CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-624/S-009

Trade Name: Anzemet

Generic Name: dolasetron mesylate

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: July 18, 2003

Indications: (1) the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin; (2) the prevention of postoperative nausea and vomiting; (3) the treatment of postoperative nausea and vomiting.
## Center for Drug Evaluation and Research

**Application Number:**
20-624/S-009

## Contents

### Reviews / Information Included in this NDA Review.

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<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
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</tbody>
</table>
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
Attention: Philip E. Page, R.Ph.
Regulatory Affairs-CMC
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-0720

Dear Mr. Page:


We acknowledge receipt of your submission dated March 19, 2003 that constituted a complete response to our February 11, 2003 action letter.

This supplemental new drug application provides for the addition of a 12.5mg/0.625mL single-use vial.

We have completed the review of this 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 labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert, carton, and immediate container labeling submitted October 11, 2002).

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 mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled, Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-624/S-009”. 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:
MEDWATCH, 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, call Brian Strongin, R.Ph., M.B.A., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
7/18/03 09:31:25 AM
APPLICATION NUMBER:
20-624/S-009

APPROVABLE LETTER
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
Attention: Alan Martin
U.S. Drug Regulatory Affairs - CMC
P.O. Box 9720
Mail Stop J5-M1540
Kansas City, MO 64134-0720

Dear Mr. Martin:


This supplemental new drug application provides for the addition of a 12.5mg vial.

We have completed the review of this supplemental new drug application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to address the following:

1. Describe the circumstances for use of the Level 2 acceptance

2

3. Include the validation protocol, deviations from the protocol and the actions taken to rectify these deviations.

In addition, it will be necessary for you to submit final printed labeling revised as follows:

Vial Label

Please add the following information to the vial label:
1. The place of business of the manufacturer, packer of distributor.
2. The usual or recommended dosage or a reference to the package insert for this information.
3. The established names and quantities of inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.
4. The recommended storage conditions.
5. The NDC code.

Carton Label

Please add the following information to the carton label:

1. The symbol “Rx Only”.
2. The quantities of the inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.

In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling, 10 of which are mounted individually on heavy-weight or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry entitled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intention to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.
If you have any questions, call Brian Strongin, R.Ph., M.B.A. at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team leader for the
Division of Gastrointestinal and
Coagulation Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Liang Zhou
7/15/02 11:57:35 AM
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
Attention: Philip E. Page, R.Ph.
Regulatory Affairs - CMC
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-0720

Dear Mr. Page:


We acknowledge receipt of your submission dated October 11, 2002 that constituted a complete response to our July 15, 2002 action letter.

This supplemental new drug application provides for the addition of a 12.5mg vial.

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1. 

2. 

3. 

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(See appended electronic signature page)

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DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
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/s/

Liang Zhou
2/11/03 10:06:36 AM
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
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U.S. Drug Regulatory Affairs - CMC
P.O. Box 9720
Mail Stop J5-M1540
Kansas City, MO 64134-0720

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Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team leader for the
Division of Gastrointestinal and
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DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Liang Zhou
7/15/02 11:57:35 AM
100%

Anzemet® Injection 12.5mg
dolasetron mesylate (20mg/mL)
injection
Mfd for: Aventis Pharmaceuticals Inc.
506061716

200%

Anzemet® Injection 12.5mg
dolasetron mesylate (20mg/mL)
injection
Mfd for: Aventis Pharmaceuticals Inc.
506061716
Anzemet® Injection

dolasent mesylate injection

Anzemet® injection (dolasent mesylate injection)

CLINICAL STUDIES

Prevention of Cancer Chemotherapy-Induced Nausea and Vomiting

Anzemet® injection administered intravenously at a dose of 1.8 mg/kg gave similar results in preventing nausea and vomiting as the other selective 5-HT3 receptor antagonists studied as active comparators. It was more effective than metoclopramide. Efficacy was based on complete response rates (no emetic episodes and no rescue medication).

Gastrin Bond Chemosensory

A randomized, double-blind trial compared single intravenous doses of ANZEMET injection with metoclopramide in 212 men and 213 women adult cancer patients receiving 60 mg/m2 cisplatin. ANZEMET injection at a dose of 1.8 mg/kg was significantly more effective than metoclopramide in the prevention of chemotherapy-induced nausea and vomiting in this study (Table 2).

Table 2. Prevention of Chemotherapy-Induced Nausea and Emesis from Cisplatin Chemosensory

<table>
<thead>
<tr>
<th>ANZEMET Injection</th>
<th>Metoclopramide</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Hours</td>
<td>72</td>
<td>69</td>
</tr>
<tr>
<td>Complete Response</td>
<td>41 (57)</td>
<td>24 (35)</td>
</tr>
<tr>
<td>Rescue Rate</td>
<td>4</td>
<td>31</td>
</tr>
</tbody>
</table>

A second randomized, double-blind trial compared single intravenous doses of ANZEMET injection with intravenous ondansetron in 605 (373 men and 232 women) adult cancer patients receiving 270 mg/m2 cisplatin. A single intravenous 1.8 mg/kg dose of ANZEMET injection was shown to be equivalent to a single intravenous 32 mg dose of ondansetron (Table 3).

Table 3. Prevention of Chemotherapy-Induced Nausea and Emesis from Cisplatin Chemosensory

<table>
<thead>
<tr>
<th>ANZEMET Injection</th>
<th>Ondansetron</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Over</td>
<td>198</td>
<td>205</td>
</tr>
<tr>
<td>Complete Response</td>
<td>88 (44%)</td>
<td>88 (44%)</td>
</tr>
<tr>
<td>Rescue Rate</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

Another randomized, double-blind trial compared single intravenous doses of ANZEMET with 3.0 mg/kg intravenous ondansetron in 474 (315 men and 159 women) patients receiving 280 mg/m2 cisplatin chemotherapy. A single intravenous 3.0 mg/kg dose of ANZEMET gave similar results as those from ondansetron.

Cisplatin-Based Chemosensory

A study of ANZEMET injection (2.4 mg/kg) in 96 men and 213 women receiving moderately emetogenic chemotherapy such as cisplatin-based regimens, a single intravenous 1.8 mg/kg dose of ANZEMET injection was equivalent to metoclopramide administered as a 10 mg intravenous bolus followed by 3 mg intravenous hourly over 8 hours. Complete response rates were 69% and 32%, respectively, p<0.12.

Prevention of Postoperative Nausea and Vomiting

ANZEMET injection administered intravenously at a dose of 1.25 mg/kg approximately 15 minutes before the creation of general anesthesia (short-acting barbiturates, nitrous oxide, narcotics, and anesthetic agents) was significantly more effective than placebo in preventing postoperative nausea and vomiting. No increased efficacy was seen with higher doses.

One trial compared single intravenous ANZEMET injection doses of 12.5, 25, and 50 mg/kg with placebo in 670 women surgical patients undergoing gynecologic procedures. ANZEMET injection at a dose of 12.5 mg/kg was statistically superior to placebo for complete response (no nausea, no rescue medication) (p<0.001). Complete response rates were 79%, 50%, and 30%, respectively.

Another trial compared single intravenous ANZEMET injection doses of 12.5, 25, 50, and 100 mg/kg with placebo in 610 (722 women and 388 men) surgical patients. Women in the 12.5 mg/kg dose was statistically superior to placebo for complete response. The complete response rates were 59% and 42%, respectively. However, in men, there was no statistically significant difference in complete response between any ANZEMET dose and placebo.

Treatment of Postoperative Nausea and Vomiting

Two randomized, double-blind trials compared single intravenous ANZEMET injection doses of 12.5, 25, 50, and 100 mg/kg with placebo in 124 men and 83 female patients who had undergone surgery with general balanced anesthesia and presented with early postoperative nausea and vomiting, using standardized antimetic treatment.

In both studies, the 12.5 mg/kg dose of ANZEMET was significantly superior to placebo for complete response (no nausea, no rescue medication). No significant increased efficacy was seen with higher doses.

INDICATIONS AND USAGE

Anzemet® Injection is indicated for the following:

1. The prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin.

2. The prevention of nausea and vomiting associated with metoclopramide-resistant chemotherapy.
ANZEmET® Injection (doxorubicin mesylate injection)

encephalopathic toxicity in patients. Doxorubicin mesylate did not inhibit the antitumor activity of four chemotherapeutic agents (cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide) in four murine models.

Cardiographic Abnormalities: Development of Cardiomyopathy

In a 24-month carcinogenicity study, there was a statistically significant (P=0.001) increase in the incidence of combined hemorrhagic alveolitis and carcinoma in male rats treated with 150 mg/kg/day and above. In this study, mice (0.3)-treated animals were treated daily with doxorubicin mesylate, 75, 150 or 300 mg/kg (225, 450 or 900 mg/m²). For a 30 kg person of average height (1.65 m), blood surface area, doxorubicin mesylate doses ranged from 0.6.6 to 13.5 times the recommended clinical dose (60 mg/m²). Interventions on body surface area, doses increased in unformulated fashion. No intervention for human patients was observed at a dose of 75 mg/kg in male mice and at doses of 300 mg/kg in female mice.

In a 24-month rat (Sprague-Dawley) carcinogenicity study, oral doxorubicin mesylate was not carcinogenic. At doses up to 150 mg/kg (900 mg/m²), 13.5 times the recommended human dose based on body surface area in male rats and up to 300 mg/kg (1800 mg/m²), 27 times the recommended human dose based on body surface area in female rats. Doxorubicin mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosome aberration test, the Chinese hamster ovary (CHO) cell (V79) forward mutation test, the rat hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test.

Doxorubicin mesylate was found to have no effect on fertility and reproductive performance at oral doses up to 60 mg/kg in mice (5.4 times the recommended human dose based on blood surface area) and doses up to 400 mg/kg (2400 mg/m²) in rats and 10 times the recommended human dose based on body surface area in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether doxorubicin mesylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ANZEmET injection is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of doxorubicin mesylate were evaluated in a total of 108 pediatric patients receiving emtropic chemotherapy or undergoing surgery with general anesthesia. These patients received ANZEmET injection either intramuscularly or orally in a trial that included intravenous ANZEmET injection doses of 0.9, 1.2, 1.8, 2.4 mg/kg, and oral doses of 0.6, 1.2, 1.8 mg/kg. There is no experience in pediatric patients under 2 years of age. However, ANZEmET injection was well tolerated in these pediatric patients. Efficacy information collected in pediatric patients receiving cancer chemotherapy or treatment was consistent with those observed in adults. No efficacy information was collected in the pediatric postoperative nausea and vomiting studies in elderly patients.

Drug administration is not needed in patients over 65. Efficacy is based on the nausea and vomiting in elderly patients was no different than in younger age groups.

Adverse Reactions

Chemotherapy Patients

In controlled clinical trials, 2245 adult patients received ANZEmET injection. The overall adverse event rates were similar with 1.8 mg/kg ANZEmET injection and prednisolone or prednisolone. Patients were receiving concurrent chemotherapy, predominantly high-dose (305 mg/m²) cisplatin. In a combined analysis of all adverse events reported in 2245 of patients in three controlled trials (Table 4).

Table 4. Adverse Events 2% from Chemotherapy-Induced Nausea and Vomiting Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>ANZEmET Injection 1.8 mg/kg (n=65)</th>
<th>Cisplatin/ Prednisone (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/ Vomiting</td>
<td>16 (24.6%)</td>
<td>13 (17.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (12.3%)</td>
<td>6 (7.9%)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (7.7%)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (7.7%)</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Hepatic Function Abnormality</td>
<td>2 (3.1%)</td>
<td>3 (4.0%)</td>
</tr>
</tbody>
</table>

Abdominal Pain 22 (3.2%) 7 (0.9%)
Hypertension 20 (2.9%) 9 (1.2%)
Dizziness 15 (2.2%) 7 (0.9%)
Cholelithiasis 14 (2.1%) 6 (7.9%)
* Includes events coded as G4T and/or G4T-increased

+ includes events coded as SOI and/or SOI-increased (see also Life and fertility profile below)

Postoperative Patients

In controlled clinical trials with 2550 adult patients, nausea and distress were reported more frequently with 12.5 mg ANZEmET injection than with placebo. Rates of other adverse events were similar. Following is a listing of all adverse events reported in 2550 of patients entering other placebo or 12.5 mg ANZEmET injection for the prevention or treatment of postoperative nausea and vomiting in controlled clinical trials (Table 5).

Table 5. Adverse Events 5% from Placebo-Controlled Postoperative Nausea and Vomiting Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>ANZEmET Injection 12.5 mg (n=610)</th>
<th>Placebo (n=670)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>36 (5.9%)</td>
<td>39 (5.9%)</td>
</tr>
</tbody>
</table>

HYPNOSLEEP® Injection (doxorubicin mesylate injection) is supplied as a clear, colorless solution in single-use ampoules and multidose vials, and Carupen® sterile cartridges with Luer lock.

Table 6. Adverse Events 5% from Placebo-Controlled Postoperative Nausea and Vomiting Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>ANZEmET Injection 12.5 mg (n=610)</th>
<th>Placebo (n=670)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>36 (5.9%)</td>
<td>39 (5.9%)</td>
</tr>
</tbody>
</table>

ANZEmET® Injection (doxorubicin mesylate injection) 30 mg/mL

Strengths

<table>
<thead>
<tr>
<th>Description</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 mg</td>
<td>0.625 mg, single-use ampoule*</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>0.625 mg, single-use vial**</td>
</tr>
<tr>
<td>100 mg/mL</td>
<td>5 mL, single-use vial*</td>
</tr>
<tr>
<td>500 mg/25 mL</td>
<td>25 mL multidose vial*</td>
</tr>
</tbody>
</table>

* Use at 25°C (77°F) with excipients permitted to 15°C (59°F) [see USP Compressed Dosing Temperature]. Protect from light.

Precautions:

- Preparing information as of October 2003.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-624/S-009

CHEMISTRY REVIEW(S)
### CHEMIST’S REVIEW # 2

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>1.</strong> Organization:</td>
<td>HFD-180</td>
</tr>
<tr>
<td><strong>2.</strong> NDA number:</td>
<td>20-624</td>
</tr>
<tr>
<td><strong>3.</strong> Name and Address of Applicant (City &amp; State):</td>
<td>Aventis 10236 Marion Park Drive PO Box 9720 Kansas City, MO 64134-0720</td>
</tr>
<tr>
<td><strong>4.</strong> AF Number:</td>
<td></td>
</tr>
<tr>
<td><strong>5.</strong> Supplement(s)</td>
<td></td>
</tr>
<tr>
<td><strong>6.</strong> Name of Drug:</td>
<td>Anzmet® Injection</td>
</tr>
<tr>
<td><strong>7.</strong> Nonproprietary Name:</td>
<td>Dolasteron Mesylate</td>
</tr>
<tr>
<td><strong>8.</strong> Supplement Provides for:</td>
<td>The addition of a 12.5 mg vial is added to the existing dosage forms which are a 12.5 mg ampoule and a 100 mg vial.</td>
</tr>
<tr>
<td><strong>9.</strong> Amendments &amp; Other (Reports, etc.) Dates:</td>
<td>10/11/2002 03/19/2003</td>
</tr>
<tr>
<td><strong>10.</strong> Pharmacological Category:</td>
<td>antinauseant and antiemetic agent</td>
</tr>
<tr>
<td><strong>11.</strong> How Dispensed:</td>
<td>RX X OTC</td>
</tr>
<tr>
<td><strong>12.</strong> Related DMF(s):</td>
<td></td>
</tr>
<tr>
<td><strong>13.</strong> Dosage Form:</td>
<td>Intravenous Injection</td>
</tr>
<tr>
<td><strong>14.</strong> Potency:</td>
<td>12.5mg and 100mg</td>
</tr>
<tr>
<td><strong>15.</strong> Structure and Chemical Name:</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td></td>
<td>(2(alpha),6(alpha),8(alpha),9a(beta))-octahydro-3-oxo-2,6-methano-2 H-quino-lizin-8-yl-l H-indole-3-carboxylate monomethanesulfonate, monohydrate empirical formula is C_{19}H_{20}N_{3}O_{3}·CH_{3}SO_{3}H·H_{2}O molecular weight of 438.50</td>
</tr>
<tr>
<td><strong>16.</strong> Records and Reports:</td>
<td>Current Yes X No</td>
</tr>
<tr>
<td></td>
<td>Reviewed Yes X No</td>
</tr>
<tr>
<td><strong>17.</strong> Comments:</td>
<td>Original submission for this supplement was deemed approvable due to Microbiology concerns. However, the sponsor provided additional microbiological information, which was reviewed by the Microbiology reviewer, Dr. James McVey, who indicated in his review dated May 29, 2003 that the responses are satisfactory and therefore, the supplement may be approved.</td>
</tr>
<tr>
<td><strong>18.</strong> Conclusions and Recommendations:</td>
<td>Recommend that the regulatory Health Project Manager issue An-Approved letter for this supplement.</td>
</tr>
<tr>
<td><strong>19.</strong> Reviewer</td>
<td></td>
</tr>
<tr>
<td><strong>Name:</strong></td>
<td>Ali Al-Hakim, Ph.D.</td>
</tr>
<tr>
<td><strong>Date Completed:</strong></td>
<td>05/30/03</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ali Al-Hakim
5/30/03 11:35:27 AM
CHEMIST

Liang Zhou
5/30/03 04:12:26 PM
CHEMIST
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls Supplement
NDA #: 20-624 SUPPLEMENT #: SCS-009 CHEM REVIEW #: 2 REVIEW DATE: Jan 28, 2003

SUBMISSION TYPE DOCUMENT CDER ASSIGNED DATES

PREVIOUS DOCUMENTS
TYPE DATE
ORIGINAL 14-MAR-2002
MICRO REVIEW #1 16-MAY-2002
CHEM REVIEW #1 15-JUL-2002
AE LETTER 15-JUL-2002

SUPPLEMENT PROVIDES FOR: addition of 12.5 mg vial

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel
10326 Marion Park Drive P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME:
Proprietary: Anzemet Nonproprietary/USAN: Dolasetron mesylate

DOSAGE FORM: Liquid STRENGTH: 12.5 mg ampoule and 500 mg (20.0 mg/mL) multi-
dose vial

ROUTE OF ADMINISTRATION: Injection

HOW DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(2, 6, 8, 9a)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-
carboxylate monomethanesulfonate monohydrate.

\[\text{CH}_3\text{SO}_2\text{H} \cdot \text{H}_2\text{O}\]


RELATED DOCUMENTS: NDA 20-623

CONSULTS: Microbiology continues to be Not acceptable. See review dated 15-
Nov-2002

REMARKS/COMMENTS: All aspects of the CMC are the same as the currently
approved multi-dose vial. However there are still a number of questions from
the Microbiology review.

CONCLUSIONS & RECOMMENDATIONS: APPROVABLE (AE) The applicant should be sent
an Approvable letter with the comments from the Microbiology reviewer.
R/D init by LZhou 28-Jan-2003

ABS/F/T ABS 28-Jan-2003 M:\My Documents Back\Word\F\20-624 Anzemet SCS-009
Review 2.doc
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/s/

Arthur B. Shaw
1/28/03 12:23:26 PM
CHEMIST
provides for addition of 12.5 mg vial

Liang Zhou
1/28/03 12:51:51 PM
CHEMIST
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls Supplement
NDA #:20-624 SUPPLEMENT #:SCS-009 CHEM REVIEW #:1 REVIEW DATE: Jul 15, 2002
SUBMISSION TYPE
DOCUMENT CDER ASSIGNED REVIEW DATES
SUPPLEMENT PROVIDES FOR: addition of 12.5 mg vial
NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel
10326 Marion Park Drive P.O. Box 9627
Kansas City, MO 64134-0627
DRUG PRODUCT NAME: Proprietary: Anzemet Nonproprietary/USAN: Dolasetron mesylate
DOSAGE FORM: Liquid STRENGTH: 20.0 mg/mL
ROUTE OF ADMINISTRATION: Injection HOW DISPENSED: X Rx __ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(2 , 6 , 8 , 9a )-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate monohydrate.

SUPPORTING DOCUMENTS: All DMFs are the same as for the approved 100 mL vial. RELATED DOCUMENTS: NDA 20-623
CONSULTS: Microbiology Not acceptable. See review dated 16-May-2002
REMARKS/COMMENTS: All aspects of the CMC (components, Composition, Manufacturing, In-Process Controls and Container/Closure in product contact, and Finished Product Specifications) are the same as the currently approved multi-dose vial except for the size of the vial and the color of the flip-off cap. Stability data (3 months, provided in Exhibit J. The data show no significant change. A stability protocol is provided in Exhibit K. The applicant has committed to placing the validation batches, the first three commercial batches and one batch per year thereafter on stability. The only change in the package insert is to add the new vial in the "How supplied" section. ACCEPTABLE Comments on the vial label and the carton label are being provided by the Regulatory Project Manager. There are a number of questions from the Microbiology review that should be conveyed to the applicant.
CONCLUSIONS & RECOMMENDATIONS: The applicant should be sent an Approvable (AB) letter with the Microbiology and an Labeling information requests.
Signed Arthur B. Shaw, Ph.D. Review Chemist, HFD-180
Concur Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180
R/D init by LZhou 15-Jul-2002
ABS/F/T ABS 15-Jul-2002 M:\My Documents Back\Word\F\20-624 SCS-009 Chem Review #1.doc
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/s/
Arthur B. Shaw
7/15/02 09:22:16 AM
CHEMIST

Liang Zhou
7/15/02 11:40:50 AM
CHEMIST
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-624/S-009

MICROBIOLOGY REVIEW
Product Quality Microbiology Review
Review for HFD-180
May 5, 2003

NDA: 20-624/S-009 Amendment (Second)

Drug Product Name
Proprietary: Anzemet® Injection
Non-proprietary: dolasetron mesylate
Drug Product Classification: anti-emetic

Review Number: 2

Subject of this Review
Submission Date: March 19, 2003
Receipt Date: March 20, 2003
Consult Date: March 25, 2003
Date Assigned for Review: April 29, 2003

Submission History (for amendments only):
Date(s) of Previous Submission(s): March 15, 2002; October 11, 2002
Date(s) of Previous Micro Review(s): May 9, 2002; November 15, 2002

Applicant/Sponsor
Name: Aventis Pharmaceuticals
Address: 10236 Marion Park Drive
         Kansas City, MO 64134-9720
Representative: Alan Martin
Telephone: (816) 966-6794

Name of Reviewer: James L. McVey

Conclusion: The supplement is recommended for approval.
Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Prior Approval

2. SUPPLEMENT PROVIDES FOR: A 12.5 mg vial is added to the existing dosage forms which are a 12.5 mg ampoule and a 100 mg vial.

3. MANUFACTURING SITE: The 12.5 mg vials will be manufactured and tested at: Gruppo Lepetit S.p.A.
   A wholly owned subsidiary of Aventis Pharmaceuticals
   Localita Valcanello
   03012 Anagni (Frosinone) Italy
   Release testing and stability testing on the finished product will be done here.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Each dose of 12.5 mg in 0.625 mL is administered by I.V. injection. The proposed 12.5 mg single dose vial contains 0.827 mL of a 20 mg/mL solution.

5. METHOD(S) OF STERILIZATION:


B. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS: This submission includes the response to three separate letters addressing Supplements 003, 008 and 009. This Microbiology consult and review only address responses to Supplement 9 deficiencies.

filename: 20624s9r3.doc
Executive Summary

I. Recommendations

A. Recommendation on Approvability - This supplemental application is recommended for approval from a product quality microbiology perspective.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – n.a.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – A 12.5 mg vial is added to the existing 12.5 mg ampoule and 100 mg vial line. No difference in formulation or testing is indicated. Vials and stoppers are

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – Minimal risk is perceived from the addition of the 12.5 mg vial to the product line.

III. Administrative

A. Reviewer's Signature ____________________________

B. Endorsement Block
   Microbiologist; J. McVey
   Microbiology Supervisor; P. Cooney

C. CC Block
   DFS
   HFD- 805/McVey/20624s9r3.doc
Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process
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/s/

James McVey
5/29/03 12:40:40 PM
MICROBIOLOGIST

Peter Cooney
5/29/03 12:52:21 PM
MICROBIOLOGIST
Product Quality Microbiology Review
Review for HFD-180
November 15, 2002

NDA: 20-624/S-009 Amendment

Drug Product Name
Proprietary: Anzemet® Injection
Non-proprietary: dolasetron mesylate
Drug Product Classification: anti-emetic

Review Number: 2

Subject of this Review
Submission Date: October 11, 2002
Receipt Date: October 23, 2002
Consult Date: October 24, 2002
Date Assigned for Review: October 31, 2002

Submission History (for amendments only):
Date(s) of Previous Submission(s): March 15, 2002
Date(s) of Previous Micro Review(s): May 9, 2002

Applicant/Sponsor
Name: Aventis Pharmaceuticals
Address: 10236 Marion Park Drive
         Kansas City, MO 64134-9720
Representative: Alan Martin
Telephone: (816) 966-6794

Name of Reviewer: James L. McVey

Conclusion: The supplement is recommended for approval pending resolution of the microbiology concerns.
Product Quality Microbiology Data Sheet

A.  1. TYPE OF SUPPLEMENT: Prior Approval

2. SUPPLEMENT PROVIDES FOR: A 12.5 mg vial is added to the existing dosage forms which are a 12.5 mg ampoule and a 100 mg vial.

3. MANUFACTURING SITE: The 12.5 mg vials will be manufactured and tested at: Gruppo Lepetit S.p.A.
   A wholly owned subsidiary of Aventis Pharmaceuticals
   Localita Valcanello
   03012 Anagni (Frosinone) Italy
   Release testing and stability testing on the finished product will be done here.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Each dose of 12.5 mg in 0.625 mL is administered by I.V. injection. The proposed 12.5 mg single dose vial contains 0.827 mL of a 20 mg/mL solution.

5. METHOD(S) OF STERILIZATION:


B. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS: This submission includes the response to three separate letters addressing Supplements 003, 008 and 009. This Microbiology consult and review only address responses to Supplement 9 deficiencies.

filename: 20624s9r2.doc
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending response to microbiology deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – n.a.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – A 12.5 mg vial is added to the existing 12.5 mg ampoule and 100 mg vial line. No difference in formulation or testing is indicated. Vials and stoppers are

B. Brief Description of Microbiology Deficiencies – The applicants response to the deficiencies indicated in the approvable letter is that they will do the validations before the product is manufactured. The information must be submitted and found acceptable before the application can be recommended for approval.

C. Assessment of Risk Due to Microbiology Deficiencies – The possibility

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
   Microbiologist; J. McVey
   Microbiology Supervisor; P. Cooney

C. CC Block
   DFS
   HFD- 805/McVey/20624s9r2.doc
2 Page(s) Withheld

☑️ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(4) Draft Labeling

☐ § 552(b)(5) Deliberative Process
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/b/

-----------------------
James McVey
11/15/02 02:20:50 PM
MICROBIOLOGIST

-----------------------
Peter Cooney
11/15/02 03:24:46 PM
MICROBIOLOGIST
Product Quality Microbiology Review
Review for HFD-180
May 9, 2002

NDA: 20-624/S-009

Drug Product Name
Proprietary: Anzemet® Injection
Non-proprietary: dolasetron mesylate
Drug Product Classification: anti-emetic

Review Number: 1

Subject of this Review
Submission Date: March 14, 2002
Receipt Date: March 15, 2002
Consult Date: March 18, 2002
Date Assigned for Review: April 1, 2002

Applicant/Sponsor
Name: Aventis Pharmaceuticals
Address: 10236 Marion Park Drive
         Kansas City, MO  64134-9720
Representative: Alan Martin
Telephone: (816) 966-6794

Name of Reviewer: James L. McVey

Conclusion: The supplemental submission is approvable pending resolution of product quality microbiology concerns.
Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Prior Approval

2. SUPPLEMENT PROVIDES FOR: A 12.5 mg vial is added to the existing dosage forms which are a 12.5 mg ampoule and a 100 mg vial.

3. MANUFACTURING SITE: The 12.5 mg vials will be manufactured and tested at: Gruppo Lepetit S.p.A. A wholly owned subsidiary of Aventis Pharmaceuticals Localita Valcanello 03012 Anagni (Frosinone) Italy Release testing and stability testing on the finished product will be done here.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Each dose of 12.5 mg in 0.625 mL is administered by I.V. injection. The proposed 12.5 mg single dose vial contains 0.827 mL of a 20 mg/mL solution.

5. METHOD(S) OF STERILIZATION:


B. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS:

filename: 20624s9r1.doc
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending response to microbiology deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – n.a.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – A 12.5 mg vial is added to the existing 12.5 mg ampoule and 100 mg vial line. No difference in formulation or testing is indicated. Vials and stoppers are

B. Brief Description of Microbiology Deficiencies –

C. Assessment of Risk Due to Microbiology Deficiencies – Risk cannot be assessed until the microbiology deficiencies have been resolved.

III. Administrative

A. Reviewer's Signature __________________________

B. Endorsement Block
   Microbiologist: J. McVey
   Microbiology Supervisor; P. Cooney

C. CC Block
   Original NDA 20-624/S009 in DFS
   HFD- 805/McVey/20624s9r1.doc
   HFD-180/ Strongin
Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process
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/s/
James McVey
5/16/02 07:26:44 AM
MICROBIOLOGIST

Peter Cooney
5/16/02 09:45:19 AM
MICROBIOLOGIST
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-624/S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-624/SCS-009

Name of Drug: Anzemet® (dolasetron mesylate) Injection

Applicant: Aventis Pharmaceuticals, Inc.

Material Reviewed:

Submission Dates: October 11, 2002

Receipt Dates: October 15, 2002

Background and Summary

NDA 20-624 was approved September 11, 1997 for Anzemet® Injection for the following indications: 1) prevention of chemotherapy-induced nausea and vomiting; 2) prevention of post-operative nausea and vomiting; 3) treatment of post-operative nausea and vomiting. Supplement SCS-009, submitted March 14, 2002, provides for the addition of a 12.5mg/0.625ml single-use vial. The supplement was Approvable July 15, 2002 pending sterilization process and labeling issues. The following revisions to the draft labeling were requested in the Approvable letter:

In addition, it will be necessary for you to submit final printed labeling revised as follows:

Vial Label

Please add the following information to the vial label:

1. The place of business of the manufacturer, packer or distributor.
2. The usual or recommended dosage or a reference to the package insert for this information.
3. The established names and quantities of inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.
4. The recommended storage conditions.
5. The NDC code.

Carton Label

Please add the following information to the carton label:
1. The symbol “Rx”.
2. The quantities of the inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.

On October 11, 2002, Aventis submitted a response, including revised immediate container and carton labeling, to the Approvable letter.

Review

The labeling submitted October 11, 2002 [carton (ID #50065701), immediate container (ID# 50065700), and package insert (Prescribing Information as of September 2002)] was compared to the draft labeling submitted with SCS-009 on March 14, 2002 [carton (ID #50065701), immediate container (ID# 50065700), and package insert (Prescribing Information as of January 2002)]. The following changes have been made.

I. Immediate Container

The additions requested were not made. Aventis cited 21 CFR 201.10(i)(1) and (2) regarding labels with insufficient space to include all the information required to appear on the label.

This is acceptable.

II. Carton (6 x 12.5mg Vials)

A. The symbol “Rx Only” was added.

This is acceptable per FDAMA 1997.

B. The quantity “23.875mg” and the designation “USP” were added before and after the word “mannitol”.

The quantity is acceptable per CMC reviewer, Art Shaw, Ph.D. The USP designation was requested in the March 22, 2002 Approval letter for SLR-008. Therefore, these changes are acceptable.

III. Package Insert, HOW SUPPLIED section

A line for the 12.5mg vial was added to the table describing package sizes of Anzemet Injection currently available for marketing.

This change is consistent with SCF-009 and, therefore, is acceptable.
Conclusions

The immediate container, carton, and package insert labeling for the 12.5mg/0.625mL single-use vial of Anzemet® Injection submitted October 11, 2002 to NDA 20-624/SCS-009 incorporate all changes requested in the July 15, 2002 Approvable letter for this supplement and are therefore acceptable.

[See electronic signature page]
Brian Strongin, R.Ph., M.B.A.
Regulatory Project Manager

[See electronic signature page]
Arthur Shaw, Ph.D.
Review Chemist

Supervisory Comment/Concurrence:

[See electronic signature page]
Julieann DuBeau, RN, MSN
Chief, Project Management Staff

Revised/Initialed: JD/February 4, 2003
Finalized: BKS/February 10, 2003
Filename: Anzemet S-008  Labeling Review

PM LABELING REVIEW
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/s/
---------------------
Brian Strongin
2/10/03 09:39:42 AM
CSO

Please sign ASAP. This is due 2/14/03.

Arthur B. Shaw
2/10/03 09:49:53 AM
CHEMIST
The phrase proposed by the applicant is used in our CDBR’s draft Stability guidance (Line 588):
Store at ———excursions permitted to 15-30°C (59-86°F)
[see USP
Controlled Room Temperature]

Julieann DuBeau
2/10/03 04:17:22 PM
CSO
Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER’S REVIEW

Application Number: NDA 20-624/S-009

Name of Drug: Anzemet® (dolasetron) Injection

Sponsor: Aventis Pharmaceuticals Inc.

Material Reviewed:

Submission Date: March 14, 2002

Receipt Date: March 15, 2002

Background and Summary

NDA 20-624 for Anzemet® Injection was approved September 11, 1997 for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. Anzemet Injection is currently approved in 12.5 mg/0.625mL ampuls, 12.5 mg/0.625mL Carpuject syringes, and 100 mg/5mL single-use vials. Supplement S-009 proposes the addition of a 12.5 mg/0.625mL single-use vial. The supplement includes new carton (ID number 50065701) and immediate container (ID number 50065700) labels and revisions to the HOW SUPPLIED section of the package insert (January 2002). The currently approved package insert (July 2001) will be compared to the proposed package insert and the differences noted below. The proposed immediate container and carton labels were reviewed for conformance to the labeling regulations and areas of non-conformance are noted below.

Review

I. Vial Label

The following required information is not included in the proposed vial label:

A. The place of business of the manufacturer, packer of distributor as required by 21 CFR 201.1.
B. The usual or recommended dose or a reference to the package insert for this information per 21 CFR 201.100(b)(2).
C. The established names and quantities of inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effects. This information is required per 21 CFR 201.100(b)(5).
D. The recommended storage conditions per 21 CFR 211.137 and 211.166.
Aventis should be requested to submit FPL for the vial label including this information.

II. Carton Label

The following required information is not included in the proposed carton label:

A. The symbol “Rx only”.
B. The quantities of the inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effects. This information is required per 21 CFR 201.100(b)(5).

Aventis should be requested to submit FPL for the carton label including this information.

III. Package Insert

A. The identifier above the Description section and at the end of the package insert was changed from “
B. HOW SUPPLIED section

The strength, description, and NDC number of the proposed 12.5mg/0.625mL single-use vial have been added to the table of currently approved package sizes.

These changes are acceptable.

Conclusions

Aventis should be directed to make the following changes to the draft labeling when FPL is submitted:

Vial Label

Please add the following information to the vial label:

1. The place of business of the manufacturer, packer of distributor.
2. The usual or recommended dosage or a reference to the package insert for this information.
3. The established names and quantities of inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.
4. The recommended storage conditions.
5. The NDC code.
Carton Label

Please add the following information to the carton label:

1. The symbol “Rx Only”.
2. The quantities of the inactive ingredients. Ingredients added for final pH adjustment or to make the drug isotonic may be declared by name and a statement of their effect.

The submitted draft labeling is otherwise acceptable. An action letter will be drafted when the other reviews have been completed.

\textit{[See appended electronic signature page]}

Brian Strongin, R.Ph., M.B.A.
Regulatory Project Manager

Supervisory Comment/Concurrence:

\textit{[See appended electronic signature page]}

Julieann DuBeau
Chief, Project Management Staff

Drafted: BKS/July 15, 2002
Revised/Initialed:
Finalized:
Filename: 20624702.0

PM LABELING REVIEW
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/s/
Brian Strongin
7/15/02 11:28:46 AM
CSO

Julieann DuBeau
7/15/02 11:53:20 AM
CSO
# REQUEST FOR CONSULTATION

## TO (Division/Office):

Peter Cooney, Ph.D., HFD-805  
Parklawn Building, 18B-08

## FROM:

Brian Strongin, R.Ph., M.B.A., HFD-180  
Parklawn Building 68-45

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<td>Standard</td>
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## NAME OF FIRM: Aventis Pharmaceuticals, Inc.

## REASON FOR REQUEST

### I. GENERAL

- [ ] NEW PROTOCOL
- [ ] PROGRESS REPORT
- [ ] NEW CORRESPONDENCE
- [ ] DRUG ADVERTISING
- [ ] ADVERSE REACTION REPORT
- [ ] MANUFACTURING CHANGE/ADDITION
- [ ] MEETING PLANNED BY
- [ ] PRE-NDA MEETING
- [ ] END OF PHASE II MEETING
- [ ] RESUBMISSION
- [ ] SAFETY/EFFICACY
- [ ] PAPER NDA
- [ ] CONTROL SUPPLEMENT
- [ ] RESPONSE TO DEFICIENCY LETTER
- [ ] FINAL PRINTED LABELING
- [ ] LABELING REVISION
- [ ] ORIGINAL NEW CORRESPONDENCE
- [ ] FORMULATIVE REVIEW
- [ ] OTHER (SPECIFY BELOW):
  - [ ] See comments below

## COMMENTS/SPECIAL INSTRUCTIONS:
Attached is a complete response to our February 11, 2003 AE letter for NDA 20-624/SCS-009. I've also included the micro review by James L. McVey, the CMC review by Art Shaw, and the AE letter. Let me know if you need anymore information. Thanks.

## SIGNATURE OF REQUESTER

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/s/

Brian Strongin
3/25/03 04:25:17 PM
REQUEST FOR CONSULTATION

TO (Division/Office):
Peter Cooney, Ph.D., HFD-805
Parklawn Building, 18B-08

FROM:
Brian Strongin, R.Ph., M.B.A., HFD-180
Parklawn Building 6B-45

DATE
October 24, 2002

IND NO.
NDA NO.
20-624

SCS-009

TYPE OF DOCUMENT

DATE OF DOCUMENT
October 11, 2002

NAME OF DRUG
Anzemet (dolasetron mesylate) Injection

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
January 15, 2003

NAME OF FIRM: Questcor Pharmaceuticals, Inc.

REASON FOR REQUEST

L. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER (SPECIFY BELOW):
☐ See comments below

COMMENTS/SPECIAL INSTRUCTIONS: Attached is a complete response to our July 15, 2002 AE letter for NDA 20-624/SCS-009. I’ve also included the Micro review by James L. McVey and the CMC review by Art Shaw. Let me know if you need anymore information. Thanks.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
☐ MAIL
☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER
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/s/

Brian Strongin
10/24/02 01:10:19 PM
REQUEST FOR CONSULTATION

TO (Division/Office):
Peter Cooney, Ph.D., HFD-805
Parklawn Building, 18B-08

FROM:
Brian Strongin, R.Ph., M.B.A., HFD-180
Parklawn Building 6B-45

DATE
March 18, 2002

IND NO.

NDA NO.
20-624

TYPE OF DOCUMENT
S-009

DATE OF DOCUMENT
March 14, 2002

NAME OF DRUG
Anzemet® ( dolasetron mesylate) Injection

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESERVED COMPLETION DATE
June 15, 2002

NAME OF FIRM: Aventis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

See comments below

COMMENTS/SPECIAL INSTRUCTIONS: Attached is prior approval supplement S-009 to NDA 20-624 for Anzemet Injection. It provides for a 12.5 mg vial. Please let me know if you need anymore information. Thanks.

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METHOD OF DELIVERY (Check one)
- MAIL
- HAND

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/s/

Brian Strongin
3/18/02 10:54:36 AM
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
Attention: Philip E. Page, R.Ph.
Regulatory Affairs - CMC
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-0720

Dear Mr. Page:

We acknowledge receipt on March 20, 2003 of your March 19, 2003 resubmission to your supplemental new drug application for Anzemet® (dolasetron mesylate) Injection.

We consider this a complete response to our February 11, 2003 action letter. Therefore, the user fee goal date is July 20, 2003.

If you have any question, call me at (301)827-7473.

Sincerely,

[See appended electronic signature page]

Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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/s/

Brian Strongin
3/25/03 04:20:42 PM
Aventis Pharmaceuticals, Inc.
Attention: Philip E. Page, R.Ph.
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-0720

Dear Mr. Page:

We acknowledge receipt on October 15, 2002 of your October 11, 2002 resubmission to your supplemental new drug applications for Anzemet® (dolasetron mesylate) Injection.

We consider this a complete response to our June 6, 2000 action letter for Supplement S-003 and our July 15, 2002 action letter for Supplement S-009. Therefore, the user fee goal date is February 15, 2003.

If you have any question, call me at (301) 827-7310.

Sincerely,

(See appended electronic signature page)

Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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/s/

Brian Strongin
10/22/02 11:32:28 AM
NDA 20-624/S-009

Aventis Pharmaceuticals, Inc.
Attention: Alan Martin
U.S. Drug Regulatory Affairs-CMC
P.O. Box 9720
Mail Stop J5-M1540
Kansas City, MO 64134-0720

Dear Mr. Martin:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Anzemet® (dolasetron mesylate) Injection

NDA Number: 20-624

Supplement number: S-009

Date of supplement: March 14, 2002

Date of receipt: March 15, 2002

This supplemental application proposes the following change: the addition of a 12.5 mg vial.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 14, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 15, 2002.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857
If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

[See appended electronic signature page]

Brian Strongin, R.Ph., M.B.A.
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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/s/

Brian Strongin
3/18/02 10:31:43 AM