# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 125085Orig1s331

| | |
|---|---|
| ***Trade Name:*** | AVASTIN |
| ***Generic or Proper Name:*** | bevacizumab |
| ***Sponsor:*** | Genentech, Inc. |
| ***Approval Date:*** | June 20, 2019 |
| ***Indication:*** | Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:<br>• Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.<br>• Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.<br>Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer.<br>• Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment.<br>• Recurrent glioblastoma in adults.<br>• Metastatic renal cell carcinoma in combination with |

interferon alfa.

- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
    - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection.
    - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens
    - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease.

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

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# APPROVAL LETTER

BLA 125085/S-331

**SUPPLEMENT APPROVAL**

Genentech, Inc.
Attention: Jason Puskas, B.Sc., CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Puskas:

Please refer to your supplemental biologics license application (sBLA), dated April 30, 2019, received April 30, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Avastin (bevacizumab) injection, for intravenous use.

This Prior Approval supplemental (PAS) biologics application was submitted in response to the February 20, 2019, PAS Request letter. As approved, this PAS supplement provides for the removal of the Boxed Warning; incorporates changes in the package insert to comply with the Physician Labeling Rule; and incorporates editorial changes for consistency with labeling guidance recommendations and best labeling practices and policies.

Editorial changes were made to the container labels and carton labeling. Carton labeling were also revised to update the ingredient list to be consistent with the package insert and applicable regulations.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling for Prescribing Information and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 125085/S-331**." Approval of this submission by FDA is not required before the labeling is used.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Gina Mehta, Regulatory Project Manager, at (301) 796-7910.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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PATRICIA KEEGAN
06/20/2019 08:06:04 AM

# CENTER FOR DRUG EVALUATION AND RESEARCH

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# LABELING

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.**

**AVASTIN® (bevacizumab) injection, for intravenous use**
**Initial U.S. Approval: 2004**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Boxed Warning | Removed 06/2019 |
| Indications and Usage, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (1.6) | 06/2018 |
| Dosage and Administration, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (2.7) | 06/2018 |

**----------INDICATIONS AND USAGE----------**

Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection (1.6)
  - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (1.6)
  - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease (1.6)

**----------DOSAGE AND ADMINISTRATION----------**

Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
Metastatic colorectal cancer (2 2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen

First-line non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell carcinoma (2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Administer as an intravenous infusion. (2 9)

**----------DOSAGE FORMS AND STRENGTHS----------**

Injection: 100 mg/4 mL (25mg/mL) or 400 mg/16 mL (25mg/mL) in a single-dose vial (3)

**----------CONTRAINDICATIONS----------**

None (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ (5.1)
- Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention or necrotizing fasciitis. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed (5.2)
- Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion-Related Reactions: Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy. (5.9)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue Avastin in patients who develop CHF. (5.12)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------USE IN SPECIFIC POPULATIONS----------**

- Lactation: Advise not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 06/2019**

**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the Full Prescribing Information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Metastatic Colorectal Cancer

Avastin, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with metastatic colorectal cancer (mCRC).

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line Avastin-containing regimen.

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

### 1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer

Avastin, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

### 1.3 Recurrent Glioblastoma

Avastin is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

### 1.4 Metastatic Renal Cell Carcinoma

Avastin, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

### 1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

### 1.6 Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Information

Do not administer Avastin until at least 28 days following surgery and the wound is fully healed.

### 2.2 Metastatic Colorectal Cancer

The recommended dosage when Avastin is administered in combination with intravenous fluorouracil-based chemotherapy is:

- 5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
- 10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line Avastin-containing regimen.

### 2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

### 2.4 Recurrent Glioblastoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks.

### 2.5 Metastatic Renal Cell Carcinoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

### 2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

### 2.7 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Disease Following Initial Surgical Resection

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Recurrent Disease

*Platinum Resistant*

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

*Platinum Sensitive*

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

### 2.8 Dosage Modifications for Adverse Reactions

Table 1 describes dosage modifications for specific adverse reactions. No dose reductions for Avastin are recommended.

**Table 1: Dosage Modifications for Adverse Reactions**

| Adverse Reaction | Severity | Dosage Modification |
|---|---|---|
| Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*. | • Gastrointestinal perforation, any grade<br>• Tracheoesophageal fistula, any grade<br>• Fistula, Grade 4<br>• Fistula formation involving any internal organ | Discontinue Avastin |
| Wound Healing Complications *[see Warnings and Precautions (5.2)]*. | • Wound healing complications requiring medical intervention<br>• Necrotizing fasciitis | Discontinue Avastin |
| Hemorrhage *[see Warnings and Precautions (5.3)]*. | • Grade 3 or 4 | Discontinue Avastin |
| | • Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more | Withhold Avastin |
| Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*. | • Arterial thromboembolism, severe | Discontinue Avastin |
| | • Venous thromboembolism, Grade 4 | Discontinue Avastin |
| Hypertension *[see Warnings and Precautions (5.6)]*. | • Hypertensive crisis<br>• Hypertensive encephalopathy | Discontinue Avastin |
| | • Hypertension, severe | Withhold Avastin if not controlled with medical management; resume once controlled |
| Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*. | • Any | Discontinue Avastin |
| Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*. | • Nephrotic syndrome | Discontinue Avastin |
| | • Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome | Withhold Avastin until proteinuria less than 2 grams per 24 hours |
| Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*. | • Severe | Discontinue Avastin |
| | • Clinically significant | Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve |
| | • Mild, clinically insignificant | Decrease infusion rate |
| Congestive Heart Failure *[see Warnings and Precautions (5.12)]*. | Any | Discontinue Avastin |

### 2.9 Preparation and Administration

Preparation

- Use appropriate aseptic technique.
- Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2°C to 8°C (36°F to 46°F) for up to 8 hours.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

Administration

- Administer as an intravenous infusion.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated. Administer all subsequent infusions over 30 minutes if second infusion over 60 minutes is tolerated.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) clear to slightly opalescent, colorless to pale brown solution in a single-dose vial.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Gastrointestinal Perforations and Fistulae

Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose *[see Adverse Reactions (6.1)]*.

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ.

### 5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

Discontinue Avastin in patients with wound healing complications requiring medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following surgery and until the wound is fully healed.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin in patients who develop necrotizing fasciitis.

### 5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3-4 hemorrhage.

### 5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or >65 years *[see Use in Specific Populations (8.5)]*.

Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

### 5.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) was observed across clinical studies *[see Adverse Reactions (6.1)]*. In Study GOG-0240, Grades 3-4 VTE occurred in 11% of patients receiving Avastin with chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grades 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.
Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism.

### 5.6 Hypertension
Severe hypertension occurred at a higher incidence in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

### 5.7 Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

### 5.8 Renal Injury and Proteinuria
The incidence and severity of proteinuria was higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria *[see Adverse Reactions (6.1)]*.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4 proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grades 2-4 proteinuria.

Nephrotic syndrome occurred in < 1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per

24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)].

### 5.9 Infusion-Related Reactions

Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion-related reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.2% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion-related reactions. Interrupt the infusion in patients with clinically significant infusion-related reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

### 5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Avastin may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

### 5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or an FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

### 5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone. Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*.
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety data in Warnings and Precautions and described below reflect exposure to Avastin in 4134 patients including those with mCRC (AVF2107g, E3200), non-squamous NSCLC (E4599), GBM (EORTC 26101), mRCC (BO17705), cervical cancer (GOG-0240), and epithelial ovarian, fallopian tube, or primary peritoneal cancer (MO22224, AVF4095, GOG-0213, and GOG-0218) at the recommended dose and schedule for a median of 6 to 23 doses. The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with chemotherapy at a rate $>10\%$ were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

Metastatic Colorectal Cancer

*In Combination with bolus-IFL*

The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus-IFL in patients with mCRC *[see Clinical Studies (14.1)]*. Patients were randomized (1:1:1) to placebo with bolus-IFL, Avastin with bolus-IFL, or Avastin with fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population. All Grades 3–4 adverse reactions and selected Grades 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 2.

**Table 2: Grades 3-4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g**

| **Adverse Reaction[a]** | **Avastin with IFL (N=392)** | **Placebo with IFL (N=396)** |
|---|---|---|
| **Hematology** | | |
| Leukopenia | 37% | 31% |

| Adverse Reaction[a] | Avastin with IFL (N=392) | Placebo with IFL (N=396) |
|---|---|---|
| Neutropenia | 21% | 14% |
| **Gastrointestinal** | | |
| Diarrhea | 34% | 25% |
| Abdominal pain | 8% | 5% |
| Constipation | 4% | 2% |
| **Vascular** | | |
| Hypertension | 12% | 2% |
| Deep vein thrombosis | 9% | 5% |
| Intra-abdominal thrombosis | 3% | 1% |
| Syncope | 3% | 1% |
| **General** | | |
| Asthenia | 10% | 7% |
| Pain | 8% | 5% |

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*In Combination with FOLFOX4*

The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200) in patients who were previously treated with irinotecan and fluorouracil for initial therapy for mCRC. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population.

Selected Grades 3–5 non-hematologic and Grades 4–5 hematologic occurring at a higher incidence (≥ 2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse reaction rates due to the reporting mechanisms.

First-Line Non Squamous Non-Small Cell Lung Cancer

The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599) *[see Clinical Studies (14.3)]*. Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The demographics of the safety population were similar to the demographics of the efficacy population.

Only Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions were collected. Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without

neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma

The safety of Avastin was evaluated in a multicenter, randomized, open-label study (EORTC 26101) in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable *[see Clinical Studies (14.4)]*. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with mRCC. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa *[see Clinical Studies (14.5)]*. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-5 adverse reactions occurring at a higher incidence ( >2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 3.

**Table 3: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705**

| Adverse Reaction[a] | Avastin with Interferon Alfa (N=337) | Placebo with Interferon Alfa (N=304) |
|---|---|---|
| **Metabolism and nutrition** | | |
| Decreased appetite | 36% | 31% |
| Weight loss | 20% | 15% |
| **General** | | |
| Fatigue | 33% | 27% |
| **Vascular** | | |
| Hypertension | 28% | 9% |
| **Respiratory, thoracic and mediastinal** | | |
| Epistaxis | 27% | 4% |
| Dysphonia | 5% | 0% |
| **Nervous system** | | |
| Headache | 24% | 16% |
| **Gastrointestinal** | | |
| Diarrhea | 21% | 16% |
| **Renal and urinary** | | |
| Proteinuria | 20% | 3% |
| **Musculoskeletal and connective tissue** | | |
| Myalgia | 19% | 14% |
| Back pain | 12% | 6% |

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The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer*[see Clinical Studies (14.6)]*. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving Avastin with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%). Adverse reactions are presented in Table 4.

**Table 4: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240**

| Adverse Reaction[a] | Avastin with Chemotherapy (N=218) | Chemotherapy (N=222) |
|---|---|---|
| **General** | | |
| Fatigue | 80% | 75% |
| Peripheral edema | 15% | 22% |
| **Metabolism and nutrition** | | |
| Decreased appetite | 34% | 26% |
| Hyperglycemia | 26% | 19% |
| Hypomagnesemia | 24% | 15% |
| Weight loss | 21% | 7% |
| Hyponatremia | 19% | 10% |
| Hypoalbuminemia | 16% | 11% |
| **Vascular** | | |
| Hypertension | 29% | 6% |
| Thrombosis | 10% | 3% |
| **Infections** | | |
| Urinary tract infection | 22% | 14% |
| Infection | 10% | 5% |
| **Nervous system** | | |
| Headache | 22% | 13% |
| Dysarthria | 8% | 1% |
| **Psychiatric** | | |
| Anxiety | 17% | 10% |
| **Respiratory, thoracic and mediastinal** | | |
| Epistaxis | 17% | 1% |
| **Renal and urinary** | | |
| Increased blood creatinine | 16% | 10% |
| Proteinuria | 10% | 3% |
| **Gastrointestinal** | | |
| Stomatitis | 15% | 10% |
| Proctalgia | 6% | 1% |
| Anal fistula | 6% | 0% |
| **Reproductive system and breast** | | |
| Pelvic pain | 14% | 8% |
| **Hematology** | | |
| Neutropenia | 12% | 6% |
| Lymphopenia | 12% | 5% |

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Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

*Stage III or IV Following Initial Surgical Resection*
The safety of Avastin was evaluated in GOG-0218, a multicenter, randomized, double-blind, placebo controlled, three arm study, which evaluated the addition of Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection *[see Clinical Studies (14.7)]*. Patients were randomized (1:1:1) to carboplatin and paclitaxel without Avastin (CPP), carboplatin and paclitaxel with Avastin for up to six cycles (CPB15), or carboplatin and paclitaxel with Avastin for six cycles followed by Avastin as a single agent for up to 16 additional doses (CPB15+). Avastin was given at 15 mg/kg every three weeks. On this trial, 1215 patients received at least one dose of Avastin. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the Avastin arms versus the control arm were fatigue (CPB15+ - 9%, CPB15 - 6%, CPP - 6%), hypertension (CPB15+ - 10%, CPB15 - 6%, CPP - 2%), thrombocytopenia (CPB15+ - 21%, CPB15 - 20%, CPP - 15%) and leukopenia (CPB15+ - 51%, CPB15 - 53%, CPP - 50%). Adverse reactions are presented in Table 5.

**Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in GOG-0218**

| **Adverse Reaction[a]** | **Avastin with carboplatin and paclitaxel followed by Avastin alone[*] (N=608)** | **Avastin with carboplatin and paclitaxel[**] (N= 607)** | **Carboplatin and paclitaxel[***] (N= 602)** |
|---|---|---|---|
| **General** | | | |
| Fatigue | 80% | 72% | 73% |
| **Gastrointestinal** | | | |
| Nausea | 58% | 53% | 51% |
| Diarrhea | 38% | 40% | 34% |
| Stomatitis | 25% | 19% | 14% |
| **Musculoskeletal and connective tissue** | | | |
| Arthralgia | 41% | 33% | 35% |
| Pain in extremity | 25% | 19% | 17% |
| Muscular weakness | 15% | 13% | 9% |
| **Nervous system** | | | |
| Headache | 34% | 26% | 21% |
| Dysarthria | 12% | 10% | 2% |
| **Vascular** | | | |
| Hypertension | 32% | 24% | 14% |
| **Respiratory, thoracic and mediastinal** | | | |
| Epistaxis | 31% | 30% | 9% |
| Dyspnea | 26% | 28% | 20% |
| Nasal mucosal disorder | 10% | 7% | 4% |

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*Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or chemotherapy alone in patients with platinum resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum based therapy *[see Clinical*

*Studies (14.8)]*. Patients were randomized to receive Avastin 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence ( ≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
Adverse reactions are presented in Table 6.

**Table 6: Grades 2−4 Adverse Reactions Occurring at Higher Incidence (≥5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224**

| Adverse Reaction[a] | Avastin with Chemotherapy (N=179) | Chemotherapy (N=181) |
|---|---|---|
| **Hematology** | | |
| Neutropenia | 31% | 25% |
| **Vascular** | | |
| Hypertension | 19% | 6% |
| **Nervous system** | | |
| Peripheral sensory neuropathy | 18% | 7% |
| **General** | | |
| Mucosal inflammation | 13% | 6% |
| **Renal and urinary** | | |
| Proteinuria | 12% | 0.6% |
| **Skin and subcutaneous tissue** | | |
| Palmar-plantar erythrodysaesthesia | 11% | 5% |
| **Infections** | | |
| Infection | 11% | 4% |
| **Respiratory, thoracic and mediastinal** | | |
| Epistaxis | 5% | 0% |

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*Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*

*Study AVF4095g*
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer *[see Clinical Studies (14.9]*. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%). Adverse reactions are presented in Table 7.

**Table 7: Grades 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g**

| Adverse Reaction[a] | Avastin with Carboplatin and Gemcitabine (N=247) | Placebo with Carboplatin and Gemcitabine (N=233) |
|---|---|---|
| **General** | | |
| Fatigue | 82% | 75% |
| Mucosal inflammation | 15% | 10% |
| **Gastrointestinal** | | |
| Nausea | 72% | 66% |
| Diarrhea | 38% | 29% |
| Stomatitis | 15% | 7% |
| Hemorrhoids | 8% | 3% |
| Gingival bleeding | 7% | 0% |
| **Hematology** | | |
| Thrombocytopenia | 58% | 51% |
| **Respiratory, thoracic and mediastinal** | | |
| Epistaxis | 55% | 14% |
| Dyspnea | 30% | 24% |
| Cough | 26% | 18% |
| Oropharyngeal pain | 16% | 10% |
| Dysphonia | 13% | 3% |
| Rhinorrhea | 10% | 4% |
| Sinus congestion | 8% | 2% |
| **Nervous system** | | |
| Headache | 49% | 30% |
| Dizziness | 23% | 17% |
| **Vascular** | | |
| Hypertension | 42% | 9% |
| **Musculoskeletal and connective tissue** | | |
| Arthralgia | 28% | 19% |
| Back pain | 21% | 13% |
| **Psychiatric** | | |
| Insomnia | 21% | 15% |
| **Renal and urinary** | | |
| Proteinuria | 20% | 3% |
| **Injury and procedural** | | |
| Contusion | 17% | 9% |
| **Infections** | | |
| Sinusitis | 15% | 9% |

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*Study GOG-0213*

The safety of Avastin was evaluated in an open-label, controlled study (GOG-0213) in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy*[see Clinical Studies (14.9)]*. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).
Adverse reactions are presented in Table 8.

**Table 8: Grades 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213**

| Adverse Reaction[a] | Avastin with Carboplatin and Paclitaxel (N=325) | Carboplatin and Paclitaxel (N=332) |
|---|---|---|
| **Musculoskeletal and connective tissue** | | |
| Arthralgia | 45% | 30% |
| Myalgia | 29% | 18% |
| Pain in extremity | 25% | 14% |
| Back pain | 17% | 10% |
| Muscular weakness | 13% | 8% |
| Neck pain | 9% | 0% |
| **Vascular** | | |
| Hypertension | 42% | 3% |
| **Gastrointestinal** | | |
| Diarrhea | 39% | 32% |
| Abdominal pain | 33% | 28% |
| Vomiting | 33% | 25% |
| Stomatitis | 33% | 16% |
| **Nervous system** | | |
| Headache | 38% | 20% |
| Dysarthria | 14% | 2% |
| Dizziness | 13% | 8% |
| **Metabolism and nutrition** | | |
| Decreased appetite | 35% | 25% |
| Hyperglycemia | 31% | 24% |
| Hypomagnesemia | 27% | 17% |
| Hyponatremia | 17% | 6% |
| Weight loss | 15% | 4% |
| Hypocalcemia | 12% | 5% |
| Hypoalbuminemia | 11% | 6% |
| Hyperkalemia | 9% | 3% |
| **Respiratory, thoracic and mediastinal** | | |
| Epistaxis | 33% | 2% |
| Dyspnea | 30% | 25% |
| Cough | 30% | 17% |
| Rhinitis allergic | 17% | 4% |
| Nasal mucosal disorder | 14% | 3% |
| **Skin and subcutaneous tissue** | | |
| Exfoliative rash | 23% | 16% |
| Nail disorder | 10% | 2% |
| Dry skin | 7% | 2% |
| **Renal and urinary** | | |
| Proteinuria | 17% | 1% |
| Increased blood creatinine | 13% | 5% |
| **Hepatic** | | |

| Adverse Reaction[a] | Avastin with Carboplatin and Paclitaxel (N=325) | Carboplatin and Paclitaxel (N=332) |
|---|---|---|
| Increased aspartate aminotransferase | 15% | 9% |
| **General** | | |
| Chest pain | 8% | 2% |
| **Infections** | | |
| Sinusitis | 7% | 2% |

a NCI-CTC version 3

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab in the studies described below with the incidence of antibodies in other studies or to other bevacizumab products may be misleading.

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2233) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-bevacizumab antibodies is not known.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Avastin. 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.

*General:* Polyserositis
*Cardiovascular:* Pulmonary hypertension, Mesenteric venous occlusion
*Gastrointestinal:* Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
*Hemic and lymphatic:* Pancytopenia
*Hepatobiliary disorders:* Gallbladder perforation
*Musculoskeletal and Connective Tissue Disorders:* Osteonecrosis of the jaw
*Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)
*Respiratory:* Nasal septum perforation

## 7 DRUG INTERACTIONS

Effects of Avastin on Other Drugs

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Avastin may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data).* Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Animal Data*

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

### 8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

### 8.3 Females and Males of Reproductive Potential

Contraception

*Females*

Avastin may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose.

Infertility

*Females*

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

### 8.4 Pediatric Use

The safety and effectiveness of Avastin in pediatric patients have not been established.

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed GBM who received bevacizumab and irinotecan. Addition of Avastin to standard of care did not result in improved event-free survival in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma (n= 121) and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (n= 154).

Based on the population pharmacokinetics analysis of data from 152 pediatric and young adult patients with cancer (7 months to 21 years of age), bevacizumab clearance normalized by body weight in pediatrics was comparable to that in adults.

Juvenile Animal Toxicity Data

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

### 8.5 Geriatric Use

In an exploratory pooled analysis of 1745 patients from five randomized, controlled studies, 35% of patients were ≥65 years old. The overall incidence of ATE was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥65 years (8% vs. 3%) as compared to patients <65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

## 11 DESCRIPTION

Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining

regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Avastin (bevacizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Avastin contains bevacizumab at a concentration of 25 mg/mL in either a 100 mg/4 mL or 400 mg/16 mL single-dose vial.

Each mL of solution contains 25 mg bevacizumab, α,α-trehalose dihydrate (60 mg), polysorbate 20 (0.4 mg), sodium phosphate dibasic, anhydrous (1.2 mg), sodium phosphate monobasic, monohydrate (5.8 mg), and Water for Injection, USP. The pH is 6.2.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

### 12.3 Pharmacokinetics

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 ($10^{th}$, $90^{th}$ percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

Distribution

The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

Elimination

The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

Specific Populations

The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In Study AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

### 13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

## 14 CLINICAL STUDIES

### 14.1 Metastatic Colorectal Cancer

Study AVF2107g

The safety and efficacy of Avastin was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m$^2$, fluorouracil 500 mg/m$^2$, and leucovorin 20 mg/m$^2$ given once weekly for 4 weeks every 6 weeks), Avastin (5 mg/kg every 2 weeks) with bolus-IFL, or Avastin (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the Avastin with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Avastin was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

The addition of Avastin improved survival across subgroups defined by age ($<65$ years, $\geq 65$ years) and sex. Results are presented in Table 9 and Figure 1.

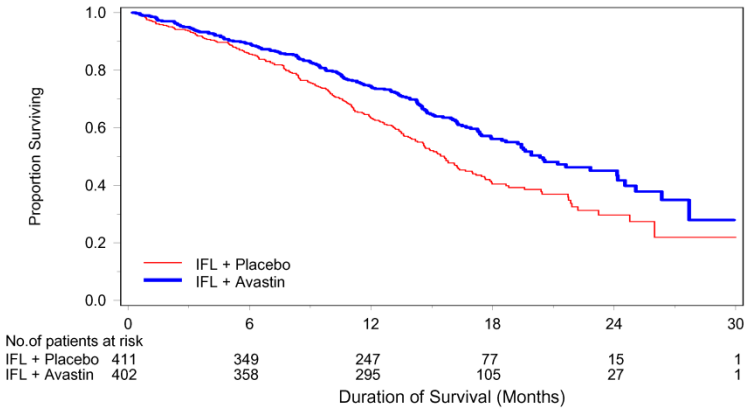
**Table 9: Efficacy Results in Study AVF2107g**

| Efficacy Parameter | Avastin with bolus-IFL (N=402) | Placebo with bolus-IFL (N=411) |
|---|---|---|
| **Overall Survival** | | |
| Median, in months | 20.3 | 15.6 |
| Hazard ratio (95% CI) | 0.66 (0.54, 0.81) | |
| p-value[a] | < 0.001 | |
| **Progression-Free Survival** | | |
| Median, in months | 10.6 | 6.2 |
| Hazard ratio (95% CI) | 0.54 (0.45, 0.66) | |
| p-value[a] | < 0.001 | |
| **Overall Response Rate** | | |
| Rate (%) | 45% | 35% |
| p-value[b] | < 0.01 | |
| **Duration of Response** | | |
| Median, in months | 10.4 | 7.1 |

[a] by stratified log-rank test.

[b] by $\chi^2$ test

**Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g**




Among the 110 patients randomized to Avastin with fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200

The safety and efficacy of Avastin were evaluated in a randomized, open-label, active-controlled study [E3200 (NCT00025337)] in 829 patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m$^2$ and leucovorin 200 mg/m$^2$ concurrently, then fluorouracil 400 mg/m$^2$ bolus followed by 600 mg/m$^2$ continuously; Day 2: leucovorin 200 mg/m$^2$, then fluorouracil 400 mg/m$^2$ bolus followed by 600 mg/m$^2$ continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without fluorouracil for metastatic disease, and 1% received prior irinotecan and fluorouracil as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log-rank test] with clinical benefit seen in subgroups defined by age (< 65 years, ≥ 65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving Avastin with FOLFOX4.

Study TRC-0301

The activity of Avastin with fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147

The safety and efficacy of Avastin were evaluated in a prospective, randomized, open-label, multinational, controlled study [ML18147 (NCT00700102)] in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line treatment was contingent upon first-line chemotherapy. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 10 and Figure 2.

**Table 10: Efficacy Results in Study ML18147**

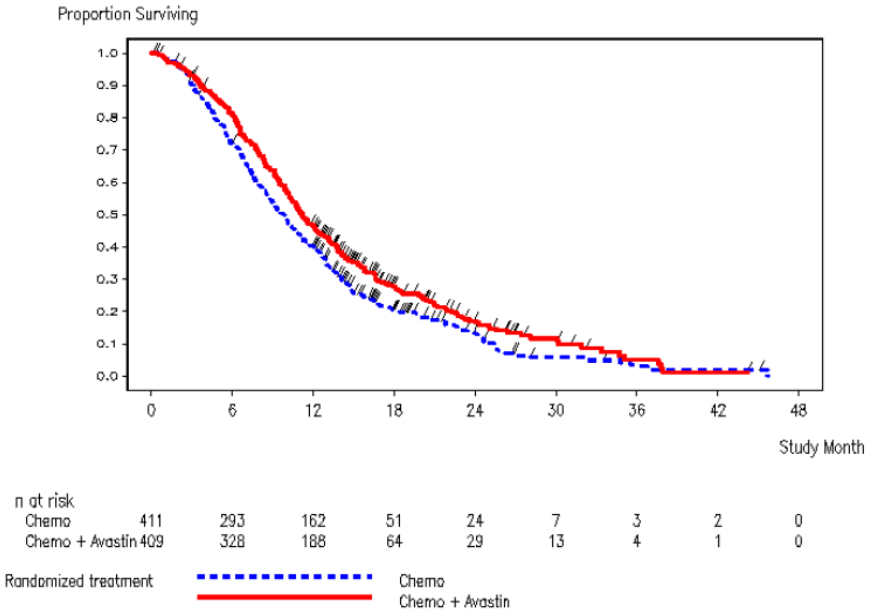
| **Efficacy Parameter** | **Avastin with Chemotherapy (N=409)** | **Chemotherapy (N=411)** |
|---|---|---|
| **Overall Survival[a]** | | |
| Median, in months | 11.2 | 9.8 |
| Hazard ratio (95% CI) | 0.81 (0.69, 0.94) | |

| **Progression-Free Survival**[b] | | |
|---|---|---|
| Median, in months | 5.7 | 4.0 |
| Hazard ratio (95% CI) | 0.68 (0.59, 0.78) | |

[a] p=0.0057 by unstratified log-rank test.

[b] p-value < 0.0001 by unstratified log-rank test.

**Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147**




## 14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies.

The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155) or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of Avastin to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the Avastin-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had

undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

### 14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer

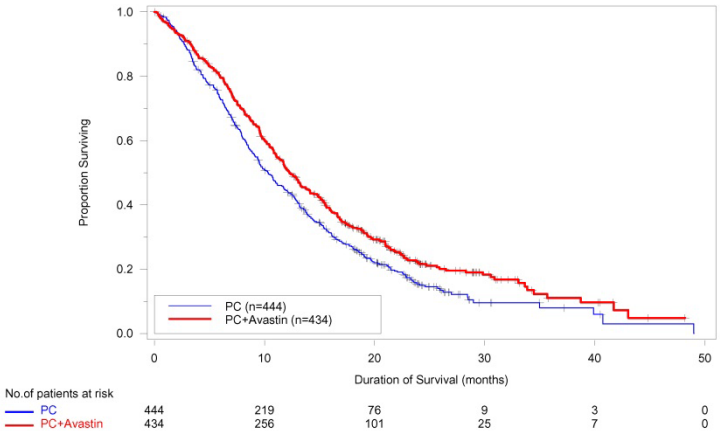
Study E4599

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m$^2$) and carboplatin (AUC 6) with or without Avastin 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

**Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599**




In an exploratory analysis across patient subgroups, the impact of Avastin on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704
The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo-controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

### 14.4 Recurrent Glioblastoma

Study EORTC 26101
The safety and efficacy of Avastin were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m$^2$ every 6 weeks) or lomustine (110 mg/m$^2$ every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or Avastin with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received Avastin following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E
The efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM were evaluated in one single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)]. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

## 14.5 Metastatic Renal Cell Carcinoma

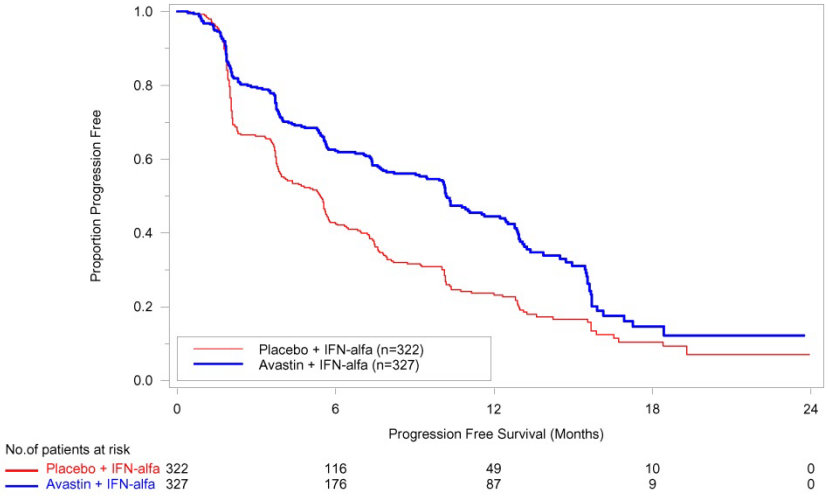
Study BO17705

The safety and efficacy of Avastin were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and Avastin versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N = 327) or placebo (every 2 weeks; N = 322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI: 0.72, 1.04)]. Results are presented in Figure 4.

**Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705**




## 14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

The safety and efficacy of Avastin were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing Avastin with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

The dosing regimens for Avastin, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m$^2$ over 24 hours, Day 2: cisplatin 50 mg/m$^2$ with Avastin;
- Day 1: Paclitaxel 175 mg/m$^2$ over 3 hours, Day 2: cisplatin 50 mg/m$^2$ with Avastin;
- Day 1: Paclitaxel 175 mg/m$^2$ over 3 hours with cisplatin 50 mg/m$^2$ with Avastin;
- Day 1: Paclitaxel 175 mg/m$^2$ over 3 hours with Avastin, Days 1-3: topotecan IV 0.75 mg/m$^2$ over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Figure 5 and Table 11.

**Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240**

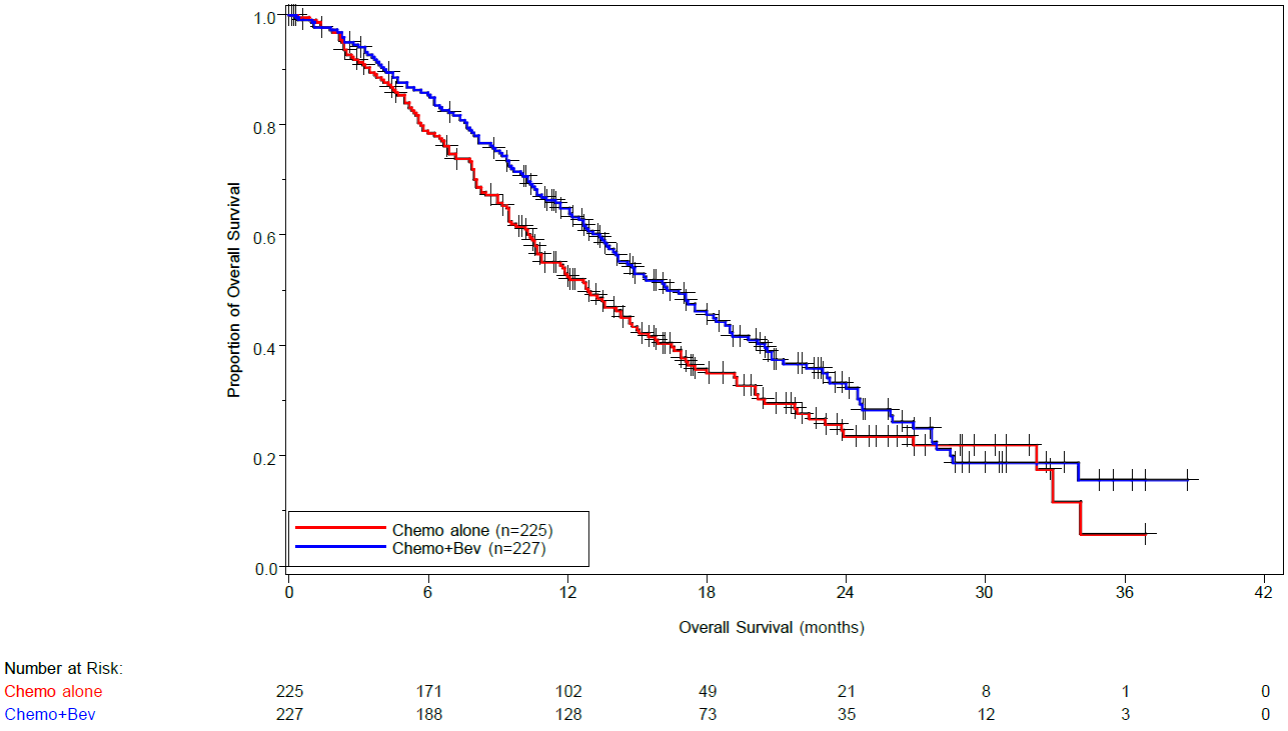



**Table 11: Efficacy Results in Study GOG-0240**

| **Efficacy Parameter** | **Avastin with Chemotherapy (N=227)** | **Chemotherapy (N=225)** |
|---|---|---|
| **Overall Survival** | | |
| Median, in months[a] | 16.8 | 12.9 |
| Hazard ratio (95% CI) | 0.74 (0.58, 0.94) | |
| p-value[b] | 0.0132 | |

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

**Table 12: Efficacy Results in Study GOG-0240**

| Efficacy Parameter | Topotecan and Paclitaxel with or without Avastin (N=223) | Cisplatin and Paclitaxel with or without Avastin (N=229) |
|---|---|---|
| **Overall Survival** | | |
| Median, in months[a] | 13.3 | 15.5 |
| Hazard ratio (95% CI) | 1.15 (0.91, 1.46) | |
| p-value | 0.23 | |

[a] Kaplan-Meier estimates.

The HR for OS with Avastin with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

### 14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218
The safety and efficacy of Avastin were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m$^2$) for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m$^2$) for six cycles, with concurrent Avastin started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m$^2$) for six cycles, with concurrent Avastin started at cycle 2, followed by Avastin as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623).

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age.
Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%).

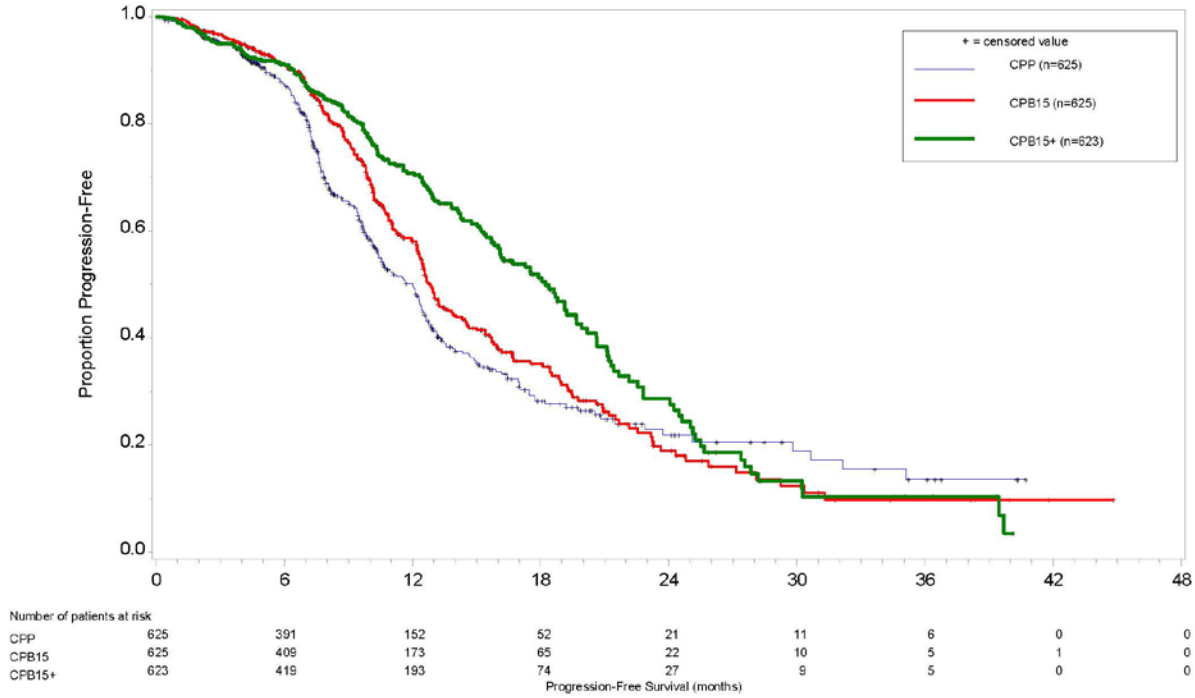
Study results are presented in Table 13 and Figure 6.

**Table 13: Efficacy Results in Study GOG-0218**

| Efficacy Parameter | Avastin with carboplatin and paclitaxel followed by Avastin alone (N=623) | Avastin with carboplatin and paclitaxel (N=625) | Carboplatin and paclitaxel (N= 625) |
|---|---|---|---|
| **Progression-Free Survival per Investigator** | | | |
| Median, in months | 18.2 | 12.8 | 12.0 |
| Hazard ratio (95% CI)[a] | 0.62 (0.52, 0.75) | 0.83 (0.70, 0.98) | |
| p –value[b] | < 0.0001 | NS | |
| **Overall Survival**[c] | | | |
| Median, in months | 43.8 | 38.8 | 40.6 |
| Hazard ratio (95% CI)[a] | 0.89 (0.76, 1.05) | 1.06 (0.90, 1.24) | |

NS=not significant
[a] Relative to the control arm; stratified hazard ratio
[b] Two-sided p-value based on re-randomization test
[c] Final overall survival analysis

**Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection in Study GOG-0218**




## 14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

The safety and efficacy of Avastin were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin with chemotherapy versus chemotherapy alone in patients with

platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m$^2$ on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m$^2$ on day 1 every 4 weeks; or topotecan 4 mg/m$^2$ on days 1, 8 and 15 every 4 weeks or 1.25 mg/m$^2$ on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

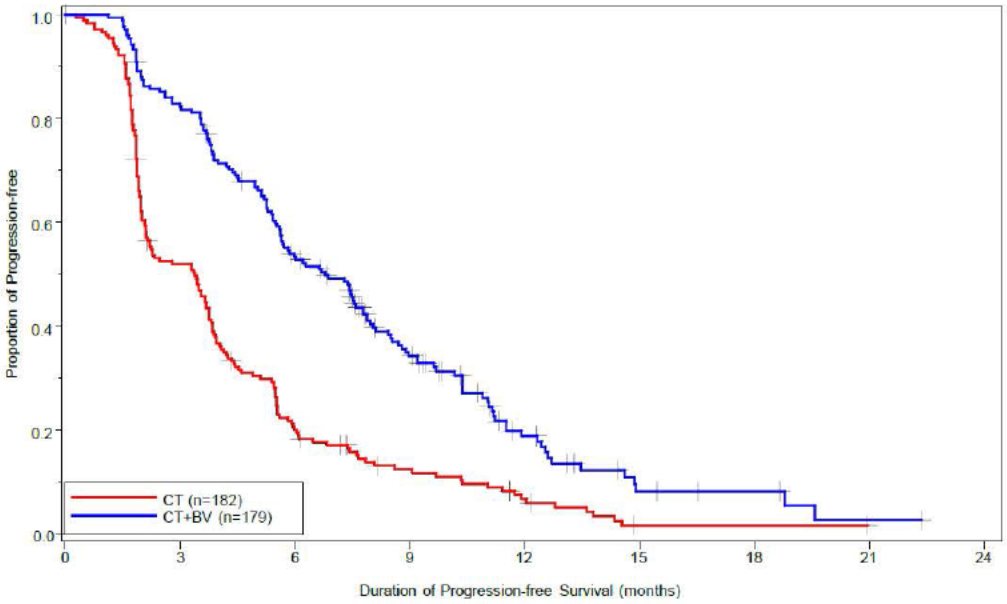
The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 14 and Figure 7. Results for the separate chemotherapy cohorts are presented in Table 15.

**Table 14: Efficacy Results in Study MO22224**

| **Efficacy Parameter** | **Avastin with Chemotherapy (N=179)** | **Chemotherapy (N=182)** |
|---|---|---|
| **Progression-Free Survival per Investigator** | | |
| Median (95% CI), in months | 6.8 (5.6, 7.8) | 3.4 (2.1, 3.8) |
| HR (95% CI)[a] | 0.38 (0.30, 0.49) | |
| p-value[b] | <0.0001 | |
| **Overall Survival** | | |
| Median (95% CI), in months | 16.6 (13.7, 19.0) | 13.3 (11.9, 16.4) |
| HR (95% CI)[a] | 0.89 (0.69, 1.14) | |
| **Overall Response Rate** | | |
| Number of Patients with Measurable Disease at Baseline | 142 | 144 |
| Rate, % (95% CI) | 28% (21%, 36%) | 13% (7%, 18%) |
| **Duration of Response** | | |
| Median, in months | 9.4 | 5.4 |

[a] per stratified Cox proportional hazards model
[b] per stratified log-rank test

**Figure 7: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224**




| Number at Risk: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CT | 182 | 92 | 35 | 18 | 9 | 1 | 1 | 0 | 0 |
| CT+BV | 179 | 144 | 91 | 51 | 19 | 6 | 4 | 1 | 0 |

**Table 15: Efficacy Results in Study MO22224 by Chemotherapy**

| Efficacy Parameter | Paclitaxel | | Topotecan | | Pegylated Liposomal Doxorubicin | |
|---|---|---|---|---|---|---|
| | Avastin with Chemotherapy (N=60) | Chemotherapy (N=55) | Avastin with Chemotherapy (N=57) | Chemotherapy (N=63) | Avastin with Chemotherapy (N=62) | Chemotherapy (N=64) |
| **Progression-Free Survival per Investigator** | | | | | | |
| Median, in months (95% CI) | 9.6 (7.8, 11.5) | 3.9 (3.5, 5.5) | 6.2 (5.3, 7.6) | 2.1 (1.9, 2.3) | 5.1 (3.9, 6.3) | 3.5 (1.9, 3.9) |
| Hazard ratio[a] (95% CI) | 0.47 (0.31, 0.72) | | 0.24 (0.15, 0.38) | | 0.47 (0.32, 0.71) | |
| **Overall Survival** | | | | | | |
| Median, in months (95% CI) | 22.4 (16.7, 26.7) | 13.2 (8.2, 19.7) | 13.8 (11.0, 18.3) | 13.3 (10.4, 18.3) | 13.7 (11.0, 18.3) | 14.1 (9.9, 17.8) |
| Hazard ratio [a] (95% CI) | 0.64 (0.41, 1.01) | | 1.12 (0.73, 1.73) | | 0.94 (0.63, 1.42) | |
| **Overall Response Rate** | | | | | | |
| Number of patients with measurable disease at baseline | 45 | 43 | 46 | 50 | 51 | 51 |
| Rate, % (95% CI) | 53 (39, 68) | 30 (17, 44) | 17 (6, 28) | 2 (0, 6) | 16 (6, 26) | 8 (0, 15) |
| **Duration of Response** | | | | | | |
| Median, in months | 11.6 | 6.8 | 5.2 | NE | 8.0 | 4.6 |

[a] per stratified Cox proportional hazards model
NE=Not Estimable

## 14.9 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g

The safety and efficacy of Avastin were evaluated in a randomized, double-blind, placebo-controlled study [AVF4095g (NCT00434642)] studying Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive Avastin (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m$^2$ on days 1 and 8) a for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

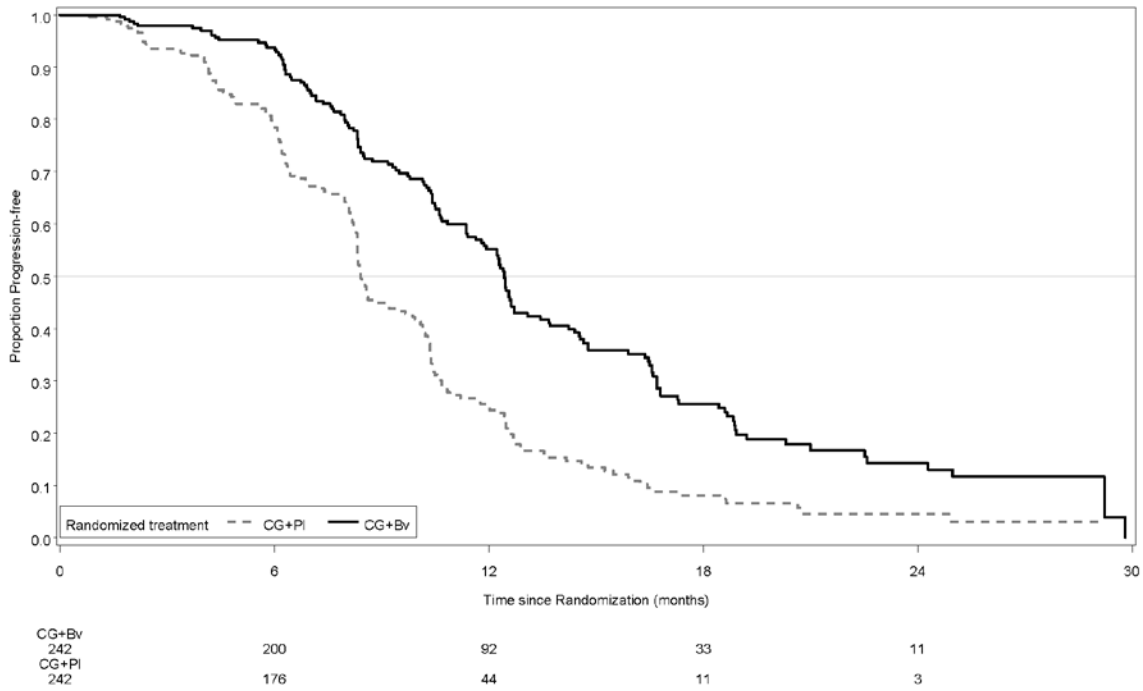
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 16 and Figure 8). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

**Table 16: Efficacy Results in Study AVF4095g**

| Efficacy Parameter | Avastin with Gemcitabine and Carboplatin (N=242) | Placebo with Gemcitabine and Carboplatin (N=242) |
|---|---|---|
| **Progression-Free Survival** | | |
| Median, in months | 12.4 | 8.4 |
| Hazard ratio (95% CI) | 0.46 (0.37, 0.58) | |
| p-value | < 0.0001 | |
| **Overall Response Rate** | | |
| % patients with overall response | 78% | 57% |
| p-value | < 0.0001 | |

**Figure 8: Kaplan-Meier Curves for Progression-Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g**




Study GOG-0213

The safety and efficacy of Avastin were evaluated in a randomized, controlled, open-label study [Study GOG-0213 (NCT00565851)] of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m$^2$ IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m$^2$ IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥ 65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients.

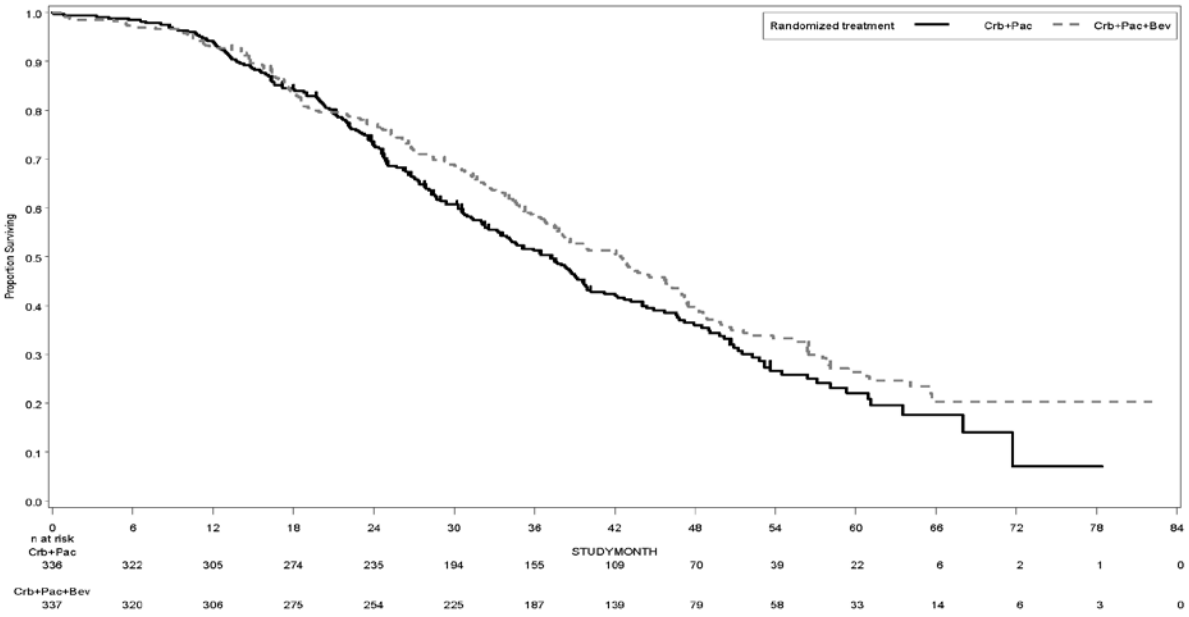
Results are presented in Table 17 and Figure 9.

**Table 17: Efficacy Results in Study GOG-0213**

| **Efficacy Parameter** | **Avastin with Carboplatin and Paclitaxel (N=337)** | **Carboplatin and Paclitaxel (N=336)** |
|---|---|---|
| **Overall Survival** | | |
| Median, in months | 42.6 | 37.3 |
| Hazard ratio (95% CI) (IVRS)[a] | 0.84 (0.69, 1.01) | |
| Hazard ratio (95% CI) (eCRF)[b] | 0.82 (0.68, 0.996) | |
| **Progression-Free Survival** | | |
| Median, in months | 13.8 | 10.4 |
| Hazard ratio (95% CI) (IVRS)[a] | 0.61 (0.51, 0.72) | |
| **Overall Response Rate** | | |
| Number of patients with measurable disease at baseline | 274 | 286 |
| Rate, % | 213 (78%) | 159 (56%) |

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

**Figure 9: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213**




## 16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

- 100 mg/4 mL: carton of one vial (NDC 50242-060-01) ; carton of 10 vials (NDC 50242-060-10).
- 400 mg/16 mL: carton of one vial (NDC 50242-061-01) ; carton of 10 vials (NDC 50242-061-10).

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

## 17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their health care provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolic Events: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion-Related Reactions: Avastin can cause infusion-related reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

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**Avastin® (bevacizumab)**

Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125085Orig1s331

# SUMMARY REVIEW

# Division Director Summary Review

| | |
|---|---|
| **Date** | June 20, 2019 |
| **From** | Patricia Keegan, M.D. |
| **Subject** | Division Director Summary Review |
| **BLA Supplement #** | BLA 125085/S-331 |
| **Applicant** | Genentech, Inc. |
| **Date of Submission** | April 30, 2019 |
| **PDUFA Goal Date** | October 30, 2019 |
| **Proprietary Name** | Avastin |
| **Established or Proper Name** | Bevacizumab |
| **Dosage Form(s)** | Injection; supplied |
| **Applicant Proposed Indication(s)/Population(s)** | Not applicable |
| **Action or Recommended Action:** | *Approval* |
| **Approved/Recommended Indication(s)/Population(s)** | No revisions to the Indications and Usage section |

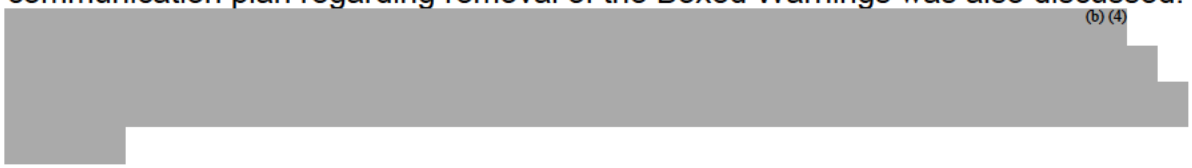
| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Regulatory Health Project Manager | Gina Mehta |
| Medical Officer Review | Sandra Casak |
| Associate Director for Labeling | Stacy Shord |

OND=Office of New Drugs

## Background

This labeling supplement was submitted in response to a teleconference held on February 14, 2019, initiated by FDA to discuss the possible removal of the Boxed Warnings from the Avastin® (bevacizumab) FDA-approved prescribing information and in response to FDA's Prior Approval Supplement (PAS) request letter issued February 20, 2019 formally requesting changes to the Avastin product labeling as discussed in the February 14, 2019 teleconference, as well as additional modifications for consistent with current labeling practices. The proposed removal of the Boxed Warning was requested by FDA based on a systematic re-assessment by FDA of product labeling for approved products that are labeled in Section 12.1 of product labeling as inhibitors of the vascular endothelial growth factor (VEGF) receptor pathway. FDA's review of this product class noted that, while the product labeling for Avastin (the first product whose mechanism of action was identified as VEGF pathway inhibition) contained a Boxed Warning for gastrointestinal (GI) perforation, impairment of wound healing, and hemorrhage, most of the other products also labeled as inhibiting the VEGF pathway did not contain similar Boxed Warnings. FDA also noted that based on the information contained in product labeling, the risks of VEGF inhibition (impaired wound healing, viscus perforation, hypertension) were similar across all drugs identified as inhibiting the VEGF pathway (per Section 12.1). Finally, there was no evidence based on post-marketing data that a Boxed Warning was required to ensure safe use for these other drugs. Therefore, FDA proposed that the Boxed Warning be removed from the Avastin product label.

FDA requested a follow up teleconference, which was held on March 7, 2019, to discuss FDA's February 20, 2019 letter and determine whether Genentech was amenable to these changes. Genentech agreed with the proposal and Genentech's communication plan regarding removal of the Boxed Warnings was also discussed.




The labeling supplement was submitted April 30, 2019. Based on FDA's requested edits to Section 10 of product labeling, Genentech submitted updated carton and container labeling, modified for consistency with the proposed product labeling.

## Information Submitted and Regulatory Interactions

No new data were submitted in the application other than proposed labeling (prescribing information and carton/container labeling).

Interactions between Genentech and FDA were limited to verbal and written proposals for additional modifications to product labeling.

# Labeling

## Prescribing Information

Genentech removed the Boxed Warning from the Highlights and full prescribing information (FPI); updated recent major changes to remove changes more than one year old; and added information on GI perforation, impairment of wound healing, and hemorrhage to the highlights under Warnings and Precautions since the Boxed Warning was removed. In addition, the recommendation to (b) (4)

Other significant modifications were

- Re-ordering of information in the Adverse Reactions and Clinical Studies sections of labeling to follow the same order as that for trespective indications under the Indications and Usage section
- Re-ordered adverse reactions presented in tables to present information in decreasing order
- Revised product description for consistency with current labeling practices.

Genentech incorporated the following additional changes requested by FDA during the review

- Corrected established pharmacologic class (EPC) to be consistent with recent changes to the EPC list
- Change single dose to single-dose
- Change 5FU to FU
- Change “infusion reactions” to Infusion-related reactions”
- Change “dose” to “dosage” in each subsection for “recommended dosage”
- Added direction discarding vial if contains particulates, discolored or cloudy

## Carton Labeling

Genentech incorporated the following modifications requested by FDA

- Added a space between “100” and “mg” and between “4” and “mL” and between “25” and “mg” for readability and consistent appearance of the strength presentation throughout the carton labeling.
- Revised the format of the storage temperature throughout all labels and labeling including carton labeling as follows: remove the dash and replace with the word “to” and ensure the temperature abbreviations are included (e.g., 2°C to 8°C (36°F to 46°F).
- Revised the statement regarding dosage from “See package insert for full prescribing information and instructions for preparation and administration” to: “Dosage: See Prescribing Information

Recommendation: I concur with the review team (clinical and labeling) that the agreed-upon labeling is acceptable.

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

---

PATRICIA KEEGAN
06/20/2019 11:28:05 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125085Orig1s331

# OTHER REVIEW(S)

# DOP2 Associate Director for Labeling Review

| | |
|---|---|
| **Product Title** | **Avastin (bevacizumab) injection, for intravenous use** |
| Applicant | Genentech |
| Application/Supplement Number | BLA 125085 |
| Type of Application/Submission[1] | Supplement 331 |
| Is Proposed Labeling in Old Format? (Y/N) | N |
| Is Labeling Being Converted to PLR? (Y/N) | N |
| Is Labeling Being Converted to PLLR? (Y/N) | N |
| Proposed Indication(s) (if applicable) | None |
| Approved Indication(s) (if applicable) | Colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer and ovarian cancer |
| | |
| Date FDA Received Application | April 30, 2019 |
| Review Classification (Priority/Standard) | Standard |
| Action Goal Date | May 31, 2019 |
| | |
| Review Date | May 23, 2019 |
| Reviewer | Stacy S Shord, Pharm.D. |

**Background:** The applicant submitted this supplement in response to a prior approval supplement (PAS) request dated February 20, 2019. The PAS request proposed changes to the approved labeling to remove the Boxed Warning and address grammatical and editoral changes throughout the labeling.

**Labeling Review:**
The approved labeling document was reviewed to help ensure that product information (PI):

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[2]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The attached PI contains the working version of the AVASTIN labeling with my recommended edits and comments and includes comments and edits from other review team members. My labeling recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) should be considered preliminary and may not represent final recommendations for the AVASTIN labeling.

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

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/s/

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STACY S SHORD
05/23/2019 04:02:02 PM

| | |
|---|---|
| **BLA** | 125085/331 |
| **Submission date** | April 30, 2019 |
| **Product** | Avastin (bevacizumab) |
| **Sponsor** | Genentech |
| **Reviewer** | Sandra J. Casak |

**Prior Approval Supplement (PAS) – Labeling Changes**

On February 14, 2019, FDA held a teleconference with Genentech (GNE) to discuss potential removal of the Boxed Warning for gastrointestinal perforations, wound healing, and hemorrhage from the Avastin USPI. On February 20, 2019, FDA issued a Prior Approval Supplement Request letter requesting submission of draft labeling for Avastin prescribing information (PI) proposing changes to the approved labeling to remove the Boxed Warning and additional changes to correct grammatical errors and editorial changes for consistency with the Physician Labeling Rule (PLR).


As requested, the Boxed Warning has been removed in the revised label. The information previously contained in the box has been incorporated into the highlights and Warnings and Precautions sections of the USPI. These labeling changes were based on FDA's systematic re-assessment of the need for prominent warnings due to VEGF inhibition across all approved drugs that inhibit the VEGF pathway, demonstrating that the risks of VEGF inhibition (impaired wound healing, visceral perforation, hypertension) were similar across all drugs identified as inhibiting the VEGF pathway and that many these drugs were approved without a Boxed Warning, yet the absence of the Boxed Warning did not results in unacceptable toxicity and a Boxed Warning was not required to ensure safe use of these other drugs based on post-marketing safety information.

In addition, Sections 1, 2, 6, and 14 have been reordered for consistency. Multiple changes to improve readability and update the label (including changes to Sections 11 and 16 following approval of supplement 329 on April 3, 2019) have also been incorporated.

The clinical team agrees with the proposed labeling changes (as negotiated after submission with GNE) and recommends approval of the supplement.

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SANDRA J CASAK
05/13/2019 09:27:33 AM

MARTHA B DONOGHUE
05/13/2019 02:15:00 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125085Orig1s331

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

| | |
|---|---|
| **From:** | Mehta, Shubhangi |
| **To:** | Agnes Bliecq; Puskas, Jason |
| **Subject:** | BLA 125085/S-331: Labeling Revision |
| **Date:** | Tuesday, June 18, 2019 4:05:00 PM |
| **Attachments:** | image001.png |
| **Importance:** | High |

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Good afternoon Agnes and Jason,

Thank you for your June 12, 2019, submission containing the final labeling for BLA 125085/S-331.

We note during review of the final labeling that the top margin of the Highlights Page is slightly greater that 0.5 inch. Although the header setting indicates that the top margin is at 0.5 inch, the labeling begins lower than 0.5 inch.

Since this is a SRPI requirement for the Highlights page, we are requesting correction to this top margin, and re-submission of the final labeling by **Noon EST tomorrow, Wednesday, June 19, 2019**.

Please let me know if you have any questions, and kindly respond to confirm receipt of this email.

Thank you,
Gina

**Shubhangi (Gina) Mehta, PharmD**
*Regulatory Health Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Oncology Products 2**
**U.S. Food and Drug Administration**
Tel: 301-796-7910
shubhangi.mehta@fda.hhs.gov

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/s/

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SHUBHANGI H MEHTA
06/18/2019 05:02:34 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# Memorandum

***Date:*** June 11, 2019

***From:*** Shubhangi (Gina) Mehta, Regulatory Health Project Manager - CDER/OHOP/DOP2

***Subject:*** **BLA 125085/S-331 – Genentech, Inc.**
***Labeling Review Comments and Information Request***

---

Genentech, Inc.
Attention: Jason Puskas, B.Sc., CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Puskas:

Please refer to your Biologics Licensing Application (BLA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Avastin (bevacizumab).

Please find attached FDA's edits and comments to your revised Prescribing Information (PI) submitted on May 23, 2019. Please provide your response via email **as soon as possible but no later than 12 PM EST, Wednesday, June 12, 2019**, and follow that with a formal submission to the BLA.

Additionally, if GNE is in agreement with all of the changes proposed, please also submit a clean version of the final label, with dates added.

Please provide a response electronically to Shubhangi.mehta@fda.hhs.gov **as soon as possible but no later than 12 PM EST, Wednesday, June 12, 2019**; followed by a formal submission to your BLA.

If you have any questions, please contact me at shubhangi.mehta@fda.hhs.gov or at (301) 796-7910.

40 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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SHUBHANGI H MEHTA
06/11/2019 11:16:29 AM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# Memorandum

***Date:*** May 21, 2019

***From:*** Shubhangi (Gina) Mehta, Regulatory Health Project Manager - CDER/OHOP/DOP2

***Subject:*** **BLA 125085/S-331 – Genentech, Inc.**
***Labeling Review Comments and Information Request***

---

Genentech, Inc.
Attention: Jason Puskas, B.Sc., CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Puskas:

Please refer to your Biologics Licensing Application (BLA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Avastin (bevacizumab).

Please find attached FDA's edits and comments to your revised Prescribing Information (PI) submitted on May 17, 2019. Please provide your response via email **as soon as possible but no later than Noon EST, Thursday, May 23, 2019**, and follow that with a formal submission to the BLA.

It appears that FDA's tracked edits were not "accepted" by Genentech in the redlined version of your May 17, 2019, PI submission, but rather placed into a new document in which GNE provided additional comments and recommended edits. Please note that in the attached draft version of the Avastin PI, FDA accepted the edits that FDA agrees with (including the edits originally proposed by FDA to Genentech that were tracked as made by Genentech in the May 17, 2019 PI submission).

Additionally, please note that if you have additional concerns or substantive edits, we may request a teleconference.

Please provide a response to the above comments electronically to Shubhangi.mehta@fda.hhs.gov **as soon as possible but no later than Noon EST, Thursday, May 23, 2019**; followed by a formal submission to your BLA.

If you have any questions, please contact me at shubhangi.mehta@fda.hhs.gov or at (301) 796-7910.

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SHUBHANGI H MEHTA
05/21/2019 09:11:25 PM

| | |
|---|---|
| **From:** | Mehta, Shubhangi |
| **To:** | Agnes Bliecq |
| **Cc:** | Sickafuse, Sharon; Jason Puskas |
| **Subject:** | RE: URGENT - FDA Labelling Request Relating to our PAS recently submitted BLA 125085/S-331 |
| **Date:** | Friday, May 10, 2019 12:03:00 PM |
| **Attachments:** | image001.png<br>AckPAS BLA 125085 S-0331 Final.pdf |
| **Importance:** | High |

Good morning Agnes and Jason,

Regarding your inquiry in the below email pertaining to carton labeling, the reviewer has indicated the following:

> **Use Option 5:**
> *Dosage: See Prescribing Information.*
> *Must be further diluted prior to intravenous administration.*
>
> **In addition, please note to add a space between "100" and "mg" and between "4" and "mL" and between "25" and "mg" for readability and consistent appearance of the strength presentation throughout the carton labeling. This also applies to the 400 mg/16 mL carton.**

Regarding your request for extension, providing response by **noon EST, Friday, May 17, 2019**, is acceptable; *however, the review team would greatly appreciate a response sooner if possible to allow time for review.*

Also, please find attached an Acknowledge Prior Approval Supplement letter, which you will also receive via postal mail.

Please let me know if you have any additional questions, and kindly respond to confirm receipt of this email with the attached letter.

Thank you,
Gina

**Shubhangi (Gina) Mehta, PharmD**
*Regulatory Health Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Oncology Products 2**
**U.S. Food and Drug Administration**
Tel: 301-796-7910
shubhangi.mehta@fda.hhs.gov

**From:** Agnes Bliecq <bliecq.agnes@gene.com>
**Sent:** Thursday, May 09, 2019 2:35 PM
**To:** Mehta, Shubhangi <Shubhangi.Mehta@fda.hhs.gov>
**Cc:** Sickafuse, Sharon <Sharon.Sickafuse@fda.hhs.gov>; Jason Puskas <jason.puskas@roche.com>
**Subject:** Re: URGENT - FDA Labelling Request Relating to our PAS recently submitted BLA 125085/S-331

Hello Gina,

I hope that you are doing well. I am the Roche/Genentech regulatory Avastin point of contact for the BLA 125085/S-331 and I wanted to ask you the following in regards to the FDA Labeling Revisions request received on May 8, 2019:

- In the memorandum letter, FDA made the following comment to the Carton Labeling: *Consider revising the statement of dosage from "See package insert for full prescribing information and instructions for preparation and administration" to read as follows: Dosage: See Prescribing Information.*

  The current carton labeling reads as :

  *DOSAGE AND ADMINISTRATION:*
  *Must be further diluted prior to IV administration.*
  *See package insert for full prescribing information and instructions for preparation and administration.*

  Could you clarify how the FDA is suggesting to implement the changes from the 4 options below:

  Option 1:

  (b) (4)

  Option 2:

  (b) (4)

  Option 3:

  (b) (4)

(b) (4)

Option 4:

(b) (4)

- Also, we would like to request for an extension to submit our response to the FDA request. Would it possible to send you our response **by Friday, May 17**?

Many thanks in advance for your clarification!

Best Regards,
Agnes

---------- Forwarded message ---------
From: Mehta, Shubhangi <Shubhangi.Mehta@fda.hhs.gov>
Date: Wed, May 8, 2019 at 4:17 PM
Subject: BLA 125085/S-331: Labeling Revisions
To: jason.puskas@roche.com <jason.puskas@roche.com>
Cc: Sickafuse, Sharon <Sharon.Sickafuse@fda.hhs.gov>

Good afternoon,

I am the Regulatory Health Project Manager responsible for managing this labeling supplement under BLA 125085/S-331. Please refer to your April 30, 2019, submission containing a revised package insert.

Please find attached proposed labeling edits to the Avastin PI and carton labeling. We are requesting a response back as soon as possible but no later than Noon EST, Friday, May 10, 2019.

Please let me know if you have any questions, and kindly respond to confirm receipt of this email with the attachments.

Thank you,
Gina

Shubhangi (Gina) Mehta, PharmD
*Regulatory Health Project Manager*

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Oncology Products 2
U.S. Food and Drug Administration
Tel: 301-796-7910
shubhangi.mehta@fda.hhs.gov


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Agnes Bliecq, PharmD.
Product Development Regulatory
Genentech Inc.
1 DNA Way, South San Francisco,
CA 94080-4990
Tel. +1 650 467 1375

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/s/

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SHUBHANGI H MEHTA
05/10/2019 12:20:51 PM

BLA 125085/S-331

**ACKNOWLEDGMENT --**
**PRIOR APPROVAL SUPPLEMENT**

Genentech, Inc.
Attention: Jason Puskas, B.Sc., CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Puskas:

We have received your supplemental biologics license application (sBLA) submitted under section 351(a)of the Public Health Service Act for the following:

**BLA NUMBER:** 125085

**SUPPLEMENT NUMBER:** 331

**PRODUCT NAME:** AVASTIN (BEVACIZUMAB) SOLUTION FOR INJECTION 100 MG/4 MLAND 400 MG/16/ML

**DATE OF SUBMISSION:** APRIL 30, 2019

**DATE OF RECEIPT:** APRIL 30, 2019

This supplemental application proposes changes to the approved Avastin USPI to remove the Boxed Warning; to update the Warnings and Precautions section in the Highlights of prescribing information, to add the safety information being removed from the Boxed Warning; to update the Adverse Reactions section, to address grammatical changes and editorial changes for consistency with the Physician Labeling Rule, as requested in the February 20, 2019, PAS Request letter, and to update the Description section in response to the April 3, 2019 approval of BLA 125085/S-329. Additionally, revised carton labeling that includes revisions to the ingredient list consistent with the proposed USPI changes were also included in this submission.

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 June 29, 2019, IN accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be October 30, 2019.

If you have questions, call Gina Mehta, Regulatory Health Project Manager, at (301) 796-7910.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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MELANIE B PIERCE
05/09/2019 04:01:24 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# Memorandum

***Date:*** May 8, 2019

***From:*** Shubhangi (Gina) Mehta, Regulatory Health Project Manager - CDER/OHOP/DOP2

***Subject:*** **BLA 125085/S-331 – Genentech, Inc.**
***Labeling Review Comments and Information Request***

---

Genentech, Inc.
Attention: Jason Puskas, B.Sc., CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Puskas:

Please refer to your Biologics Licensing Application (BLA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Avastin (bevacizumab).

Please find attached FDA's edits and comments to your revised package insert (PI) submitted on April 30, 2019. Please provide your response via email **as soon as possible but no later than Noon, EST, Friday May 10, 2019**, and follow that with a formal submission to the BLA.

In addition, we have the following carton labeling comments:

**Carton Labeling**

1. Add a space between "100" and "mg" and between "4" and "mL" and between "25" and "mg" for readability and consistent appearance of the strength presentation throughout the carton labeling.
2. Revise the format of the storage temperature throughout all labels and labeling including carton labeling as follows: remove the dash and replace with the word "to" and ensure the temperature abbreviations are included (e.g., 2°C to 8°C (36°F to 46°F).
3. Consider revising the statement of dosage from "See package insert for full prescribing information and instructions for preparation and administration" to read as follows: "Dosage: See Prescribing Information

Please provide draft carton and PI via email **as soon as possible but no later than Noon, EST, Friday May 10, 2019**, and follow that with a formal submission to the BLA.

In the areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite "From GNE" in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite "From GNE" in the comment). Lastly, when making edits to the label, please update formatting as necessary.

Please provide a response to the above comments electronically to Shubhangi.mehta@fda.hhs.gov **as soon as possible but no later than Noon, EST, Friday May 10, 2019**; followed by a formal submission to your BLA.

If you have any questions, please contact me at shubhangi.mehta@fda.hhs.gov or at (301) 796-7910.

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SHUBHANGI H MEHTA
05/08/2019 04:09:55 PM