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

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Statistical Review(s)	
Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-624/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet® (dolasetron mesylate) Injection dated March 14, 2002, received March 15, 2002.

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

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/s/

Robert Justice
7/18/03 09:31:25 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-624/S-009

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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:

Please refer to your supplemental new drug application dated March 14, 2002, received March 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet® (dolasetron mesylate) Injection.

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

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/s/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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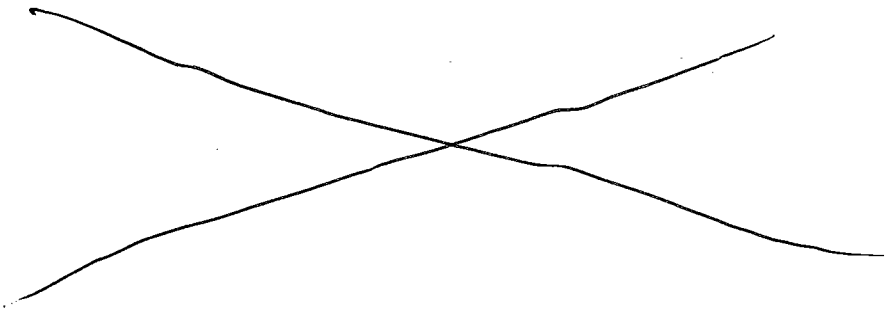
1.

2.

3.



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Coagulation Drug Products
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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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:

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

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/s/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-624/S-009

LABELING

ID number:	**50065700**
Version:	**F**
Country:	**USA**
Date:	**12-12-02**
Operator:	**DM**
Product Desc.	**Label, Anzemet Injection, 12.5mg, Vial**
Supplier:	**Anagni**

Aventis

Artwork created in: Adobe Illustrator 8.0, Mac format

Fonts used: OceanSansAV Bold, Roman, Italic

Minimum point size of text: 5 pt.

Colors Used:

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Functional: **Date:** _____

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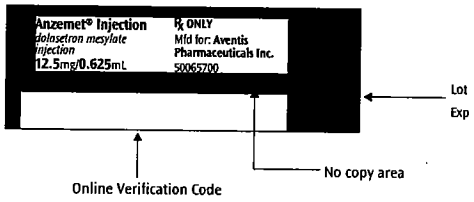

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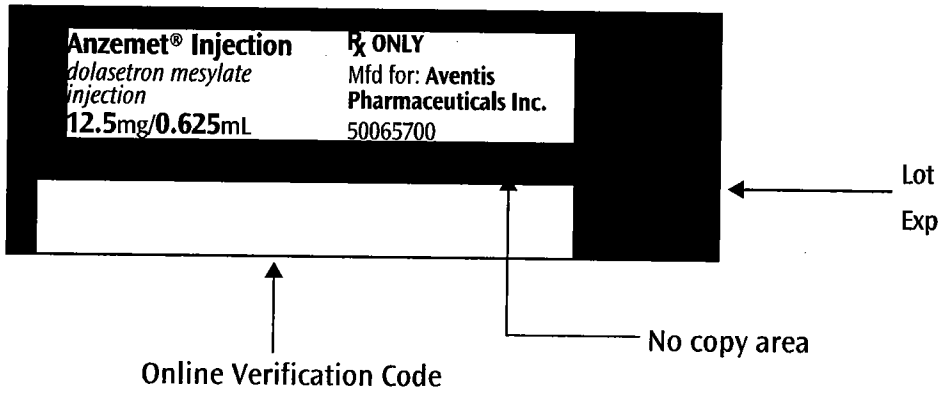

ITEM # 50061716	DATE: 3/30/01
PRODUCT: LABEL, ANZEMET INJECTION, 12.5 MG 1 Ampul	
PRINTER: ANAGNI	
PMS 221	

APPROVALS

FUNCTIONAL

PROOFREADING

REGULATORY

100%

Anzemet® Injection 12.5mg
dolasetron mesylate (20mg/mL)
injection
50061716 Mfd for: **Aventis Pharmaceuticals Inc.**

Lot Exp

200%

Anzemet® Injection 12.5mg
dolasetron mesylate (20mg/mL)
injection
50061716 Mfd for: **Aventis Pharmaceuticals Inc.**

Lot Exp

ID number:	**50065701**
Version:	**D**
Country:	**USA**
Date:	**10-1-02**
Operator:	**DM**
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Supplier:	**Anagni**

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Minimum point size of text: 5 pt.
Colors Used:
Reflex Blue ■ **PMS 221** ■ PMS 368 ▒

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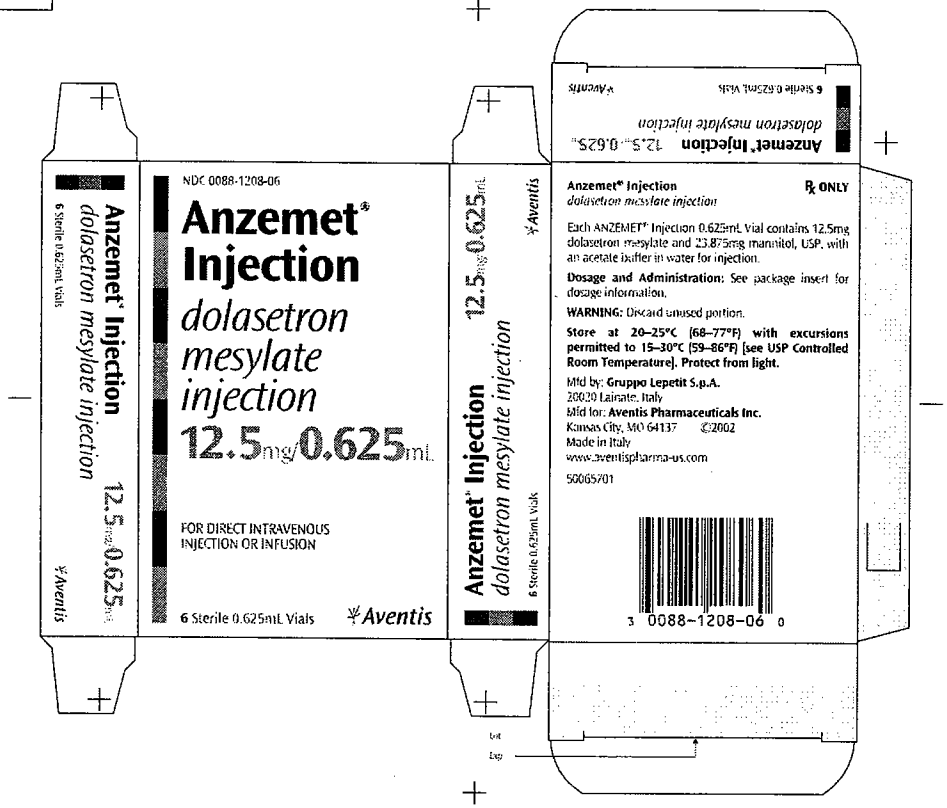

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50070880
Prescribing Information as of October 2003

Anzemet® Injection

dolasetron mesylate injection

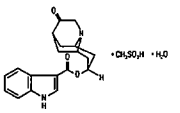
Aventis

Prescribing Information as of October 2003 Rx only.

ANZEMET® Injection
(dolasetron mesylate injection)

DESCRIPTION

ANZEMET (dolasetron mesylate) is an antinauseant and antiemetic agent. Chemically, dolasetron mesylate is (2α,6α,8α,9aβ)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl-1*H*- indole-3-carboxylate monomethanesulfonate, monohydrate. It is a highly specific and selective serotonin subtype 3 (5-HT_3) receptor antagonist both in vitro and in vivo. Dolasetron mesylate has the following structural formula:



The empirical formula is $C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$, with a molecular weight of 438.50. Approximately 74% of dolasetron mesylate monohydrate is dolasetron base.

Dolasetron mesylate monohydrate is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol, and slightly soluble in normal saline.

ANZEMET Injection is a clear, colorless, nonpyrogenic, sterile solution for intravenous administration. Each milliliter of ANZEMET Injection contains 20 mg of dolasetron mesylate and 38.2 mg mannitol, USP, with an acetate buffer in water for injection. The pH of the resulting solution is 3.2 to 3.8.

ANZEMET Injection multidose vials contain a clear, colorless, nonpyrogenic, sterile solution for intravenous administration. Each ANZEMET multidose vial contains 25 mL (500 mg) dolasetron mesylate. Each milliliter contains 20 mg dolasetron mesylate, 29 mg mannitol, USP, and 5 mg phenol, USP, with an acetate buffer in water for injection. The pH of the resulting solution is 3.2 to 3.7.

CLINICAL PHARMACOLOGY

Dolasetron mesylate and its active metabolite, hydrodolasetron (MDL 74,156), are selective serotonin 5-HT_3 receptor antagonists not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serotonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT_3 receptors located on vagal efferents to initiate the vomiting reflex.

Acute, usually reversible, ECG changes (PR and QT_c prolongation; QRS widening), caused by dolasetron mesylate, have been observed in healthy volunteers and in controlled clinical trials. The active metabolites of dolasetron may block sodium channels, a property unrelated to its ability to block 5-HT_3 receptors. QT_c prolongation is primarily due to QRS widening. Dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. The magnitude and frequency of the ECG changes increased with dose (related to peak plasma concentrations of hydrodolasetron but not the parent compound). These ECG interval prolongations usually returned to baseline within 6 to 8 hours, but in some patients were present at 24 hour follow up. Dolasetron mesylate administration has little or no effect on blood pressure.

In healthy volunteers (N=64), dolasetron mesylate in single intravenous doses up to 5 mg/kg produced no effect on pupil size or meaningful changes in EEG tracings. Results from neuropsychiatric tests revealed that dolasetron mesylate did not alter mood or concentration. Multiple daily doses of dolasetron have had no effect on colonic transit in humans. Dolasetron mesylate has no effect on plasma prolactin concentrations.

Pharmacokinetics in Humans

Intravenous dolasetron mesylate is rapidly eliminated ($t_{1/2}$ <10 min) and completely metabolized to the most clinically relevant species, hydrodolasetron.

The reduction of dolasetron to hydrodolasetron is mediated by a ubiquitous enzyme, carbonyl reductase. Cytochrome P-450 (CYP)IID6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYPIIIA and flavin monooxygenase are responsible for the N-oxidation of hydrodolasetron. Hydrodolasetron is excreted in the urine unchanged (53.0% of administered intravenous dose). Other urinary metabolites include hydroxylated glucuronides and N-oxide.

Hydrodolasetron appeared rapidly in plasma, with a maximum concentration occurring approximately 0.6 hour after the end of intravenous treatment, and was eliminated with a mean half-life of 7.3 hours (%CV=24) and an apparent clearance of 9.4 mL/min/kg (%CV=28) in 24 adults. Hydrodolasetron is eliminated by multiple routes, including renal excretion and, after metabolism, mainly glucuronidation, and hydroxylation. Hydrodolasetron exhibits linear pharmacokinetics over the intravenous dose range of 50 to 200 mg and they are independent of infusion rate. Doses lower than 50 mg have not been studied. Two thirds of the administered dose is recovered in the urine and one third in the feces. Hydrodolasetron is widely distributed in the body with a mean apparent volume of distribution of 5.8 L/kg (%CV=25, N=24) in adults.

Sixty-nine to 77% of hydrodolasetron is bound to plasma protein. In a study with ^{14}C labeled dolasetron, the distribution of radioactivity to blood cells was not extensive. The binding of hydrodolasetron to α_1-acid glycoprotein is approximately 50%. The pharmacokinetics of hydrodolasetron are linear and similar in men and women.

The pharmacokinetics of hydrodolasetron, in special and targeted patient populations following intravenous administration of ANZEMET Injection, are summarized in Table 1. The pharmacokinetics of hydrodolasetron are similar in adult healthy volunteers and in adult cancer patients receiving chemotherapeutic agents. The apparent clearance of hydrodolasetron in pediatric and adolescent patients is 1.4 times to twofold higher than in adults. The apparent clearance of hydrodolasetron is not affected by age in adult cancer patients. Following intravenous administration, the apparent clearance of hydrodolasetron remains unchanged with severe hepatic impairment and decreases 47% with severe renal impairment. No dose adjustment is necessary for elderly patients or for patients with hepatic or renal impairment.

In a pharmacokinetic study in pediatric cancer patients (ages 2 to

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 serotonin 5-HT_3 receptor antagonists studied as active comparators. It was more effective than metoclopramide. Efficacy was based on complete response rates (0 emetic episodes and no rescue medication).

Cisplatin Based Chemotherapy

A randomized, double-blind trial compared single intravenous doses of ANZEMET Injection with metoclopramide in 226 (160 men and 66 women) adult cancer patients receiving ≥80 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 Chemotherapy*

	ANZEMET Injection 1.8 mg/kg†	Metoclopramide‡	*p*-value
Number of Patients	72	69	
Response Over 24 Hours			
Complete Response§	41 (57%)	24 (35%)	0.0009
Nausea Score‖	4	30	0.0400

*: Dose ≥80 mg/m²
†: Administered intravenously
‡: 3 mg/kg intravenous bolus and 0.5 mg/kg/h intravenously over 8 h.
§: No emetic episodes and no rescue medication.
‖: Median 24-h change from baseline nausea score using visual analog scale (VAS): Score range 0="none" to 100="nausea as bad as it could be."

A second randomized, double-blind trial compared single intravenous doses of ANZEMET Injection with intravenous ondansetron in 609 (377 men and 232 women) adult cancer patients receiving ≥70 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 Chemotherapy*

	ANZEMET Injection 1.8 mg/kg†	Ondansetron 32 mg‡	*p*-value
Number of Patients	198	206	
Response Over 24 Hours			
Complete Response§	88 (44%)	88 (43%)	NS
Nausea Score‖	10	16	NS

*: Dose ≥70 mg/m²
†: Administered intravenously
‡: Includes 12 patients who received 3 doses 0.15 mg/kg of ondansetron intravenously.
§: No emetic episodes and no rescue medication.
‖: Median 24-h change from baseline nausea score using visual analog scale (VAS): Score range 0="none" to 100="nausea as bad as it could be."

Another randomized, double-blind trial compared single IV doses of ANZEMET with a single 3-mg IV dose of granisetron in 474 (315 men and 159 women) patients receiving ≥80 mg/m² cisplatin chemotherapy. A single intravenous 1.8-mg/kg dose of ANZEMET gave similar results as those from granisetron.

Cyclophosphamide Based Chemotherapy

In a study of ANZEMET Injection in 309 patients (96 men and 213 women) receiving moderately emetogenic chemotherapy such as cyclophosphamide based regimens, a single intravenous 1.8 mg/kg dose of ANZEMET Injection was equivalent to metoclopramide administered as a 2 mg/kg intravenous bolus followed by 3 mg/kg intravenously over 8 hours. Complete response rates were 63% and 52%, respectively, p=0.12.

Prevention of Postoperative Nausea and Vomiting

ANZEMET Injection administered intravenously at a dose of 12.5 mg approximately 15 minutes before the cessation of general balanced anesthesia (short-acting barbiturate, nitrous oxide, narcotic and analgesic, and skeletal muscle relaxant) 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, 50, and 100 mg with placebo in 635 women surgical patients undergoing laparoscopic procedures. ANZEMET Injection at a dose of 12.5 mg was statistically superior to placebo for complete response (no vomiting, no rescue medication) (p=.0003). Complete response rates were 50% and 31%, respectively.

Another trial compared single intravenous ANZEMET Injection doses of 12.5, 25, 50, and 100 mg with placebo in 1030 (722 women and 308 men) surgical patients. In women, the 12.5 mg dose was statistically superior to placebo for complete response. The complete response rates were 50% and 40%, respectively. However, in men, there was no statistically significant difference in complete response between any ANZEMET dose and placebo.

Treatment of Postoperative Nausea and/or Vomiting

Two randomized, double-blinded trials compared single intravenous ANZEMET Injection doses of 12.5, 25, 50, and 100 mg with placebo in 124 male and 833 female patients who had undergone surgery with general balanced anesthesia and presented with early postoperative nausea or vomiting requiring antiemetic treatment.

In both studies, the 12.5 mg intravenous dose of ANZEMET was statistically superior to placebo for complete response (no vomiting, no escape 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 postoperative nausea and vomiting.** As

ence anesthesia recovery time in patients. Dolasetron mesylate did not inhibit the antitumor activity of four chemotherapeutic agents (cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide) in four murine models.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, there was a statistically significant ($P<0.001$) increase in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated with 150 mg/kg/day and above. In this study, mice (CD-1) were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day (225, 450 or 900 mg/m²/day). For a 50 kg person of average height (1.46 m² body surface area), these doses represent 3.4, 6.8 and 13.5 times the recommended clinical dose (66.6 mg/m², intravenous) on a body surface area basis. No increase in liver tumors was observed at a dose of 75 mg/kg/day in male mice and at doses up to 300 mg/kg/day in female mice.

In a 24-month rat (Sprague-Dawley) carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day (900 mg/m²/day, 13.5 times the recommended human dose based on body surface area) in male rats and 300 mg/kg/day (1800 mg/m²/day, 27 times the recommended human dose based on body surface area) in female rats.

Dolasetron mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosomal aberration test, the Chinese hamster ovary (CHO) cell (HGPRT) forward mutation test, the rat hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test.

Dolasetron mesylate was found to have no effect on fertility and reproductive performance at oral doses up to 100 mg/kg/day (600 mg/m²/day, 9 times the recommended human dose based on body surface area) in female rats and up to 400 mg/kg/day (2400 mg/m²/day, 36 times the recommended human dose based on body surface area) in male rats.

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Teratology studies have not revealed evidence of impaired fertility or harm to the fetus due to dolasetron mesylate. These studies have been performed in pregnant rats at intravenous doses up to 60 mg/kg/day (5.4 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 20 mg/kg/day (3.2 times the recommended human dose based on body surface area). There are, however, 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 dolasetron 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

Four open-label, noncomparative pharmacokinetic studies have been performed in a total of 108 pediatric patients receiving emetogenic chemotherapy or undergoing surgery with general anesthesia. These patients received ANZEMET Injection either intravenously or orally in juice. Pediatric patients from 2 to 17 years of age participated in these trials, which included intravenous ANZEMET Injection doses of 0.6, 1.2, 1.8, or 2.4 mg/kg, and oral doses of 0.6, 1.2, or 1.8 mg/kg. There is no experience in pediatric patients under 2 years of age. Overall, ANZEMET Injection was well tolerated in these pediatric patients. Efficacy information collected in pediatric patients receiving cancer chemotherapy are consistent with those obtained in adults. No efficacy information was collected in the pediatric postoperative nausea and vomiting studies.

Use in Elderly Patients

Dosage adjustment is not needed in patients over 65. Effectiveness in prevention of nausea and vomiting in elderly patients was no different than in younger age groups.

ADVERSE REACTIONS

Chemotherapy Patients

In controlled clinical trials, 2265 adult patients received ANZEMET Injection. The overall adverse event rates were similar with 1.8 mg/kg ANZEMET Injection and ondansetron or granisetron. Patients were receiving concurrent chemotherapy, predominantly high-dose (≥50 mg/m²) cisplatin. Following is a combined listing of all adverse events reported in ≥2% of patients in these controlled trials (Table 4).

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

Event	ANZEMET Injection 1.8 mg/kg (n=695)	Ondansetron/ Granisetron* (n=356)
Headache	169 (24.3%)	73 (20.5%)
Diarrhea	86 (12.4%)	25 (7.0%)
Fever	30 (4.3%)	18 (5.1%)
Fatigue	25 (3.6%)	12 (3.4%)
Hepatic Function Abnormal†	25 (3.6%)	12 (3.4%)
Abdominal Pain	22 (3.2%)	7 (2.0%)
Hypertension	20 (2.9%)	9 (2.5%)
Pain	17 (2.4%)	7 (2.0%)
Dizziness	15 (2.2%)	7 (2.0%)
Chills/Shivering	14 (2.0%)	6 (1.7%)

*: Ondansetron 32 mg intravenous, granisetron 3 mg intravenous.
†: Includes events coded as SGOT- and/or SGPT-increased (see also Liver and Biliary System below)

Postoperative Patients

In controlled clinical trials with 2550 adult patients, headache and dizziness 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 ≥2% of patients receiving either 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 ≥2% from Placebo-Controlled Postoperative Nausea and Vomiting Studies

Event	ANZEMET Injection 12.5 mg (n=615)	Placebo (n=739)
Headache	58 (9.4%)	51 (6.9%)

Following a suspected overdose of ANZEMET Injection, a patient found to have second-degree or higher AV conduction block with ECG should undergo cardiac telemetry monitoring.

There is no known specific antidote for dolasetron mesylate, and patients with suspected overdose should be managed with supportive therapy. Individual doses as large as 5 mg/kg intravenously or 400 mg orally have been safely given to healthy volunteers or cancer patients.

It is not known if dolasetron mesylate is removed by hemodialysis or peritoneal dialysis.

A 7-year-old boy received 6 mg/kg dolasetron mesylate orally before surgery. No symptoms occurred and no treatment was required.

Single intravenous doses of dolasetron mesylate at 160 mg/kg in male mice and 140 mg/kg in female mice and rats of both sexes (6.3 to 12.6 times the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were tremors, depression and convulsions.

DOSAGE AND ADMINISTRATION

The recommended dose of ANZEMET Injection should not be exceeded.

Prevention of Cancer Chemotherapy-Induced Nausea and Vomiting

Adults: The recommended intravenous dosage of ANZEMET Injection from clinical trial results is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy (see Administration). Alternatively, for most patients, a fixed dose of 100 mg can be administered over 30 seconds.

Pediatric Patients: The recommended intravenous dosage in pediatric patients 2 to 16 years of age is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy, up to a maximum of 100 mg (see Administration). Safety and effectiveness in pediatric patients under 2 years of age have not been established.

ANZEMET Injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When ANZEMET Injection is administered orally, the recommended dosage in pediatric patients 2 to 16 years of age is 1.8 mg/kg up to a maximum 100 mg dose given within 1 hour before chemotherapy.

The diluted product may be kept up to 2 hours at room temperature before use.

Use in the Elderly, in Renal Failure Patients, or in Hepatically Impaired Patients: No dosage adjustment is recommended.

Prevention or Treatment of Postoperative Nausea and/or Vomiting

Adults: The recommended intravenous dosage of ANZEMET Injection is 12.5 mg given as a single dose approximately 15 minutes before the cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment).

Pediatric Patients: The recommended intravenous dosage in pediatric patients 2 to 16 years of age is 0.35 mg/kg, with a maximum dose of 12.5 mg, given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

ANZEMET Injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When ANZEMET Injection is administered orally, the recommended oral dosage in pediatric patients 2 to 16 years of age is 1.2 mg/kg up to a maximum 100-mg dose given within 2 hours before surgery. The diluted product may be kept up to 2 hours at room temperature before use.

Use in the Elderly, in Renal Failure Patients, or in Hepatically Impaired Patients: No dosage adjustment is recommended.

Administration

ANZEMET Injection can be safely infused intravenously as rapidly as 100 mg/30 seconds or diluted in a compatible intravenous solution (see below) to 50 mL and infused over a period of up to 15 minutes. ANZEMET Injection should not be mixed with other drugs. Flush the infusion line before and after administration of ANZEMET Injection.

Stability

After dilution, ANZEMET Injection is stable under normal lighting conditions at room temperature for 24 hours or under refrigeration for 48 hours with the following compatible intravenous fluids: 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and Lactated Ringer's injection, Lactated Ringer's injection, and 10% mannitol injection. Although ANZEMET Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative. After dilution, do not use beyond 24 hours, or 48 hours if refrigerated.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

ANZEMET Injection (dolasetron mesylate injection) is supplied as a clear, colorless solution in single-use ampules, single and multidose vials, and Carpuject® sterile cartridges with Luer Lock.

ANZEMET® Injection (dolasetron mesylate injection) 20 mg/mL		
Strength	Description	NDC Number
12.5 mg	0.625mL single-use ampules* (Box of 6)	0088-1208-65
12.5 mg	0.625mL single-use vial* (Box of 6)	0088-1208-06
12.5 mg	0.625mL fill in single-use 2mL Carpuject with Luer Lock† (Box of 10)	0088-1208-76
100 mg/5 mL	5mL single-use vial*	0088-1206-32
500 mg/25 mL	25 mL multidose vial††	0088-1209-26

Store at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Protect from light.

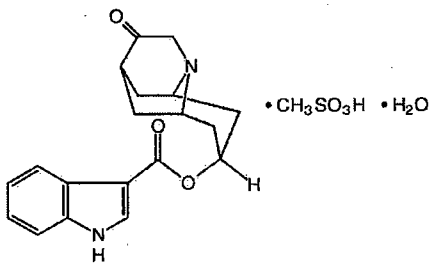
Prescribing information as of October 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-624/S-009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 2	1. Organization: HFD-180	2. NDA number: 20-624	
3. Name and Address of Applicant (City & State):		4. AF Number:	
Aventis 10236 Marion Park Drive PO Box 9720 Kansas City, MO 64134-0720		5. Supplement(s)	
6. Name of Drug: Anzmet® Injection	7. Nonproprietary Name: Dolasteron Mesylate	Numbers SCS-009	Dates 03/14/2002
8. Supplement Provides for: **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.**		9. Amendments & Other (Reports, etc.) Dates: 10/11/2002 03/19/2003	
10. Pharmacological Category: antinauseant and antiemetic agent	11.How Dispensed: RX X OTC	12. Related DMF(s):	
13.Dosage Form: Intravenous Injection	14. Potency: 12.5mg and 100mg		
15. Structure and Chemical Name:  (2(alpha),6(alpha),8(alpha),9a(beta))-octahydro-3-oxo-2,6-methano-2 *H* -quinolizin-8-yl-1 *H* -indole-3-carboxylate monomethanesulfonate, monohydrate empirical formula is $C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$ molecular weight of 438.50		16. Records and Reports:	
		Current Yes X No	
		Reviewed Yes X No	

17. Comments:
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.
CC: NDA 20-624
HFD-180/Div File/NDA 20-624/S-009
HFD-181/CSO/B.Strongin
HFD-180/B.Justice
HFD-180/A.Al-Hakim
HFD-180/L.Zhou
05/30/03 /Wordfiles\S\20624009

18. Conclusions and Recommendations:
Recommend that the regulatory Health Project Manager issue An-Approved letter for this supplement.

19.Reviewer

Name: Ali Al-Hakim, Ph.D.	Date Completed: 05/30/03

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/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	**DATES**		
	DOCUMENT	**CDER**	**ASSIGNED**
ORIGINAL	11-OCT-2002	15-OCT-2002	15-OCT-2002

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:

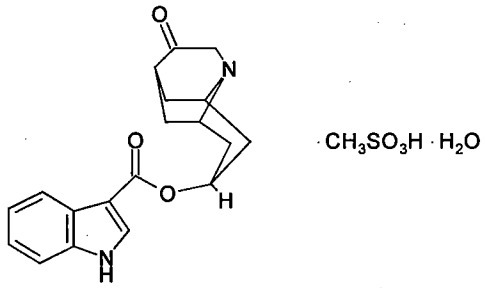
Proprietary: Anzemet **Nonproprietary/USAN:** Dolasetron mesylate

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.



$\cdot CH_3SO_3H \cdot H_2O$

SUPPORTING DOCUMENTS: Acceptable See Chem Review #1.

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	DATES			
	DOCUMENT	**CDER**	**ASSIGNED**	**REVIEW**
ORIGINAL	14-Mar-2002	15-Mar-2002	15-Mar-2002	22-Mar-2002

SUPPLEMENT PROVIDES FOR: addition of 12.5 mg vial

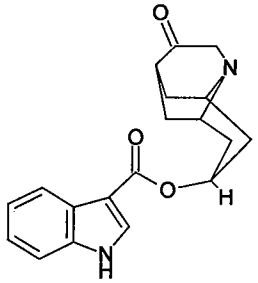
NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel
10326 Marion Park Drive P.O. Box 9627
Kansas City, MO 64134-0627

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

DOSAGE FORM: Liquid **STRENGTH:** 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.



$CH_3SO_3H \cdot H_2O$

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 providing 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 (AE) 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.

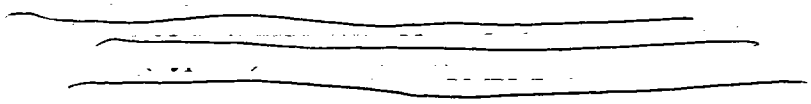
3. **MANUFACTURING SITE:** The 12.5 mg vials will be manufactured and tested at: Gruppo Lepetit S.p.A.
A wholly owned subsidiary of Aventis Pharmaceuticals
Localita Valcanello
03012 Anagni (Frosinone) Italy
Release testing and stability testing on the finished product will be done here.

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:**

6. **PHARMACOLOGICAL CATEGORY:** Antinauseant and antiemetic. A serotonin subtype 3 ($5\text{-}HT_3$) receptor agonist.

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

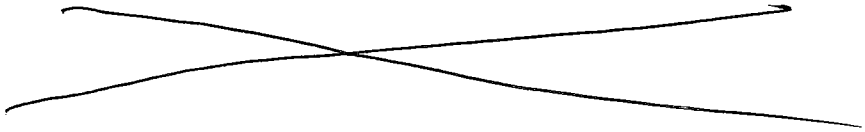
I. Recommendations

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

1 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 20-624
500 5

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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:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Antinauseant and antiemetic. A serotonin subtype 3 (5-HT_3) receptor agonist.

B. **SUPPORTING/RELATED DOCUMENTS:**

[redacted]

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

Withheld Track Number: Microbiology- 20-624
S009
Review #2

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/s/

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: [redacted]

6. PHARMACOLOGICAL CATEGORY: Antinauseant and antiemetic. A serotonin subtype 3 ($5\text{-}HT_3$) receptor agonist.

B. SUPPORTING/RELATED DOCUMENTS:

[redacted]

C. REMARKS:

filename: 20624s9r1.doc

Executive Summary

I. Recommendations

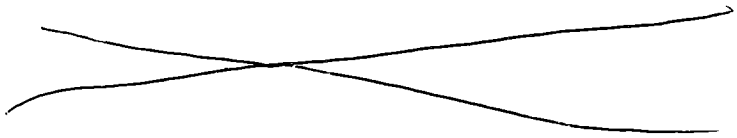
A. Recommendation on Approvability – Approvable pending response to microbiology deficiencies.

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

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 20-624
S009
Review #
1

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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

Drafted: BKS/January 29, 2003
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 CDER's draft Stability guidance (Line 588):
Store at
~~~~~~~~excursions permitted to 15-30C (59-86F)
[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 12.5mg/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.

E. The NDC code per 21 CFR 201.2.

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..

{See appended electronic signature page}
Brian Strongin, R.Ph., M.B.A.
Regulatory Project Manager

Supervisory Comment/Concurrence:

{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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Peter Cooney, Ph.D., HFD-805 **Parklawn Building, 18B-08**	Brian Strongin, R.Ph., M.B.A., HFD-180 Parklawn Building 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 25, 2003		20-624	SCS-009	March 19, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Anzemet (dolasetron mesylate) Injection	Standard		**June 25, 2003**

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	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Brian Strongin
3/25/03 04:25:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Peter Cooney, Ph.D., HFD-805 **Parklawn Building, 18B-08**	Brian Strongin, R.Ph., M.B.A., HFD-180 Parklawn Building 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 24, 2002		20-624	SCS-009	October 11, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Anzemet (dolasetron mesylate) Injection	Standard		**January 15, 2003**

NAME OF FIRM: Questcor 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 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 18, 2002		20-624	S-009	March 14, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Anzemet® (dolasetron mesylate) Injection	Standard		**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.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Brian Strongin
3/18/02 10:54:36 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-624/S-003
NDA 20-624/S-009

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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