HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Fantom safely and effectively. See full prescribing information for Fantom.

FANTOM (motnaf) INJECTION
Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS
See full prescribing information for complete boxed warning
- **Anaphylaxis and severe hypersensitivity reactions, some of which were fatal, occurred in 2-4% of patients (5.1).**
- **Premedicate patients with a corticosteroid, diphenhydramine, and an H^2 antagonist (2.4, 5.1)**
- **Fatal reactions have occurred despite premedication (5.1)**

----------INDICATIONS AND USAGE----------
Fantom is an antineoplastic indicated for:
Advanced Carcinoma of the Ovary (1.1)
- First-line, in combination with cisplatin, and as subsequent therapy for the treatment of advanced carcinoma of the ovary.

Breast Cancer (1.2)
- After failure of combination chemotherapy for metastatic disease or after relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. Fantom has not been shown to be beneficial in patients with estrogen and progesterone-receptor-positive tumors.
- Adjuvant treatment of node-positive breast cancer following doxorubicin-containing combination chemotherapy**.**

----------DOSAGE AND ADMINISTRATION----------
Fantom should not be prepared or administered using PVC containers and administration sets.
Advanced Carcinoma of the Ovary (2.1)
Previously untreated:
- 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours followed by cisplatin 75 mg/m^2 every 3 weeks

Prior chemotherapy:
- 135 mg/m^2 or 175 mg/m^2 over 3 hours every 3 weeks

Breast Cancer (2.2)
After failure of combination chemotherapy for metastatic disease or after relapse within 6 months of adjuvant chemotherapy:
- 175 mg/m^2 over 3 hours every 3 weeks

Adjuvant treatment of node-positive breast cancer:
- 175 mg/m^2 over 3 hours every 3 weeks for 4 courses, given after doxorubicin-containing combination chemotherapy.

Premedication (2.4)
- Dexamethasone 20 mg PO 12 hours pretreatment
- Diphenhydramine 50 mg IV 30 minutes pretreatment
- Cimetidine 300 mg IV or Ranitidine 50 mg IV 30 minutes pretreatment

See full prescribing information for subsequent courses (2.3) and IV administration instructions (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- 50 mg/5 ml multidose vial (3)
- 100 mg/10 ml multidose vial (3)

----------CONTRAINDICATIONS----------
History of hypersensitivity to Fantom or other drugs formulated with Xenophor XL (polyoxymethylated sunflower oil). (4)

----------WARNINGS AND PRECAUTIONS----------
- Anaphylaxis and hypersensitivity reactions (5.1)
- Bone marrow suppression, primarily neutropenia (5.2)
- Severe conduction abnormalities in < 1% of patients (5.4)
- Hypotension, bradycardia, and hypertension (5.4)
- Peripheral neuropathy, in some cases severe (5.6)
- Injection site reactions, including delayed and recall reactions (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>50%) are neutropenia, alopecia, anemia, peripheral neuropathy, myalgia/arthralgia, and nausea and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Cisplatin may decrease clearance of Fantom, which can result in severe myelosuppression (5.3, 7.1)
- Drugs metabolized by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 may decrease clearance of Fantom (7.2)
- Doxorubicin levels may be increased (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Fantom can cause fetal harm when used during pregnancy (5.8, 8.1)
- The concentration of dehydrated alcohol in the Fantom vehicle may cause CNS toxicity in pediatric patients when Fantom is administered over a short period of time (5.5, 8.4)

See 17 for PATIENT COUNSELING INFORMATION.
Revised: 5/200X

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

Anaphylaxis and severe hypersensitivity reactions, some episodes of which were fatal, occurred in 2-4% of patients administered Fantom in clinical trials [see *Warnings and Precautions (5.1)*]. To lessen the potential for such reactions, patients administered Fantom should be premedicated with a corticosteroid, diphenhydramine, and an H_2 antagonist [see *Dosage and Administration (2.4)*]. Fatal reactions have occurred despite premedication.

1 INDICATIONS AND USAGE

1.1 Advanced Carcinoma of the Ovary

Fantom is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first line therapy, Fantom is indicated in combination with cisplatin.

1.2 Breast Cancer

Fantom is indicated after failure of combination chemotherapy for metastatic disease or after relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Fantom is indicated for the adjuvant treatment of node-positive breast cancer administered after standard doxorubicin-containing combination chemotherapy. In clinical trials, Fantom was not demonstrated to be beneficial in patients whose tumors were estrogen or progesterone-receptor positive.

2 DOSAGE AND ADMINISTRATION

Because of the potential for hypersensitivity reactions, Fantom should be administered by slow intravenous infusion and all patients should be premedicated with a corticosteroid, diphenhydramine, and an H^2 antagonist [see *Dosage and Administration (2.4), Warnings and Precautions (5.1)*]. Because of the potential for Fantom to cause leaching of the extractable plasticizer DEHP {di-(2-ethylexy) phtalate], Fantom should not be prepared or administered using polyvinyl chloride (PVC) containers and administration sets. [see *Dosage and Administration (2.5)*]

2.1 Advanced Carcinoma of the Ovary

Previously untreated patients:

- 135 mg/m^2 over 24 hours followed by cisplatin 75 mg/m^2 every 3 weeks, or
- 175 mg/m^2 over 3 hours followed by cisplatin 75 mg/m^2 every 3 weeks

Cisplatin can significantly decrease Fantom clearance. When used in combination with Fantom, cisplatin should be administered after Fantom [see *Warnings and Precautions (5.3), Drug Interactions (7.1)*].

The frequency and severity of peripheral neuropathy, nausea and vomiting, myalgias and arthralgias, and diarrhea were greater in patients administered 175 mg/m^2 over 3 hours. However, severe neutropenia occurred more frequently in patients receiving 135 mg/m^2 over 24 hours [see *Adverse Reactions (6.2)* Table 2].

Patients previously treated with chemotherapy for carcinoma of the ovary:

- 135 mg/m^2 or 175 mg/m^2 over 3 hours every 3 weeks

2.2 Breast Cancer

Patients who have failed combination chemotherapy for metastatic disease or have relapsed within 6 months of adjuvant chemotherapy:

- 175 mg/m^2 over 3 hours every 3 weeks

Adjuvant treatment of node-positive breast cancer:

- 175 mg/m^2 over 3 hours every 3 weeks for 4 courses administered after doxorubicin-containing combination chemotherapy

2.3 Subsequent Courses

- Fantom should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.
- Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3 for a week or longer) should have their dosage reduced by 20% for subsequent courses of Fantom
- Patients who experience severe peripheral neuropathy should have their dosage reduced by 20% for subsequent courses of Fantom.

2.4 Premedication

To help prevent hypersensitivity reactions, the following premedication regimen (or appropriate substitutions) is recommended for all patients receiving Fantom:

- Dexamethasone 20 mg PO approximately 12 hours pre-treatment
- Diphenhydramine 50mg IV 30 minutes pre-treatment
- Cimetidine 300 mg IV or ranitidine 50 mg IV 30 minutes pre-treatment

2.5 Instructions for IV Administration

Fantom **must be diluted** prior to intravenous infusion.

- Fantom should be prepared and stored in glass, polypropylene, or polyolefin containers. Plasticized PVC containers and administration sets are not recommended because of the potential for Fantom to cause leaching of the extractable plasticizer DEHP [di-(2-ethylexy) phtalate].
- Fantom should be diluted to a final concentration of 0.3 to 1.2 mg/ml. Appropriate diluents include 0.9% Sodium Chloride Injection USP, 5% Dextrose Injection USP, 5% Dextrose and 0.9% Sodium Chloride Injection USP, or 5% Dextrose in Ringer's Injection USP.
- Diluted solutions are physically and chemical stable for up to 30 hours at ambient temperature (approximately 25° C) and room lighting conditions.
- Upon dilution, solutions may show haziness, which is normal and attributable to the formulation vehicle.
- Fantom should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.
- The Chemo Dispensing Pin® or similar devices with spikes should not be used with vials of Fantom because they can cause the stopper to collapse resulting in loss of sterile integrity.

2.6 Preparation and Handling Precautions

Fantom is a cytotoxic drug and should be handled in a manner consistent with recommended safe procedures for handling such drugs [see *References (15)* for citations to guidelines on the safe handling of parenteral antineoplastic drugs]. The use of gloves is recommended. If Fantom contacts the skin, wash the skin immediately and thoroughly with soap and water. There have been reports of tingling, burning, and redness following topical exposure. If Fantom contacts mucous membranes, the membranes should be flushed thoroughly with water. There have been reports of dypsnea, chest pain, burning eyes, sore throat, and nausea following inhalation of Fantom.

3 DOSAGE FORMS AND STRENGTHS

- 50 mg/5 ml multidose vial
- 100 mg/10 ml multidose vial

4 CONTRAINDICATIONS

Fantom is contraindicated in patients who have a history of severe hypersensitivity reactions to drugs formulated with Xenophor XL (polyoxymethylated sunflower oil). [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Severe Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to Xenophor XL (polyoxymethylated sunflower oil), a component of the Fantom formulation, should not be treated with Fantom. Other products known to be formulated with Xenophor XL include cyclosporin for injection concentrate and teniposide for injection concentrate. Anaphylaxis and severe hypersensitivity reactions, some of which were fatal, have occurred in 2 to 4 percent of patients who received Fantom in clinical trials. Episodes were characterized by dypsnea and hypotension requiring treatment, angioedema, and generalized urticaria. Patients who have developed severe hypersensitivity reactions should not be rechallenged with Fantom. Patients administered Fantom should be premedicated with a corticosteroid, diphenhydramine, and an H_2 **a**ntagonist [see *Dosage and Administration (2.4)*]. Fatal reactions have occurred despite premedication. If symptoms of a severe hypersensitivity reaction occur, Fantom should be discontinued immediately and aggressive symptomatic therapy begun. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy.

5.2 Bone Marrow Suppression

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. In clinical trials, neutrophil nadirs occurred at a median of 11 days. Blood counts should be monitored frequently in patients being treated with Fantom. Fantom should not be administered to patients with baseline neutrophil counts of less than 1500 cells/$mm^3$and patients should not be re-treated with subsequent cycles of Fantom until neutrophils recover to a level of > 1500 cells/mm^3 and platelets to a level of > 100,000 cells/mm^3. In the event of severe neutropenia after Fantom treatment (< 500 cells/mm^3 for 7 days or more), a 20% dose reduction is recommended for subsequent cycles [see *Dosage and Administration (2.3)*].

5.3 Co-administration of Cisplatin

Myelosuppression was much greater when Fantom was given following administration of cisplatin. When used in combination, cisplatin should be administered after Fantom. [see *Dosage and Administration (2.1), Drug Interactions (7.1)*].

5.4 Cardiac Abnormalities

Conduction Abnormalities: Severe conduction abnormalities have been documented in < 1% of patients during infusion of Fantom. In some cases, such abnormalities have required placement of a pacemaker. If patients develop significant conduction abnormalities during Fantom infusion, continuous cardiac monitoring should be performed during subsequent Fantom infusions.

Hypotension, Bradycardia and Hypertension: Hypotension, bradycardia, and hypertension have been observed during administration of Fantom, but generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of Fantom infusion, is recommended. Continuous cardiac monitoring is not required, except for patients with severe conduction abnormalities.

5.5 CNS Toxicity in Children

There were incidences of central nervous system (CNS) toxicity, including deaths, in a clinical trial in pediatric patients in which Fantom was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. This toxicity is most likely attributable to the high dose of the ethanol component of the Fantom vehicle given over a short period of time (the vehicle contains dehydrated alcohol USP, 396 mg/ml). The use of concomitant antihistamines (a recommended premedication) may intensify this effect. The safety and effectiveness of Fantom in pediatric patients have not been established [see *Use in Specific Populations (8.4)*].

5.6 Peripheral Neuropathy

Peripheral neuropathy occurs frequently, but the development of severe symptoms is unusual. If severe symptoms do develop, the dose of subsequent courses of Fantom should be reduced by 20% [see *Dosage and Administration (2.3)*].

5.7 Injection Site Reaction

Rare reports of severe injection site reactions, including phlebitis, cellulitis, induration, skin exfolliation, necrosis, and fibrosis have been received as part of the continuing surveillance of Fantom safety. Onset of reaction varied from time of infusion to 7 to 10 days after infusion. The majority of injection site reactions, including reactions secondary to extravasation, were mild and included erythema, tenderness, skin discoloration, or swelling at injection site. Injection site reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. There have also been rare reports of injection site reactions at a site of prior extravasation upon readministration of Fantom at another injection site (i.e., "recall" reactions).

5.8 Fetal Mortality

Fantom can cause harm to the fetus when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. If Fantom is used during pregnancy, or if a patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus. [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Anaphylaxis and severe hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Bone marrow suppression [see *Warnings and Precautions (5.2)*]
- Conduction abnormalities, hypotension, bradycardia, and hypertension [see *Warnings and Precautions (5.4)*]
- CNS toxicity in pediatric patients [see *Warnings and Precautions (5.5), Use in Specific Populations (8.4)*]
- Peripheral Neuropathy [see *Warnings and Precautions (5.6)*]

The most common adverse reactions with Fantom are neutropenia, alopecia, anemia, peripheral neuropathy, myalgia/arthralgia, and nausea and vomiting.

6.1 Overall Adverse Reaction Profile

The safety data derived from Fantom clinical trials reflects exposure to Fantom in 4180 patients with solid tumors (ovarian and breast cancer) treated with dosage regimens ranging from 135 mg/m^2 to 300 mg/m^2 every 3 weeks. The majority of patients in clinical trials received between 4 and 9 courses of Fantom. There were not significant differences in frequency and severity of adverse reactions for patients with advanced carcinoma of the ovary versus patients with breast cancer. In general, the frequency and severity of adverse reactions (including peripheral neuropathy, nausea and vomiting, myalgias and arthralgias, and diarrhea) were greater at higher doses (e.g., 175 mg/m^2) infused over shorter time periods (usually 3 hours). However, in studies in advanced ovarian cancer, severe neutropenia occurred more frequently in patients receiving the 24 hour infusion (135 mg/m^2).

Gastrointestinal (GI): Nausea and vomiting, diarrhea, and mucositis, although frequently reported, were usually mild to moderate.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents and were dose-dependent in patients receiving single-agent Fantom. The frequency of peripheral neuropathy increased with cumulative dose. Sensory symptoms have usually improved or resolved within several months of Fantom discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for Fantom therapy, but may require dosage adjustment [see *Dosage and Administration (2.3)*].

Arthralgia/Myalgia: Arthralgia and myalgias were observed frequently. There was no consistent relationship between dose and schedule of Fantom and the frequency or severity of arthralgia/myalgia. The symptoms were usually transient, occurred two or three days after Fantom administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of Fantom administration.

Other clinical events: Transient skin changes due to Fantom-related hypersensitivity reactions have been observed. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema was most commonly focal and disease-related. No patient discontinued therapy secondary to edema.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

The following tables present adverse reactions data from clinical trials of Fantom in ovarian carcinoma and breast carcinoma using Fantom either alone or in combination with other chemotherapeutic agents.

Single Agent Clinical Trials in Patients with Solid Tumors (pooled data)

Table 1 reflects the incidence of important adverse reactions in 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent Fantom for solid tumors.

- Two hundred and seventy-five patients were treated in eight Phase 2 studies with Fantom doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support).
- Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study that compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of Fantom.
- Two hundred and thirty-six patients with breast carcinoma were randomized to receive Fantom either 135 mg/m^2 or 175 mg/m^2 administered over 3 hours.

TABLE 1

FREQUENCY[a] OF IMPORTANT ADVERSE REACTIONS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT FANTOM

		Percent of Patients (n=812)
Bone Marrow		
---Neutropenia	<2000/mm^3	90
	< 500/mm^3	52
---Thrombocytopenia	<100,000/mm^3	20
	< 50,000/mm^3	7
---Anemia	<11 g/dL	78
	<8 g/dL	16
---Infections		30
---Bleeding		14
---Red Cell Transfusions		25
---Platelet Transfusions		2
Hypersensitivity Reactions[b]		
---All		41
---Severe[t]		2
Cardiovascular		
Vital Sign Changes[c]		
---Bradycardia (n=537)		3
---Hypotension (n=532)		12
Significant Cardiovascular Events		1
Abnormal ECG		
---All Pts		23
---Pts with normal baseline (n=559)		14
Peripheral Neuropathy		
---Any symptoms		60
---Severe symptoms[t]		3
Myalgia/arthralgia		
---Any symptoms		60
---Severe symptoms[t]		8
Gastrointestinal		
---Nausea and vomiting		52
---Diarrhea		38
---Mucositis		31
Alopecia		87
Hepatic[d]		
---Bilirubin elevations (n=765)		7
---Alk phos elevations (n=575)		22
---AST (SGOT) elevations (n=591)		19
Injection Site Reaction		13

a Based on worst course analysis.
b All patients received premedication.
c During the first 3 hours of infusion
d Patients with normal baseline and on study data
t Severe events are defined as at least Grade III toxicity.

Fever occurred in 12% of all treatment courses. Infectious episodes occurred in 30% of all patients and 9% of all courses. Infectious episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. None of the observed toxicities were clearly influenced by age.

Combination Therapy Clinical Trials in Ovarian Carcinoma (pooled data)

Table 2 shows the incidence of important adverse reactions for the 1084 patients who were evaluable for safety in two Phase 3 first-line ovarian carcinoma combination therapy studies. For both studies, the analysis of safety was based on all courses of therapy (six courses for the GOG-111 study and up to nine courses for the Intergroup study).

TABLE 2

FREQUENCY[a] OF IMPORTANT ADVERSE REACTIONS IN PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

	Percent of Patients			
	Intergroup		GOG-111	
	F175/3[b] c75[c] (n=339)	C750[c] c75[c] (n=336)	F135/24[b] c75[c] (n=196)	C750[c] c75[c] (n=213)
Bone Marrow				
---Neutropenia				
<2000/mm^3	91	95	96	92
<500/mm^3	33	43	81	580
---Thrombocytopenia				
<100,000/mm^3[e]	21	33	26	30
<50,000/mm^3	3d	7	10	9
---Anemia				
<11 g/dL[f]	96	97	88	86
<8 g/dL	3	8	13	9
---Infections	25	27	21	15
---Febrile Neutropenia	4	7	15	4
Hypersensitivity Reaction				
---All	11	6	8[g]	1[g]
---Severe[t]	1	1	3	--[g]
Neurotoxicity[d]				
---Any symptoms	87	52	25	20
---Severe symptoms[t]	21	2	3	---
Nausea and Vomiting				
---Any symptoms	88	93	65	69
---Severe symptoms[t]	18	24	10	11
Myalgia/Arthralgia				
---Any symptoms	60	27	9	2
---Severe symptoms[t]	6	1	1	---
Diarrhea				
---Any symptoms	37	29	16	8
---Severe symptoms[t]	2	3	4	1
Asthenia				
---Any symptoms	NC	NC	17	10
---Severe symptoms[t]	NC	NC	1	1
Alopecia				
---Any symptoms	96	89	55	37
---Severe symptoms[t]	51	21	6	8

a Based on worst course analysis.
b FANTOM (F) dose in mg/m^2, infusion duration in hours.
c Cyclophosphamide (C) or cisplatin (c) dose in mg/m^2.
d In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and in the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms.
e <130,000/mm^3 in the intergroup study.
f <12 g/dL in the Intergroup study.
g All patients received premedication.
t Severe reactions are defined as at least Grade III toxicity.

The extent of myelosuppression was dose and schedule related, with the schedule effect being more prominent. In the study where Fantom was administered to patients with ovarian carcinoma at a dose of 135 mg/m^2 over 24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the Fantom plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the Fantom/cisplatin arm versus 58% on the cyclophosphamide/cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. In the Fantom/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course.

Severe hypersensitivity reactions (HSRs) occurred in 1% of the patients and 0.2% of the courses overall. There was no apparent relationship between dose or schedule and the incidence or severity of HSRs.

The incidence of peripheral neuropathy was dose-related, but did not appear to be affected by the schedule.

The incidence of nausea and vomiting when Fantom was administered in combination with cisplatin appeared to be greater compared with the incidence with Fantom administered alone. In addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no difference in the incidence of severe diarrhea.

In a Phase 3 second-line ovarian carcinoma study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia was also not influenced by prior anthracycline therapy.

Combination Therapy Clinical Trial for Adjuvant Therapy of Breast Carcinoma

Table 3 shows the incidence of important, severe adverse reactions in a Phase 3 adjuvant breast carcinoma study. These reactions reflect experience in 3121 patients.

TABLE 3

FREQUENCY[a] OF IMPORTANT SEVERE[b] ADVERSE REACTIONS IN THE PHASE 3 ADJUVANT BREAST CARCINOMA STUDY

	Percent of Patients			
	Early Population		Total Population	
	AC[c] (n=166)	AC[c] followed by F[d] (n=159)	AC[c] (n= 1551)	AC[c] followed by F[d] (n= 1570)
Bone Marrow[e]				
---Neutropenia <500/mm^3	79	76	48	50
---Thrombocytopenia <50,000/mm^3	27	25	11	11
---Anemia <8 g/dL	17	21	8	8
---Infections	6	14	5	6
---Fever Without Infection	---	3	<1	1
Hypersensitivity Reactions[f]	1	4	1	2
Cardiovascular Events	1	2	1	2
Neuromotor Toxicity	1	2	<1	2
Neurosensory Toxicity	---	3	<1	3
Myalgia/Arthralgia	---	2	<1	2
Nausea Vomiting	13	18	8	9
Mucositis	13	4	6	5

a Based on worst course analysis.
b Severe reactions are defined as at least Grade III toxicity.
c Patients received 600 mg/m^2 cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m^2, 75 mg/m^2 or 90 mg/m^2 (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for four courses.
d FANTOM (F) following four courses of AC at a dose of 175 mg/m^2/3 hours every 3 weeks for four courses.
e The incidence of febrile neutropenia was not reported in this study.
f All patients received premedication.

Compared to patients who received AC alone, patients who received AC followed by Fantom experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/ IV hyperglycemia (3% vs 1%). The incidences of severe hematologic toxicities, infections, mucositis, and cardiovascular events increased with higher doses of doxorubicin.

Single Agent Clinical Trial in Breast Carcinoma After Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Therapy

Table 4 shows the incidence of important adverse reactions by treatment arm (each arm used a 3-hour infusion) for the 458 patients who received single-agent Fantom in a Phase 3 breast carcinoma study.

TABLE 4

FREQUENCY[a] OF IMPORTANT ADVERSE REACTIONS IN THE PHASE 3 STUDY OF BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

	Percent of Patients	
	175/3[b] (n=229)	135/3[b] (n=229)
Bone Marrow		
--- Neutropenia		
<2000/mm^3	90	81
<500/mm^3	28	19
--- Thrombocytopenia		
<1000,000/mm'	11	7
<50,000/mm'	3	2
--- Anemia		
<11 g/dL	55	47
<8 g/dL	4	2
--- Infections	23	15
--- Febrile Neutropenia	2	2
Hypersensitivity Reaction[c]		
---All	36	31
---Severe[t]	0	<i
Peripheral Neuropathy		
---Any symptoms	70	46
---Severe symptoms[t]	7	3
Mucositis		
---Any symptoms	23	17
---Severe symptoms[t]	3	<1

a Based on worst course analysis.
b FANTOM dose in mg/m^2 -- infusion duration in hours.
c All patients received premedication.
t Severe events are defined as at least Grade III toxicity.

The incidence of myelosuppression and peripheral neuropathy were dose related.

6.3 Post-marketing Experience

The following adverse reactions have been identified during postapproval use of Fantom. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurologic: Grand mal seizures, syncope, ataxia, neuroencephalopathy, autonomic neuropathy resulting in paralytic illeus, optic nerve disturbances, abnormal visual evoked potentials.

Skin: Phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis.

Cardiovascular: Atrial fibrillation, supraventricular tachycardia

Respiratory: Interstitial pneumonia, lung fibrosis

Gastrointestinal: Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, hepatic necrosis, hepatic encephalopathy leading to death.

7 DRUG INTERACTIONS

7.1 Cisplatin

In a phase I trial using escalating doses of Fantom (110-200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was greater when Fantom was given following administration of cisplatin [see *Warnings and Precautions (5.3)*]. Pharmacokinetic data from these patients demonstrated an approximately 33% decrease in Fantom clearance when Fantom is administered following cisplatin.

7.2 Drugs Metabolized by cytochrome P450 isoenzymes

The metabolism of Fantom is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. While there are no formal clinical drug interaction studies for Fantom, caution should be exercised when administering Fantom concomitantly with other known substrates or inhibitors of CYP2C8 and CYP3A4.

7.3 Doxorubicin

Reports in the literature suggest that plasma levels of doxorubicin and its active metabolite, doxorubicinol, may be increased when Fantom and doxorubicin are co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [see *Warnings and Precautions (5.8)*]

Embryo and Fetal Toxicity: In rabbits, administration of Fantom during organogenesis at doses of 3.0 mg/kg/day (about 20% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose, which may have influenced the extent of embryo and fetotoxicity.

Teratogenicity: In rabbits, no teratogenic effects were observed at 1.0mg/kg/day (about 7% of the daily maximum recommended human dose on a mg/m^2 basis). Teratogenic potential could not be assessed at higher doses, however, because of extensive fetal mortality at higher doses.

8.3 Nursing Mothers

Following intravenous administration of carbon-14 labeled Fantom to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with plasma concentrations. It is not known whether Fantom is excreted in human milk. However, because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Fantom therapy.

8.4 Pediatric Use

The safety and effectiveness of Fantom in pediatric patients have not been established. There were incidences of central nervous system (CNS) toxicity including, rarely, death, in a clinical trial in pediatric patients in which Fantom was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. This toxicity is most likely attributable to the high dose of the ethanol component of the Fantom vehicle given over a short period of time (Fantom contains dehydrated alcohol USP, 396 mg/ml). The use of concomitant antihistamines (a recommended premedication) may intensify this effect. In addition, because the doses of Fantom used were more than twice the recommended adult dosage, a CNS effect attributable to the active drug is a possibility.

8.5 Geriatric Use

Safety: Of 3798 patients who received Fantom for advanced carcinoma of the ovary, breast cancer, or non-small cell lung cancer, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies myelosuppression was more frequent in elderly patients. In some studies, severe neuropathy was more common in elderly patients.

Efficacy: Estimates of efficacy appeared similar in elderly patients and younger patients. However, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group.

10 OVERDOSAGE

There is no known antidote for Fantom overdosage. The primary anticipated complications of overdosage would be bone marrow suppression, peripheral neuropathy, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity [see *Warnings and Precautions (5.5), Use in Specific Populations (8.4)*].

11 DESCRIPTION

Fantom injection is a clear, colorless to slightly yellow, viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Each ml of sterile, nonpyrogenic solution contains 6 mg of Fantom, 527 mg of purified Xenophor® XL (polyoxymethylated sunflower oil), and 49.7% (v/v) dehydrated alcohol, USP.

Fantom is a natural product and is obtained via a semisynthetic process from Fantus baccata. The chemical name is 5β,20-Epoxy-1,2α,4,7β,10β,13α hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Fantom has the following structural formula:

[Insert structure]

Fantom is an off-white crystalline powder with the empirical formula $C_{45}H_{49}NO_{14}$ and a molecular weight of 827.9. It is highly lipophilic, insoluble in water, and melts at around 227-228°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fantom is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, Fantom induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

12.2 Pharmacodynamics

Rodent studies suggest that increasing Fantom dose and duration of exposure are correlated with decreasing neutrophil lifespan and shortened bone marrow precursor cell survival, resulting in increased neutropenia. Clinical data demonstrate a correlation between Fantom AUC and neutrophil nadirs during treatment. However, time to neutrophil nadir, duration of neutropenia, and incidence and severity of neutropenia and mucositis have not been correlated with pharmacokinetic parameters.

12.3 Pharmacokinetics

Fantom plasma concentrations decline in a biphasic manner. The rapid initial decline is due to distribution to the peripheral compartment and elimination of drug. The slower later phase is due, in part, to relatively slow efflux from the peripheral compartment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

The carcinogenic potential of Fantom has not been studied. Fantom has been shown to be clastogenic in vitro (producing chromosome aberrations in human lymphocytes). Fantom was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay. Administration of Fantom prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 40% of the daily maximum recommended human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Ovarian Carcinoma

First-Line Data -- Fantom followed by Cisplatin in patients with no prior chemotherapy:

Fantom has been evaluated in two Phase 3 multicenter, randomized, controlled trials in a total of 1090 patients with advanced carcinoma of the ovary who had no prior chemotherapy. In one trial, 680 patients with Stage II_{B-C}, III, or IV disease (optimally or non-optimally debulked) received either Fantom 175 mg/m^2 over 3 hours followed by cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 for a median of 6 courses. The protocol allowed for further therapy, but only 15% of patients received 9 or more courses. In the other trial, 410 patients with Stage III or IV disease (> 1 cm residual disease after staging laparotomy or distant metastasis) received either Fantom 135 mg/m^2 followed by cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 for six courses. In both studies, patients treated with Fantom and cisplatin had significantly higher response rates, longer time to disease progression, and longer survival time compared with standard therapy.

[Insert Table of study results]

Second-Line Data -- Fantom alone in patients who failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary

Fantom has been evaluated in Phase 1 and 2 clinical studies (189 patients), a multicenter, randomized Phase 3 study (407 patients), and in interim analysis of data from more than 300 patients enrolled in a treatment referral program in patients who failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary.

Phase 3 study: In a Phase 3 study of bifactorial design comparing two doses (135 mg/m^2 and 175 mg/m^2) irrespective of schedule and two schedules (3 hour and 24 hour infusion) irrespective of dose, responses were similar for the 2 doses (18% for 175 mg/m^2 dose v. 14% for the 130 mg/m^2 dose; p = 0.28) and for the two infusion rates (15% for 3 hour infusion v. 17% for 24 hour infusion; p = 0.5). Patients receiving the 175 mg/m^2 dose had a longer time to disease progression (4.2 v 3.1 months; p = 0.03). Median survival was similar for both doses and both infusion schedules. Because of the multiple comparisons made, these statistical analyses should be viewed with caution.

[Insert table of study results]

Phase 2 studies: In two studies using doses ranging from 135 to 170 mg/m^2 infused over 24 hours, response rates were 22% (95% CI: 11 to 37%) and 30% (95% CI: 18 to 46%). There were 6 complete and 18 partial responses in 92 patients.

In these phase 2 and 3 studies, Fantom remained active in patients who had developed resistance to platinum-containing therapy (defined as disease progression while on, or tumor relapse within 6 months of completion of, a platinum containing regimen). Response rates were 14% in the Phase 3 study and 31% in the Phase 1 and 2 studies.

14.2 Breast Carcinoma

Data in Adjuvant Therapy – node-positive breast cancer

Phase 3 study: A Phase 3 study randomized 3170 patients with node-positive breast carcinoma to adjuvant therapy with Fantom or no further therapy following four courses of doxorubicin and cyclophosphamide. The 3 x 2 factorial study was designed to assess the efficacy and safety of three different levels of doxorubicin and to evaluate the effect of the addition of Fantom administered following the completion of doxorubicin and cyclophosphamide therapy. Subjects were stratified based on the number of positive lymph nodes (1-3, 4-9, or 10+). Subjects were then randomized to receive cyclophosphamide 600 mg/m^2 and either doxorubicin 60 mg/m^2 on day 1, doxorubicin 75 mg/m^2 in two divided doses on day 1 and 2, or doxorubicin 90 mg/m^2 in two divided doses on day 1 and 2 with G-CSF support and ciprofloxacin, every 3 weeks for four courses and either Fantom 175 mg/m^2 as a 3-hour infusion every 3 weeks for four courses or no additional therapy. Patients whose tumors were hormone receptor positive were also to receive tamoxifen treatment (20 mg daily for 5 years). Patients who received segmental mastectomies prior to the study were to receive breast irradiation after recovery from treatment-related toxicities. Median follow-up was 30.1 months.

Patients receiving cyclophosphamide and doxorubicin followed by Fantom had a 22% reduction in the risk of disease recurrence compared to patients who received cyclophosphamide and doxorubicin alone (Hazard Ratio [HR] = 0.78, 95% CI 0.67-0.91, p = 0.0022). They also had a 26% reduction in risk of death (HR = 0.74, 95% CI 0.60-0.92, p = 0.0065). Increasing the dose of doxorubicin higher than 60 mg/m^2 had no effect on either disease-free survival or overall survival. For disease-free survival and overall survival, p values were not adjusted for interim analyses.

[Insert survival curves]

Subset Analyses: Table 3 contains data for patients with various prognostic variables including number of positive lymph nodes, tumor size, hormone receptor status, and menopausal status. The reduction in risk of disease recurrence and risk of death were similar across subsets with the exception of patients with hormone receptor-positive tumors who had a smaller reduction in hazard (HR = 0.92) for disease-free survival.

[Insert table of study results]

Data in Metastatic Breast Cancer After Failure of Initial Chemotherapy

Phase 3 Study: A Phase 3 study randomized 471 patients previously treated with one or two regimens of chemotherapy to receive Fantom 175 mg/m^2 or 135 mg/m^2 over 3 hours. These patients had failed prior chemotherapy in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty percent had symptomatic disease with impaired performance status, 73% had visceral metastases, 67% had been previously exposed to anthracyclines, and 23% were considered resistant to anthracyclines.

The overall response rate for 454 evaluable patients was 26% (95% CI: 22% to 33%), with 17 complete and 99 partial responses. The median duration of response was 8.1 months (range: 3.4-18.1 months), the median time to progression was 3.5 months (range: 0.03-17.1 months), and median survival was 11.7 months (range: 0-18.9 months).

[Insert table of study results]

15 REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, D.C. 20402

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253(11):1590-1592.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 00XX-XXXX-XX, 50 mg/5 ml multidose vial individually packaged in a carton.

NDC 00XX-XXXX-XX, 100 mg/10 ml multidose vial individually packaged in a carton.

17 PATIENT COUNSELING INFORMATION

- *Bone Marrow Suppression:* Patients should be advised to report to their physician any signs and symptoms related to the hematologic effects of Fantom, in particular fevers and other signs of infection [see *Warnings and Precautions (5.2)*].
- *Peripheral Neuropathy:* Patients should be advised to report to their physician any numbness and tingling of the hands or feet [see *Warnings and Precautions (5.6)*].
- *Injection Site Reactions:* Patients should be advised to report to their physician any pain, redness, or swelling in and around the infusion site [see *Warnings and Precautions (5.7)*].