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 0.4% 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 4463 patients including those with mCRC (AVF2107g, E3200), non-squamous NSCLC (E4599), GBM (EORTC 26101), mRCC (BO17705), cervical cancer (GOG-0240), epithelial ovarian, fallopian tube, or primary peritoneal cancer (MO22224, AVF4095, GOG-0213, and GOG-0218), or HCC (IMbrave150) 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 other anti-cancer therapies at a rate > 10% were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, 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%
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		

https://www.gene.com/download/pdf/avastin_prescribing.pdf

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%

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Hepatocellular Carcinoma (HCC)

The safety of Avastin in combination with atezolizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.10)]*. Patients received 1,200 mg of atezolizumab intravenously followed by 15 mg/kg Avastin (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to Avastin was 6.9 months (range: 0-16 months) and to atezolizumab was 7.4 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the Avastin and atezolizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of Avastin occurred in 15% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to Avastin discontinuation were hemorrhages (4.9%), including bleeding varicose vein, hemorrhage and gastrointestinal, subarachnoid, and pulmonary hemorrhages; and increased transaminases or bilirubin (0.9%).

Adverse reactions leading to interruption of Avastin occurred in 46% of patients in the Avastin and atezolizumab arm; the most common (≥ 2%) were proteinuria (6%); infections (6%); hypertension (6%); liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (4.6%); gastrointestinal hemorrhages (3%); thrombocytopenia/decreased platelet count (4.3%); and pyrexia (2.4%).

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received Avastin and atezolizumab in IMbrave150.

Table 9: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Avastin in IMbrave150

Adverse Reaction	Avastin in combination with atezolizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6
Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

https://www.gene.com/download/pdf/avastin_prescribing.pdf

Table 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving Avastin in IMbrave150

Laboratory Abnormality	Avastin in combination with atezolizumab (n=329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3
Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avastin plus atezolizumab (222-323) and sorafenib (90-153) NA = Not applicable.
[1] Graded per NCI CTCAE v4.0

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
Vascular: Arterial (including aortic) aneurysms, dissections, and rupture

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.