 16 2000
OGD

BAKER NORTON PHARMACEUTICALS, INC.®

VIA FACSIMILE: 301-443-3839

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

June 23, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AM

MINOR AMENDMENT
CHEMISTRY DEFICIENCY
and
MICROBIOLOGY DEFICIENCY

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to the pending ANDA #75-184 for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. Reference is also made to the Chemistry and Microbiology deficiencies received by facsimile on June 6, 2000 and June 16, 2000.

This correspondence addresses all the chemistry and microbiology deficiencies described in the June 6, 2000 and June 16, 2000 letters (attached in Reference). The deficiencies are repeated in bold print followed by our response in regular print.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be released without our written consent to an authorized member of your Office. We anticipate that the information provided adequately addresses the deficiencies noted in the above referenced correspondences and the application can now be approved.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 26 2000
OGD

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

July 14, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/A-M

ADDITIONAL INFORMATION

Re: ANDA 75-184: Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Buehler:

Reference is made to the pending ANDA #75-184 for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. Reference is also made to a request from Ruby Yu for us to send a copy of to the FDA Southeast Regional Laboratory and a copy to the ANDA.

Enclosed with this communication is a copy of BNP This SOP was also faxed to Stan Roberts , Supervisory Chemist at the FDA Southeast Regional Laboratory in Atlanta.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 17 2000
OGD

BAKER NORTON
PHARMACEUTICALS, INC.®

ANDA 75-184
LABELING AMENDMENT

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

August 8, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Paclitaxel Injection, 6 mg/mL in 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL Container Sizes

Dear Mr Buehler,

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes. Reference is also made to our Labeling Amendment of June 5, 2000, agency's faxed letter of August 4, 2000 and a telephone call with Elaine Hu on Monday August 7, 2000.

This labeling amendment responds to the agency's letter of August 4, 2000, a copy of which follows this letter . Included in **Appendix 1** is an exclusivity statement updated to include exclusivity D-57, as requested by the agency.

All requested changes to the labeling have been included in the final printed physician's insert/patient information leaflet labeling in **Appendix 2**. The changes are also detailed in the side-by-side comparison located in **Appendix 3.** On Monday August 7, 2000 clarification was sought on question **4.c** of the fax and Elaine advised us to prepare the labeling change as per innovator labeling.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

Should any questions arise, please do not hesitate to call me at (305) 575-6336 or via fax at (305) 575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

August 14, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

Revised Patent
cert. to include
PIV for '331
8/21/00

RE: ANDA 75-184, Paclitaxel Injection, 6mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes

Paragraph IV Patent Certification

Dear Mr. Buehler:

We wish to amend our pending application for Paclitaxel Injection to revise Section III, Patent Certification and Exclusivity Statement, to add reference to Patent No. 6,096,331, which has just been added to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition (Orange Book).

If you have any questions regarding this information, please contact me at (305) 575-6336.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

CENTER FOR DRUG
RECD
AUG 14 2000

BAKER NORTON
PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

August 22, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT
N/A

TELEPHONE AMENDMENT

Re: ANDA 75-184: Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes.

Dear Mr. Buehler:

Reference is made to our pending ANDA 75-184 for Paclitaxel Injection 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes. Reference is also made to a telephone call from Dr. Allen Rudman to Dr. Jane Hsiao on Monday, August 21, 2000.

As requested by the Agency, we enclose a copy of Standard Test Procedure( ) This method has been revised to include an additional standard pH buffer

Baker Norton Pharmaceuticals certifies that it will send a field copy of this Amendment to the Orlando District Office. We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be released without our written consent to an authorized member of your Office.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at (305) 575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

Enclosure

cc: Orlando District Office

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

August 22, 2000

Via FAX: (301) 594- 0180

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

TELEPHONE AMENDMENT

RE: ANDA 75-184, Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL Container Sizes

Dear Mr. Buehler:

Kindly refer to the Agency's request today for additional information with regard to the pending ANDA No. 75-184. Hereby, I am enclosing the recommended changes to certain documents related to the subjects committed to in Baker Norton's Amendment dated June 23, 2000.

Please find the following enclosed documents that support the agreed change to tighten the in-process control specification for the bulk solution:

1. Revised statement in subsection 2.1 (1) of the Section 2, IN-PROCESS CONTROLS for the drug product as originally submitted on April 2, 1999 Major Amendment, page 400228, to read
   (1) The bulk solution is checked for potency prior to filtration. The in-process limits are: Potency: %

2. An approved Change Approval Form, CA no. RD00-182. This form describes all the changes to be made on all relevant documents in detail. Please note that similar changes are being made on all three vial sizes and cover the control documents, Master Mixing , Product Master Card and Test Protocol Sheet as enclosed. However, as noted on

the Change Approval Form, the change will also apply to the other two vial sizes.

Please do not hesitate to contact me at 305-575-6004 should you require further information.

Sincerely,

Jane Hsiao, Ph.D.
Vice President

JHH/kmg

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NEW CORRESP
NC

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NOEL I SMITH

TECHNICAL ASSISTANTS
DAVID J. SCHODIN
HEATHER R KISSLING
DAVID M. MOTT

September 8, 2000

Via Facsimile
Confirmation via Federal Express

Mr. Gary J. Buehler
Acting Director
Office Of Generic Drugs
Food and Drug Administration
7500 Standish Place
(HFD-600) Room 286
Rockville, MD 20855

Re: Baker Norton Pharmaceuticals, Inc. **ANDA 75-184**

Notification Pursuant to 21 CRF § 314.107 (f) (2)
Regarding the Filing of Legal Action

This notification is made pursuant to 21 CFR § 314.107 (f)(2) regarding the filing of legal action by American BioScience, Inc., owner of U.S. Patent No. 6,096,331 ("the '331 patent") against Baker Norton Pharmaceuticals, Inc. et al. The relevant information is as follows:

(i) The Abbreviated New Drug Application No. to which legal action relates is **ANDA 75-184.**

(ii) the name of the Abbreviated New Drug Application applicant is **Baker Norton Pharmaceuticals, Inc.**

(iii) The established name of the drug product is **Taxol®.**

(iv) A certification by Robert F. Green is attached, in which certification is made that an action for infringement of the '331 patent was filed in the U.S. District Court for the Central District of California, under Case No. 00-09589 AHM (JWJx) on September 7, 2000.

Attached is a "Supplemental Declaration of Neil Flanzraich," filed on August 29, 2000 by Baker Norton Pharmaceuticals, Inc. ("Baker Norton"), in a case captioned *American BioScience, Inc. v. Bristol Myers Squibb et al.*, Case No. 00-08577 WMB (AJWx), and its attached copy of a tentative approval letter dated August 28, 2000, issued in the above-referenced ANDA 75-184. In that tentative approval letter it is stated that the application "contains a patent certification under Section 505 (j)(2)(A)(viii)(IV) of the Act stating that [the] manufacture use, or sale of this drug product will not infringe on the .... '331 [patent]." Additionally, in that same litigation, Baker Norton filed a "Supplemental Declaration of Michael H. Teschner" that alleged that "[f]or the reasons explained below, to the extent claims 31, 36, 39, 41, and 42 of the '331 patent cover BMY's Taxol® product as asserted by ABI, they are invalid as anticipated by extensive prior art well known to BMY and anyone else conversant with the development of Taxol®." The Teschner Declaration went on to set forth arguments with respect to why the '331 patent was allegedly invalid.

The Supplemental Teschner Declaration was filed on August 29, 2000. Thus, as of August 29, 2000, Baker Norton may argue that it had notified ABI that a Paragraph IV Certification had been filed with respect to the '331 patent in ANDA No. 75-184 and that Baker Norton contended that the '331 patent was invalid for the reasons set forth in the Supplemental Declaration of Michael H. Teschner. Accordingly, the referenced patent infringement action was filed within 45 days of receipt of any arguable notice to ABI from Baker Norton of the filing of the Paragraph IV Certification in ANDA No. 75-184 and the reasons why Baker Norton asserts that the '331 patent is allegedly invalid.

In view of the fact that Civil Action No. 00-09589 AHM (JWJx) was filed within 45 days of receipt of the aforementioned information (and thus any alleged "notice"), in accordance with 21 USC § 355(j)(5)(A)(iii), any final approval with respect to ANDA No. 75-184 "shall be made effective upon the expiration of the 30 month period beginning on [at the earliest, August 29, 2000] or such shorter or longer period as the court may order" subject to the exceptions set forth in 355(j)(5)(B)(iii)(I-III).

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

By: Robert F. Green

RFG/krs

cc: Margaret J. Porter, Esq.
Mr. Donald B. Hare

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

September 8, 2000

By Facsimile (301-594-0180)

Mr. Gary J. Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-184, Paclitaxel Injection, 6mg/mL (packaged in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL multiple-dose vials)

Minor Amendment

Dear Mr. Buehler:

FDA tentatively approved the above ANDA on August 28, 2000. This amendment is submitted pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(B), which requires an ANDA applicant to amend its patent certification "if the patent is removed from the list." Baker Norton Pharmaceuticals (BNP) withdraws the paragraph IV certification to Patent No. 6,096,331 ('331) submitted on August 14, 2000. With the withdrawal of the certification to the '331 patent, BNP requests that FDA grant final approval to this ANDA 75-184 Paclitaxel Injection, 6mg/mL.

The '331 patent was listed in the Orange Book pursuant to a patent information filed by Bristol-Myers Squibb (Bristol) on August 11, 2000. According to the letter transmitting it, the submission was filed "pursuant to an order of the United States District Court" in the case of American BioScience, Inc. v. Bristol-Myers Squibb, CV 00-08577-WMB (U.S.D.C. C.D. Cal.), issued on that date.

On September 7, 2000, the court dismissed the case. A copy of the court's order of dismissal is attached. The court ordered that "[Bristol] shall use its best efforts to cause the delisting of plaintiff's '331 Patent from the Orange Book." The court granted a stay of the order until "the close of business on September 13, 2000, to allow [the parties] to seek a stay from the United States Court of Appeals." The court added that the "Court recommends to the FDA that the time that the [August 11 order] . . . was in effect sh

toll the period in which [Bristol] may timely cause . . . listing" under 21 U.S.C. § 355(c)(2).[1]

Unless a stay is obtained from the court of appeals before the close of business on September 13, 2000, Bristol is under court order to delist the '331 patent from the Orange Book. Accordingly, BNP withdraws the paragraph IV certification to the '331 patent effective upon the delisting of that patent.

If Bristol attempts to resubmit the '331 patent information before the delisting of the '331 patent, or resubmits it after delisting the '331 patent pursuant to the court order, the patent information will have been submitted more than 30 days from the date the '331 patent was issued (August 1, 2000). Under 21 C.F.R. § 314.94(a)(vi), BNP "is not required to submit an amended certification" to the '331 patent if it is listed after 30 days from the date of issuance of the '331 patent.

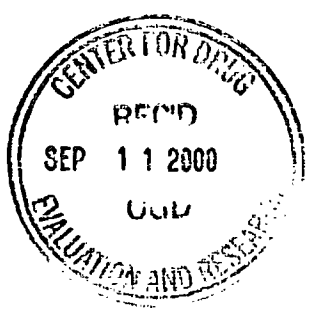
Therefore, as of the delisting of patent '331, ANDA 75-184, tentatively approved on August 28, 2000, will be complete in all respects. BNP further states that no changes have been made to the labeling or to the chemistry, manufacturing, and controls section of the application since August 28, 2000.

If you have any questions regarding this information, please contact me at (305) 575-6004.

Sincerely,

Jane Hsiao, Ph.D.
Vice President

Enclosure: Order of the District Court, Sept. 7, 2000, in American BioScience, Inc. v. Bristol-Myers Squibb, CV 00-08577-WMB (U.S.D.C. C.D. Cal.).



cc: Bob West (301-594-0183)
Liz Dickinson (301-443-0739)
Janet Woodcock, Director, CDER (301-594-6197)

---

[1] The Agency cannot accept the court's recommendation that the 30-day period be "tolled" by the length of time the court order was in effect. The 30-day period is statutory, 21 U.S.C. § 355(c)(2), and the regulation does not authorize an exception based on events occurring in private litigation.

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

September 14, 2000

By Facsimile (301-594-0180)

Mr. Gary J. Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-184, Paclitaxel Injection, 6mg/mL (packaged in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL multiple-dose vials)

Minor Amendment

Dear Mr. Buehler:

This letter relates to our minor amendment dated September 8, 2000. Baker Norton Pharmaceuticals, Inc. (BNP) hereby amends its certification in the above ANDA pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(B) to withdraw the paragraph IV certification to Patent No. 6,096,331 ('331). BNP certifies under 21 C.F.R. § 314.94(a)(12)(ii) that no relevant patents as described in 21 C.F.R. § 314.94(a)(12)(i) claim the listed drug other than those identified in the certification prior to August 14, 2000. The reason for this change in certification is that Bristol-Myers Squibb has withdrawn from the Orange Book the '331 patent listing submitted on August 11, 2000, and pursuant to 21 C.F.R. § 314.94(a)(12)(vi) BNP is not required to certify to any subsequent listing of the '331 patent that was made more than 30 days after August 1, 2000. BNP further states that no changes have been made to the labeling or to the chemistry, manufacturing, and controls section of the application since August 28, 2000.

If you have any questions regarding this information, please contact me at (305) 575-6004.

Sincerely,

Jane Hsiao, Ph.D.
Vice President

cc: Peter Rickman (301-594-0183)
Liz Dickinson (301-443-0739)
Janet Woodcock, Director, CDER (301-594-6197)

BAKER NORTON PHARMACEUTICALS, INC.

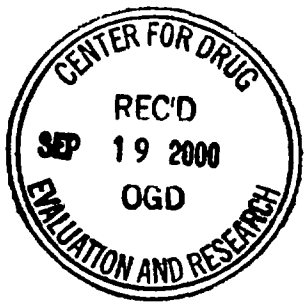
4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

September 11, 2000

By Facsimile (301-594-0180)

NEW CORRESP
NC

Mr. Gary J. Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855



RE: ANDA 75-184, Paclitaxel Injection, 6mg/mL (packaged in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL multiple-dose vials)

Dear Mr. Buehler:

This letter is to inform you of a lawsuit filed by American BioScience, Inc. (ABI) against Baker Norton Pharmaceuticals, Inc. (BNP) and Zenith Goldline, Inc. (ZG). This lawsuit has no effect on the eligibility of the above ANDA for final approval, as requested in my letter of September 8, 2000. Nevertheless, ABI may communicate with your office, or other offices in the Food and Drug Administration (FDA), to argue that the filing of the lawsuit is relevant to OGD's action on this ANDA. I am providing the information below to facilitate your evaluation of any such communication from ABI.

1. ABI v. Bristol. As you know, ABI sued Bristol-Myers Squibb (Bristol) on August 11, 2000, to force Bristol to list the '331 patent in the Orange Book. On September 7, 2000, the court dismissed ABI's lawsuit with prejudice. The court ruled that there was no legal basis for the lawsuit, and dissolved the order requiring the patent listing. The court ordered Bristol to delist the '331 patent. The court stayed the delisting order until the close of business on September 13, 2000.

When the court order goes into effect, Bristol must delist the '331 patent. In accordance with my September 8 letter, BNP withdraws the paragraph IV certification to the '331 patent effective upon the delisting of that patent. At that time, the ANDA will be complete and eligible for final approval.

2. ABI v. BNP and ZG. Dissatisfied, ABI has now sued BNP and ZG for allegedly infringing the '331 patent. BNP will request the court to hold ABI in contempt of the September 7 order and require ABI to withdraw its lawsuit. Even if it is not

withdrawn, the ABI lawsuit has no effect on the FDA's approval of BNP's ANDA under 21 U.S.C. § 355(j)(5)(B).

3. No 30-Month Stay. The Waxman-Hatch Act provides that approval of an ANDA with a paragraph IV certification is effective immediately "unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date of the notice provided under paragraph (2)(B)(i) is received." § 355(j)(5)(B)(iii). If "such an action" is brought before the expiration of "such" 45-day period, final approval of the ANDA is subject to a 30-month stay. Id. The 30-month stay is intended to correspond with the time necessary for patent infringement litigation pursuant to the terms of the Act.

ABI's lawsuit against BNP and ZG does not conform with the terms of the Act. Therefore, there can be no 30-month stay of the approval of BNP's ANDA based on that lawsuit. First, when Bristol delists the '331 patent, BNP's withdraw of its paragraph IV certification will take effect. The ANDA will then not be within the rule governing effective approval of paragraph IV ANDAs. The 30-month stay applies only to ANDAs subject to that rule. Second, the rule provides that the 30-month stay applies only when an infringement action is brought "within 45 days of receipt by the patent owner of the notice of [paragraph IV] certification from the [ANDA] applicant." 21 C.F.R. § 314.107(b)(3)(i)(A). BNP has provided no notice to ABI. Third, the Act authorizes only one 30-month stay, for the first patent infringement lawsuit. ABI's lawsuit is not the first.

The following provides a further explanation of these points.

a. Not a paragraph IV ANDA. An ANDA must contain a certification to a patent that "claims the listed drug" and "for which information is required to be filed." § 355(j)(2)(A)(vii). Patent information is required to be filed for any patent that "claims the drug" in the NDA and "with respect to which a claim of patent infringement could reasonably be asserted." § 355(c)(2).

Other than the FDA itself, only "the holder of an approved application" is authorized to determine whether a patent qualifies for an information filing. Id. The NDA-holder must "submit information about any patent that meets the statutory description whether or not the applicant owns or is licensed under such a patent." 54 Fed. Reg. 28872, 28908 (July 10, 1989). However, whether a patent "meets the statutory description" and is thus one for which information must be filed can be determined only by the NDA-holder. See 21 C.F.R. § 314.53(f).

The FDA requires ANDA applicants to certify to Orange Book listed patents, irrespective of the ANDA applicant's opinion. 21 C.F.R. § 314.94(a)(12)(vii).

Conversely, patents not listed in the Orange Book require no certification. Indeed, even if "in the opinion of the [ANDA] applicant" a patent should be listed, the FDA will defer to the NDA-holder's contrary determination by requiring withdrawal of an ANDA patent certification "[i]f a patent is removed from the list." Id. § 314.94(a)(12)(viii)(B). (The only exception is if the patent "is the subject of a lawsuit under § 314.107(c)," relating to 180-day exclusivity. An invalidated patent will remain on the list to preserve the first-filed paragraph IV applicant's ability to block approval of subsequent paragraph IV ANDAs. See 59 Fed. Reg. 50338, 50348 (comment 50) (Oct. 3, 1994).)

In sum, if a patent is listed in the Orange Book, the ANDA must contain a certification to it. Only the NDA-holder can list a patent. If a patent is not listed, the ANDA may not contain a certification to it.

In the case of BNP's paclitaxel ANDA, the certification to the '331 patent has been withdrawn effective upon Bristol delisting the '331 patent. When an ANDA applicant changes its certification, the original certification is considered never to have been made.[1] See id. ("there is no need for the agency to pronounce such changes in certification nunc pro tunc"). BNP's ANDA will not, with respect to the '331 patent, be within the rule governing final approval of paragraph IV ANDAs at § 355(j)(5)(B)(iii). Accordingly, there is no circumstance, including ABI's patent infringement lawsuit, in which the 30-month stay can affect the final approval of BNP's ANDA.

b. Not a Waxman-Hatch Act lawsuit. The 30-month stay provided by § 355(j)(5)(B)(iii) is an unusual remedy: a statutory preliminary injunction without any of the showings usually required for preliminary relief. To obtain this remedy, a patent holder must comply with the orderly procedure specified in the statute. The statute provides that a paragraph IV certification must include a statement that the ANDA applicant will give notice to the NDA-holder and patent owner of the factual and legal basis of its opinion that the patent is invalid or will not be infringed. 21 U.S.C. § 355(j)(2)(B)(i)-(ii). When that notice has been given, and the recipient brings an infringement action before the expiration of 45 days from the date it received the notice, the FDA may not approve the ANDA for 30 months. § 355(j)(5)(B)(iii).

This provision allows for the orderly disposition of patent challenges made by ANDA applicants. It does not require NDA-holders and patent owners to file lawsuits. The notice requirement gives the NDA-holder or patent owner the information it needs -- "a detailed statement of the factual and legal basis of the [ANDA] applicant's opinion that the patent is not valid or will not be infringed" -- to determine whether the patent is

---

[1] BNP's certification to the '331 patent stated that it was subject to the "view that there is no legal obligation to certify with respect to this patent."

valid and covers the proposed ANDA drug. After notice is provided, recipients may conclude that an infringement action is not justified. Many paragraph IV certifications do not result in lawsuits.

It would defeat the purpose of the Waxman-Hatch Act's patent challenge procedures for patent owners to file infringement actions before receiving the ANDA applicant's notice under § 355(j)(2)(B). The patent owner cannot know the basis for the ANDA applicant's opinion that the patent is invalid or will not be infringed. For instance, the ANDA drug may differ in formulation from the listed drug, a fact the ANDA applicant would disclose to the patent owner in a notice under the statute, but would otherwise treat as confidential proprietary information. A patent owner that sues before receiving notice undermines the Act's carefully-balanced procedures for protecting intellectual property rights while facilitating the approval of generic drugs, and burdens the judicial system with litigation that may be completely unnecessary.

The patent owner has no cause to circumvent the Act's procedures by filing a lawsuit before receiving the notice. An ANDA with a paragraph IV certification will not be made effective until the 45-day period has expired. 21 C.F.R. § 314.107(f)(2)-(3). But that period -- during which the patent owner can evaluate whether it has a valid complaint -- cannot start until the ANDA applicant gives, and the patent owner receives, the notice. Id. § 314.107(f)(1). The notice and 45-day period are statutory prerequisites to the applicability of the procedures specified in § 355(j)(5)(B)(iii), including the 30-month stay.

In sum, a patent infringement action brought before the plaintiff has received notice of the ANDA applicant's basis for a paragraph IV certification does not meet the conditions set forth in § 355(j)(5)(B)(iii) and therefore cannot be the basis for a 30-month stay of ANDA approval.

Because of the precipitate nature of the '331 patent listing and because BNP is doubtful that the patent listing is lawful, BNP has not provided notice of its paragraph IV certification to the '331 patent. Moreover, Bristol -- the NDA-holder -- did not believe the patent qualified for listing at all, submitting patent information only pursuant to court order. Bristol will delist the patent, and BNP has withdrawn its paragraph IV certification effective upon that delisting. BNP's ANDA will no longer be one containing a paragraph IV certification to the '331 patent. The ANDA will be complete and eligible for final approval.

ABI may be dissatisfied with this turn of events. But that does not change the legal requirements that apply to BNP's ANDA. ABI is not entitled to sue BNP for patent infringement pursuant to the Waxman-Hatch Act unless and until it receives a notice of a paragraph IV certification to the '331 patent. BNP is not required to certify to a patent

that is not listed in the Orange Book by Bristol. The '331 patent will be delisted from the Orange Book by or after September 13, 2000.

ABI is free to pursue its legal remedies under the patent law consistent, if possible, with the court's September 7, 2000, order. If it believes that BNP has infringed the '331 patent, ABI may file a lawsuit requesting a preliminary injunction against BNP's selling generic paclitaxel under its approved ANDA. ABI has filed just such a court proceeding. But that proceeding is not "an action . . . brought before the expiration of forty-five days from the date the notice" of BNP's paragraph IV certification is received, and therefore it can have no effect on the FDA's final approval of BNP's ANDA.

c. No second 30-month stay. BNP's ANDA has already been the subject of a 30-month stay under § 355(j)(5)(B)(iii). Bristol listed patents in the Orange Book beginning in 1997. BNP and other companies submitted ANDAs with paragraph IV certifications. They gave notice to Bristol, and Bristol filed infringement actions. The filing of the actions resulted in a stay of ANDA approval for 30 months from the date of the notice under each ANDA. The 30-month stay for BNP's ANDA ended in June 2000. That stay is the only stay authorized by the Waxman-Hatch Act for BNP's ANDA.

The Act states that the NDA-holder and patent owner have 45 days after receiving notice of a paragraph IV certification to file an infringement action in court. § 355(j)(5)(B)(iii). It then provides that "[i]f such an action is brought before the expiration of such [45] days, the approval [of the ANDA containing the paragraph IV certification] shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice . . . ." Id.

This directive to the FDA is mandatory and unconditional. It states that the ANDA "shall be made effective," and it specifies that this action must occur 30 months[2] after receipt of "the notice." It does not include an implied additional condition that the ANDA shall be made effective unless a second action is brought within 45 days of a second notice of a second paragraph IV certification.

The FDA is required to apply the Waxman-Hatch Act as it is written. BNP's ANDA satisfies all statutory requirements for final approval. The applicant for the ANDA certified to Bristol's patents in 1997. Bristol filed an infringement action within 45 days. The 30-month period expired in June 2000. Accordingly, BNP having satisfied the technical requirements of § 355 for ANDA approval, the ANDA "shall be made effective" at this time under § 355(j)(5)(B)(iii). The '331 patent, and any related

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[2] Or when there is a court decision favorable to the ANDA applicant.

certification, notice, or infringement action, do not affect the explicit requirements in the text of the Waxman-Hatch Act.

* * * *

We believe this letter provides necessary clarifying information about ABI's continuing attempt to misuse the Waxman-Hatch Act as leverage to enforce the '331 patent.

If the Agency intents to take any action contrary to our request of the final approval for ANDA #75-184 as stated in our letter of September 8, 2000, we request that the Agency grants us a meeting to discuss this matter.

Sincerely,

Jane Hsiao, Ph.D.
Vice President

cc: Bob West (301-594-0183)
Liz Dickinson (301-443-0739)
Janet Woodcock, Director, CDER (301-594-6197)

BAKER NORTON PHARMACEUTICALS, INC.®

VIA FACSIMILE: 301-594-0180

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

July 25, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AM

TELEPHONE AMENDMENT

Re: ANDA 75-184: Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes.

Dear Mr. Buehler:

Reference is made to the pending ANDA #75-184 for Paclitaxel Injection 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes. Reference is also made to a telephone call from Elaine Hu, Project Manager, Office of Generic Drugs to Dr. Jane Hsiao yesterday and a teleconference between the Agency and Baker Norton Pharmaceuticals today.

Pursuant to the Agency's requests and the available data, BNP hereby submits amended product specifications to include:

1. the clarification of references to USP<1> injection specification,
2. the identification of as an individual impurity with limits of % at initial release and shelf-life specifications, respectively and
3. the reduction of the limit for from % .

In addition, BNP commits to use the qualified source of excipient, polyoxyl 35 castor oil, NF, manufactured by Should it be necessary to change the source of this substance, a prior approval will be requested.

Based on the available data, the Agency has recommended approval for a two-year expiration date for the 30 mg/5 mL container size and an eighteen-month expiration date for the 150 mg/25 mL and 300 mg/50 mL container sizes. It is further agreed that the Agency will accept a post-approval supplemental application under §314.70 (c) Special Supplement-Changes Being Effected, to extend the expiration date for the 150 mg/25 mL and 300 mg/50 mL container sizes to two-years with supportive real time controlled room temperature data for the two exhibit batches, 8026859 and 8016861.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be released without our written consent to an authorized member of your Office.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at 305-575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

IVAX

IVAX Research, Inc.
4400 Biscayne Boulevard
Miami, Florida • 33137
Telephone: 305-575-6000

VIA FAX: (301) 594-0183

Mr. Gary J. Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NC NEW CORRESP

January 24, 2002

RE: Abbreviated New Drug Application (No. 75-184) for Paclitaxel Injection, 6mg/ml packaged in 30mg/ml, 150mg/25ml, and 300mg/50ml

Correspondence

Dear Mr. Buehler:

Reference is made to the approved ANDA 75-184 for the subject drug product. The original full approval was granted on September 15, 2000. Reference is also made to the October 5, 2001 pending prior approval supplement, which request for an increase in filling time of the drug product.

IVAX Research, Inc. (IRI) formerly Baker Norton Pharmaceuticals, Inc. hereby withdraws the October 5, 2001 pending supplements without prejudice.

In the attached document, IRI also states that IRI is not seeking approval to claims covered by U.S. patent No. 6,150,398 relating to the use of Taxol® in combination with cisplatin for treatment of ovarian and non-small cell lung cancer.

IVAX Research requests that information contained in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information be released without our written consent. Should you require any clarification, please do not hesitate to contact Jane H. Hsiao, Vice Chairman, Technical Affairs, IVAX Corporation at 305-575-6004.

Sincerely,

Steven M. Viti, Ph.D.
Director Regulatory Affairs

CENTER FOR DRUG
JAN 25 2002
EVALUATION AND RESEARCH

IVAX

IVAX Research, Inc.
4400 Biscayne Boulevard
Miami, Florida • 33137
Telephone: 305-575-6000

January 25, 2002

Mr. Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-600)
Metro Park North 2, Room 286
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

Minor Amendment

Re: Abbreviated New Drug Application (No. 75-184) for Paclitaxel Injection, 6mg/mL, packaged in 30mg/5mL, 150mg/25mL, and 300mg/50mL

Dear Mr. Buehler:

Reference is made to ANDA 75-184 for the subject drug product. The ANDA is owned by IVAX Research Inc. (IRI) (formerly Baker Norton Pharmaceuticals, Inc.). The ANDA was approved by the Agency on September 15, 2000. And the ANDA has since been supplemented several times. By letter dated January 25, 2002, you advised us that the September 15, 2000 approval and as supplemented, has been rescinded due to a court order. The January 25, 2002 letter also advised us that the ANDA is tentatively approved.

We hereby request approval of ANDA 75-184 on the basis of the following.

1. The information in ANDA 75-184 as of September 15, 2000, supported a conclusion by FDA at that time that, as stated in the September 15, 2000, approval letter, "the drug is safe and effective for use as recommended in the submitted labeling."

2. The information in the supplements approved after September 15, 2000, was found acceptable by OGD. Therefore, that information further supports the conclusion that the drug is safe and effective for its proposed uses.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 28 2002
OGD

3. IRI has made no change in the labeling, or in the chemistry, manufacturing and control section of the ANDA, since the ANDA received tentative approval status as stated in your January 25, 2002 letter.

4. The statements in your January 25, 2002 approval letter concerning the 5,641,803, 5,496,804, 5,670,537 and 6,150,398 patents applicable to Taxol, owned by Bristol-Myers Squibb Company (Bristol) and referenced in ANDA 75-184 are correct.

5. There is no other patent applicable to Taxol listed in the Orange Book. By letter dated January 17, 2002, Bristol withdrew the 6,096,331 patent "completely."

6. The statement in your January 25, 2002 letter concerning the periods of Waxman-Hatch exclusivity, D-57, I-270, I-226, and I-230 and Orphan Drug Exclusivity are correct.

Based on the above, ANDA 75-184 is complete and meets all requirements for approval. We therefore request that you approve ANDA 75-184.

IRI requests that information contained in this file be treated as confidential within the meaning of 21 C.F.R. § 314.430, and that no information be released without our written consent. Should you require any clarification, please do not hesitate to contact Dr. Jane Hsiao, Vice Chairman, Technical Affairs, IVAX Corporation at 305-575-6004.

Sincerely yours,

Steve M. Viti, Ph.D.
Director, Regulatory Affairs

BAKER NORTON PHARMACEUTICALS, INC.®

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

VIA FACSIMILE: 301-594-0180

August 7, 2000

ORIG AMENDMENT
N/AM

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

Re: ANDA 75-184: Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes.

Dear Mr. Buehler:

Reference is made to the pending ANDA #75-184 for Paclitaxel Injection 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL container sizes. Reference is also made to a telephone call from Elaine Hu on Friday, August 4, 2000.

The revised Post-Approval Stability Protocol requested by Elaine Hu on Friday August 4th, is enclosed in this Telephone Amendment. The protocol reflects the 18-month expiration dating for the 150 mg/25 mL and the 300 mg/50 mL products as agreed to by the Agency in our teleconference of July 25, 2000. The protocol also reflects the changes to the specifications requested by the Agency and submitted to the ANDA in our Telephone Amendment of July 25, 2000.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be released without our written consent to an authorized member of your Office.

Should any questions arise, please do not hesitate to contact the undersigned at (305) 575-6336, or via fax at (305) 575-6339, or via e-mail to steve_viti@ivax.com.

Sincerely,

Steven M. Viti, Ph.D.
Director, Regulatory Affairs

BAKER NORTON PHARMACEUTICALS, INC.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

August 24, 2000

Via FAX: (301) 594- 0180

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

TELEPHONE AMENDMENT

RE: ANDA 75-184, Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL Container Sizes

Dear Mr. Buehler:

As a follow up to the request by the Agency of today, I am enclosing the data for the sterility and particulate matter for the 150 mg/25 mL and 300 mg/50 mL exhibit batches.

Baker Norton Pharmaceuticals also commits to conduct post-approval stability studies with product stored upright and inverted. Attached please find the revised post-approval stability study protocol that reflects the modification. Furthermore, in BNP's commitment dated July 25, 2000, with regard to change in the excipient, polyoxyl 35 castor oil, the change will also include the grade in addition to the source, and a prior approval will be requested.

Please do not hesitate to contact me at 305-575-6004 should you require further information.

Sincerely,

Jane Hsiao, Ph.D.
Vice President

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 25 2000
OGD

NDA 20-262/S-032

DEC 1 0 1999

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Attention: Susan H. Behling, Director
Global Oncology Strategic Unit
Regulatory Sciences

Dear Ms. Behling:

Please refer to your supplemental new drug application dated February 5, 1999, received February 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAXOL (paclitaxel) Injection.

We acknowledge receipt of your submissions dated July 12, and September 14, 1999.

This supplemental new drug application provides a patient information leaflet.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon patient information labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

In addition, please revise the approved package insert dated October 25, 1999 to include the following statement at the end of the **PRECAUTIONS** section:

Information for Patients: (See **Patient Information Leaflet**.)

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the patient package insert) and the October 25, 1999 approved package insert with the revision requested above.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-262/S-032." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we

request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Leslie Vaccari, Project Manager, at (301) 594-5784. Sincerely.

Richard Pazdur, M.D.
Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPROVED
DEC 10 1999

Patient Information

TAXOL® Injection

(generic name - **paclitaxel**)

What is TAXOL?

TAXOL is a prescription cancer medicine, it is injected into a vein and it is used to treat different types of tumors. The tumors include advanced ovary and breast cancer. The tumors also include certain lung cancers (non-small cell) in people who cannot have surgery or radiation therapy. TAXOL may also be used to treat AIDS-related Kaposi's sarcoma.

What is cancer?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

How does TAXOL work?

TAXOL is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. TAXOL may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by TAXOL causing some of the side effects. (See **What are the possible side effects of TAXOL?** below.)

Who should not take TAXOL?

Patients who have a history of hypersensitivity (allergic reactions) to TAXOL or other drugs containing Cremophor® EL* (polyoxyethylated castor oil), like cyclosporine or teniposide, should not be given TAXOL. In addition,TAXOL should not be given to patients with dangerously low white blood cell counts.

How is TAXOL given?

TAXOL is injected into a vein (intravenous (IV) infusion]. Before you are given TAXOL, you will have to take certain medicines (premedications) to prevent or reduce the chance you will have a serious allergic reaction. Such reactions have occurred in a small number of patients while receiving TAXOL and have been rarely fatal. (See **What are the possible side effects of TAXOL?** below.)

What are the possible side effects of TAXOL?

Most patients taking TAXOL will experience side effects, although it is not always possible to tell whether such effects are caused by TAXOL, another medicine they may be taking, or the cancer itself. Important side effects are described below; however some patients may experience other side effects that are less common. Report any unusual symptoms to your doctor.

Important side effects observed In studies of patients taking TAXOL were as follows:

—*allergic reactions.* Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during TAXOL infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash. The likelihood of a serious allergic reaction is lowered by the use of several kinds of medicines that are given to you before the TAXOL infusion.

—*heart and blood vessel (cardiovascular) effects.* TAXOL may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. Your heart function, including blood pressure and pulse, will be monitored while you are receiving the medicine. You should notify your doctor if you have a history of heart disease.

—*infections due to low white blood cell count.* Among the body's defenses against bacterial infections are white blood cells. Between your TAXOL treatment cycles, you will often have blood tests to check your white blood cell counts.

TAXOL usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4° F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

—*hair loss.* Complete hair loss, or alopecia, almost always occurs with TAXOL. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your TAXOL treatment.*

—*joint and muscle pain.* You may get joint and muscle pain a few days after your TAXOL treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

—irritation *at the injection site.* TAXOL sometimes causes irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the IV (intravenous) fluid leaking into the surrounding area. If *you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away*

—*low red blood cell count.* Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following TAXOL treatment causing anemia. Some patients may need a blood transfusion to treat the anemia.

Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following TAXOL treatment.

—*mouth or lip sores (mucositis).* Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the TAXOL treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

—*numbness, tingling, or burning in the hands and/or feet (neuropathy).* These symptoms occur often with TAXOL and usually get better or go away without medication within several months of completing treatment. However, if you are uncomfortable, tell your doctor so that he/she can decide the best approach for relief of your symptoms.

—stomach *upset and diarrhea.* Some patients experience nausea, vomiting, and/or diarrhea following TAXOL use. If you experience nausea or stomach upset, tell your doctor. Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area* pain and/or severe diarrhea, tell your doctor right away.

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with TAXOL, it is important to talk with your doctor about other possible side effects.

Can I take TAXOL if I am pregnant or nursing a baby?

TAXOL could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with TAXOL. Tell your doctor if you become pregnant or plan to become pregnant while taking TAXOL. Because studies have shown TAXOL to be present in the breast milk of animals receiving the drug, it may be present in human breast milk as well. Therefore, nursing a baby while taking TAXOL is NOT recommended.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about TAXOL. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about TAXOL, your doctor or pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

*Cremophor ® EL is the registered trademark of BASF Aktiengesellschaft
Cremophor® EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

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

1109663
Issue date: XXXXX 1999
Based on 347630DIM-06 (10/99)