

**BEVACIZUMAB**Rx **Avastin** (Genentech)**Injection:** 25 mg/mL

Preservative-free. In single-use 4 and 16 mL vials.

**WARNING**

**GI perforation/wound healing complications:** Bevacizumab administration can result in the development of GI perforation and wound dehiscence, in some instances resulting in fatality. GI perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with bevacizumab (ie, was not correlated to duration of exposure). The incidence of GI perforation in patients receiving bolus-IFL (125 mg/m<sup>2</sup> irinotecan IV, 500 mg/m<sup>2</sup> 5-fluorouracil IV, and 20 mg/m<sup>2</sup> leucovorin IV given once weekly for 4 weeks every 6 weeks) with bevacizumab was 2%. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Include GI perforation in the differential diagnosis of patients receiving bevacizumab presenting with abdominal pain. Permanently discontinue bevacizumab in patients with GI perforation or wound dehiscence requiring medical intervention. The appropriate interval between termination of bevacizumab and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined (see Warnings and Administration and Dosage).

**Hemorrhage:** Serious and, in some cases, fatal hemoptysis has occurred in patients with nonsmall cell lung cancer treated with chemotherapy and bevacizumab. In a small study, the incidence of serious or fatal hemoptysis was 31% in patients with squamous histology and 4% in patients with adenocarcinoma receiving bevacizumab as compared with no cases in patients treated with chemotherapy alone. Do not administer bevacizumab to patients with recent hemoptysis (see Warnings and Administration and Dosage).

**Indications**

► **Metastatic carcinoma:** In combination with IV 5-fluorouracil-based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

► **Unlabeled uses:** Adjunctive therapy in breast cancer; renal cell carcinoma.

**Administration and Dosage**

► **Approved by the FDA:** February 26, 2004.

► **Dosage:** 5 mg/kg given once every 14 days as an IV infusion until disease progression is detected.

► **Administration:** Do not administer as an IV push or bolus. Deliver the initial bevacizumab dose over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

**Dose modification:**

**Permanent discontinuation** – Permanently discontinue bevacizumab in patients who develop GI perforation, wound dehiscence requiring medical intervention, serious bleeding, nephrotic syndrome, or hypertensive crisis.

**Temporary suspension** –

**Proteinuria:** Temporary suspension of bevacizumab is recommended in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension that is not controlled with medical management. The risk of continuation or temporary suspension of bevacizumab in patients with moderate to severe proteinuria is unknown.

**Surgery:** Suspend bevacizumab at least several weeks prior to elective surgery. Do not resume bevacizumab until the surgical incision is fully healed. Do not initiate bevacizumab for at least 28 days following major surgery. Ensure that the surgical incision is fully healed prior to initiation of bevacizumab.

► **Preparation for administration:** Withdraw the necessary amount of bevacizumab for a dose of 5 mg/kg and dilute in a total volume of 100 mL 0.9% sodium chloride injection. Discard any unused portion because the product is preservative-free.

► **Admixture incompatibilities:** Do not administer or mix bevacizumab infusions with dextrose solutions. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

► **Storage/Stability:** Refrigerate bevacizumab vials at 2° to 8°C (36° to 46°F). Diluted solutions for infusion may be stored at 2° to 8°C (36° to 46°F) for up to 8 hours. Protect bevacizumab vials from light. Store in the original carton until time of use. Do not freeze or shake.

**Actions**

► **Pharmacology:** Bevacizumab is a recombinant, humanized, monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in vitro and in vivo assay systems. 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.

► **Pharmacokinetics:** The assay used to assess bevacizumab's pharmacokinetic profile 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 bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated half life of bevacizumab was approximately 20 days (range, 11 to 50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg bevacizumab every 2 weeks was 2.8.

**Special populations** –

**Gender:** After correcting for body weight, males had a higher bevacizumab clearance vs females (0.262 L/day vs 0.207 L/day). However, in a randomized study of 813 patients, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males as compared with females.

**Tumor burden:** Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs 0.199 L/day) than patients with tumor burdens below the median. However, in a randomized trial of 813 patients, there was no evidence of lesser efficacy (hazard ratio for overall survival) in patients with higher tumor burden as compared with patients with low tumor burden.

**Contraindications**

No known contraindications (see Warnings).

**Warnings**

► **GI perforation/wound healing complications:** GI perforation and wound dehiscence, complicated by intra-abdominal abscesses, occurred at an increased incidence in patients receiving bevacizumab as compared with controls. Bevacizumab also has been shown to impair wound healing in preclinical animal models. In a clinical study, 0.3% of patients receiving bolus-IFL plus placebo, 2% of patients receiving bolus-IFL plus bevacizumab, and 4% of patients receiving 5-FU/LV (500 mg/m<sup>2</sup> 5-fluorouracil and 500 mg/m<sup>2</sup> leucovorin weekly for 6 weeks every 8 weeks) plus bevacizumab developed GI perforation, in some instances with fatal outcome. These episodes occurred with or without intra-abdominal abscesses and at various time points during treatment. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. In addition, 0.5% of patients receiving bolus-IFL plus placebo, 1% of patients receiving bolus-IFL plus bevacizumab, and 1% of patients receiving 5-FU/LV plus bevacizumab developed a wound dehiscence during study treatment.

The appropriate interval between surgery and subsequent initiation of bevacizumab required to avoid the risks of impaired wound healing has not been determined. In a clinical study, the clinical protocol did not permit initiation of bevacizumab for at least 28 days following surgery. There was 1 patient (among 501 patients receiving bevacizumab) in whom an anastomotic dehiscence occurred when bevacizumab was initiated per protocol. In this patient, the interval between surgery and initiation of bevacizumab was greater than 2 months.

Similarly, the appropriate interval between termination of bevacizumab and subsequent elective surgery required to avoid risks of impaired wound healing has not been determined. In the same study, 39 patients who were receiving bolus-IFL plus bevacizumab underwent surgery following bevacizumab therapy and, of these patients, 15% had wound healing/bleeding complications. In the same study, 25 patients in the bolus-IFL arm underwent surgery and, of these patients, 4% had wound healing/bleeding complications. The longest interval between the last dose of study drug and dehiscence was 56 days; this occurred in a patient on the bolus-IFL plus bevacizumab arm. Ensure the interval between termination of bevacizumab and subsequent elective surgery takes into consideration the calculated half life of bevacizumab (approximately 20 days).

Discontinue bevacizumab therapy in patients with GI perforation or wound dehiscence requiring medical intervention (see Administration and Dosage).

► **Hemorrhage:** Two distinct patterns of bleeding have occurred in patients receiving bevacizumab. The first is minor hemorrhage, most commonly grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events. Serious hemorrhagic events occurred primarily in patients with nonsmall cell lung cancer. In a randomized study in patients with nonsmall cell lung cancer receiving chemotherapy with or without bevacizumab, 31% of bevacizumab-treated patients with squamous cell histology and 4% of bevacizumab-treated patients with nonsquamous histology experienced life-threatening or fatal pulmonary hemorrhage as compared with 0% of patients receiving chemotherapy alone. Of the patients experiencing events of life-threatening pulmonary hemorrhage, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. These serious hemorrhagic events occurred suddenly and presented as major or massive hemoptysis.

**BEVACIZUMAB**

The risk of CNS bleeding in patients with CNS metastases receiving bevacizumab has not been evaluated because these patients were excluded from studies following development of CNS hemorrhage in a patient with a CNS metastasis in phase 1 studies.

Other serious bleeding events reported in patients receiving bevacizumab were uncommon and included GI hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. Discontinue bevacizumab treatment in patients with serious hemorrhage (ie, requiring medical intervention) and administer aggressive medical management. Do not give bevacizumab to patients with recent hemoptysis (see Administration and Dosage).

►**Hypertension:** The incidence of hypertension and severe hypertension was increased in patients receiving bevacizumab in a study (see Adverse Reactions).

Among patients with severe hypertension in the bevacizumab arms, slightly over half the patients (51%) had a diastolic reading greater than 110 associated with a systolic reading less than 200. Four months after discontinuation of therapy, persistent hypertension was present in 18 of 26 patients that received bolus-IFL plus bevacizumab and 8 of 10 patients that received bolus-IFL plus placebo. Across all clinical studies (n = 1032), development or worsening of hypertension resulted in hospitalization or discontinuation of bevacizumab in 17 patients. Four of these 17 patients developed hypertensive encephalopathy. Severe hypertension was complicated by subarachnoid hemorrhage in 1 patient.

Permanently discontinue bevacizumab in patients with hypertensive crisis. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management (see Administration and Dosage).

►**Proteinuria:** In a randomized study, the incidence and severity of proteinuria (defined as a urine dipstick reading of 1+ or greater) was increased in patients receiving bevacizumab as compared with those receiving bolus-IFL plus placebo. Urinary dipstick readings of 2+ or greater occurred in 14% of patients receiving bolus-IFL plus placebo, in 17% receiving bolus-IFL plus bevacizumab, and in 28% of patients receiving 5-FU/LV plus bevacizumab. Twenty-four-hour urine collections were obtained in patients with new onset or worsening proteinuria. None of the 118 patients receiving bolus-IFL plus placebo, 3 of 158 patients receiving bolus-IFL plus bevacizumab, and 2 of 50 patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (more than 3.5 g protein/24 h).

In a dose-ranging, placebo-controlled, randomized study of bevacizumab in patients with metastatic renal cell carcinoma, 24-hour urine collections were obtained in approximately half the patients enrolled. Among patients in whom 24-hour urine collections were obtained, 4 of 19 (21%) patients receiving bevacizumab at 10 mg/kg every 2 weeks, 2 of 14 (14%) receiving bevacizumab at 3 mg/kg every 2 weeks, and none of the 15 placebo patients experienced National Cancer Institute common toxicity criteria (NCI-CTC) grade 3 proteinuria (more than 3.5 g protein/24 h).

Nephrotic syndrome occurred in 5 of 1032 (0.5%) patients receiving bevacizumab in studies. One patient died and 1 required dialysis. In 3 patients, proteinuria decreased in severity several months after discontinuation of bevacizumab. No patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of bevacizumab.

Discontinue bevacizumab in patients with nephrotic syndrome (see Administration and Dosage). The safety of continued bevacizumab treatment in patients with moderate to severe proteinuria has not been evaluated. In most clinical studies, bevacizumab was interrupted for at least 2 g proteinuria/24 h and resumed when proteinuria was less than 2 g/24 h. Regularly monitor patients with moderate to severe proteinuria based on 24-hour collections until improvement and/or resolution is observed.

►**Congestive heart failure (CHF):** CHF, defined as grade 2 to 4 left ventricular dysfunction, was reported in 2% of patients receiving bevacizumab in studies. CHF occurred in 14% of patients receiving bevacizumab and concurrent anthracyclines. CHF occurred in 4% of patients who received prior anthracyclines and/or left chest wall irradiation. In a controlled study, the incidence was higher in patients receiving bevacizumab plus chemotherapy as compared with patients receiving chemotherapy alone. The safety of continuation or resumption of bevacizumab in patients with cardiac dysfunction has not been studied.

►**Hypersensitivity reactions:** Use bevacizumab with caution in patients with known hypersensitivity to bevacizumab or any component of this drug product.

►**Fertility impairment:** Bevacizumab may impair fertility. Dose-related decreases in ovarian and uterine weights, endometrial proliferation, number of menstrual cycles, and arrested follicular development or absent corpora lutea were observed in female cynomolgus monkeys treated with 10 or 50 mg/kg bevacizumab for 13 or 26 weeks. Following a 4- or 12-week recovery period that examined only the high-dose group, trends suggestive of reversibility were noted in the 2 females for each regimen that were assigned to recover. 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, but uterine weight decreases were still notable, corpora lutea were absent in 1 of 2 animals, and the number of menstrual cycles remained reduced (67%).

►**Elderly:** Severe adverse events that occurred at a higher incidence (2% or more) in the elderly when compared with patients younger than 65 years of age were anemia, anorexia, asthenia, CHF, constipation, deep thrombophlebitis, dehydration, diarrhea, dyspepsia, edema, epistaxis, GI hemorrhage, hypertension, hypokalemia, hyponatremia, hypotension, increased cough, leukopenia, myocardial infarction, sepsis, and voice alteration. The effect of bevacizumab on overall survival was similar in elderly patients as compared with younger patients.

►**Pregnancy: Category C.** Bevacizumab has been shown to be teratogenic in rabbits when administered in doses that are 2-fold greater than the recommended human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested.

Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of bevacizumab is likely to result in adverse effects on pregnancy. There are no adequate and well-controlled studies in pregnant women. Use bevacizumab during pregnancy or in any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. Counsel all patients regarding the potential risk of bevacizumab to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving bevacizumab, apprise her of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Also counsel patients who discontinue bevacizumab concerning the prolonged exposure following discontinuation of therapy (half life of approximately 20 days) and the possible effects of bevacizumab on fetal development.

►**Lactation:** It is not known whether bevacizumab is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown. Advise women to discontinue nursing during treatment with bevacizumab and for a prolonged period following the use of bevacizumab, taking into account the half life of the product, approximately 20 days (range, 11 to 50 days).

►**Children:** The safety and efficacy of bevacizumab in pediatric patients have not been studied. However, physeal dysplasia was observed in juvenile cynomolgus monkeys with open growth plates treated for 4 weeks with doses that were less than the recommended human dose based on mg/kg and exposure. The incidence and severity of physeal dysplasia were dose-related and were at least partially reversible upon cessation of treatment.

**Precautions**

►**Monitoring:** Monitor blood pressure every 2 to 3 weeks during bevacizumab treatment. Patients who develop hypertension on bevacizumab may require blood pressure monitoring at more frequent intervals. Continue to monitor at regular intervals the blood pressure of patients with bevacizumab-induced or exacerbated hypertension who discontinue bevacizumab.

Monitor patients receiving bevacizumab for the development or worsening of proteinuria with serial urinalysis. Further assess (eg, a 24-hour urine collection) patients with a 2+ or greater urine dipstick reading (see Warnings and Administration and Dosage).

►**Infusion reactions:** Infusion reactions with the first dose of bevacizumab were uncommon (less than 3%). Severe reactions during the infusion of bevacizumab occurred in 2 patients. One patient developed stridor and wheezing during their first dose. A second patient, receiving paclitaxel followed by bevacizumab, developed a grade 3 hypersensitivity reaction requiring hospitalization during their third infusion of bevacizumab. Both patients responded to medical management. Information on rechallenge is not available.

Interrupt bevacizumab infusion in all patients with severe infusion reactions and administer appropriate medical therapy. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with bevacizumab after experiencing a severe infusion reaction.

►**Surgery:** Do not initiate bevacizumab therapy for at least 28 days following major surgery. Ensure that the surgical incision is fully healed prior to initiation of bevacizumab. Because of the potential for impaired wound healing, suspend bevacizumab prior to elective surgery. The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half life of bevacizumab is estimated to be 20 days. Ensure the interval chosen takes into consideration the half life of the drug (see Warnings).

►**Cardiovascular disease:** Patients were excluded from participation in bevacizumab clinical trials, if, in the previous year, they had experienced clinically significant cardiovascular disease. Thus, the safety of bevacizumab in patients with clinically significant cardiovascular disease has not been adequately evaluated.

►**Immunogenicity:** As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in

**BEVACIZUMAB**

patients receiving bevacizumab has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with bevacizumab, primarily in combination with chemotherapy. High-titer human anti-bevacizumab antibodies were not detected.

**Adverse Reactions**

The most serious adverse events associated with bevacizumab were CHF (see Warnings), GI perforations/wound healing complications, hemorrhage, hypertensive crises, and nephrotic syndrome. The most common severe (grade 3 to 4) adverse events among 1032 patients receiving bevacizumab in studies were asthenia, diarrhea, hypertension, leukopenia, and pain. The most common adverse events of any severity among the 742 patients receiving bevacizumab in studies were abdominal pain, anorexia, asthenia, constipation, diarrhea, dyspnea, epistaxis, exfoliative dermatitis, headache, hypertension, nausea, pain, proteinuria, stomatitis, upper respiratory tract infection, and vomiting.

Severe and life-threatening (grade 3 and 4) adverse events that occurred at a higher incidence (2% or more) in patients receiving bolus-IFL plus bevacizumab as compared with bolus-IFL plus placebo are presented in the following table.

Bevacizumab Grade 3 and 4 Adverse Events (%)		
Adverse reaction	Arm 1 IFL + placebo (n = 396)	Arm 2 IFL + bevacizumab (n = 392)
<b>Grade 3 to 4 events</b>	<b>74</b>	<b>87</b>
<i>Cardiovascular</i>		
Deep vein thrombosis	5	9
Hypertension	2	12
Intra-abdominal thrombosis	1	3
Syncope	1	3
<i>GI</i>		
Abdominal pain	5	8
Constipation	2	4
Diarrhea	25	34
<i>Hemic/Lymphatic</i>		
Leukopenia	31	37
Neutropenia <sup>a</sup>	14	21
<i>Miscellaneous</i>		
Asthenia	7	10
Pain	5	8

<sup>a</sup> Central laboratories were collected on days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in arm 1 and 276 in arm 2.

Adverse events of any severity that occurred at a higher incidence (5% or more) in the initial phase of the study in patients receiving bevacizumab (bolus-IFL plus bevacizumab or 5-FU/LV plus bevacizumab) as compared with the bolus-IFL plus placebo arm are presented in the following table.

Bevacizumab Grade 1 to 4 Adverse Events (%)			
Adverse reaction	Arm 1 IFL + placebo (n = 98)	Arm 2 IFL + bevacizumab (n = 102)	Arm 3 5-FU/LV + bevacizumab (n = 109)
<i>Cardiovascular</i>			
Deep vein thrombosis	3	9	6
Hypertension	14	23	34
Hypotension	7	15	7
<i>CNS</i>			
Abnormal gait	0	1	5
Confusion	1	1	6
Dizziness	20	26	19
Headache	19	26	26
<i>GI</i>			
Abdominal pain	55	61	50
Anorexia	30	43	35
Colitis	1	6	1
Constipation	29	40	29
Dry mouth	2	7	4
Dyspepsia	15	24	17
Flatulence	10	11	19
GI hemorrhage	6	24	19
Stomatitis	18	32	30
Weight loss	10	15	16
Vomiting	47	52	47
<i>GU</i>			
Proteinuria	24	36	36
Urinary frequency/ urgency	1	3	6

Bevacizumab Grade 1 to 4 Adverse Events (%)			
Adverse reaction	Arm 1 IFL + placebo (n = 98)	Arm 2 IFL + bevacizumab (n = 102)	Arm 3 5-FU/LV + bevacizumab (n = 109)
<i>Metabolic/Nutritional</i>			
Bilirubinemia	0	1	6
Hypokalemia	11	12	16
<i>Respiratory</i>			
Dyspnea	15	26	25
Epistaxis	10	35	32
Upper respiratory tract infection	39	47	40
Voice alteration	2	9	6
<i>Skin/Appendages</i>			
Alopecia	26	32	6
Dry skin	7	7	20
Exfoliative dermatitis	3	3	19
Nail disorder	3	2	8
Skin discoloration	3	2	16
Skin ulcer	1	6	6
<i>Special senses</i>			
Excess lacrimation	2	6	18
Taste disorder	9	14	21
<i>Miscellaneous</i>			
Asthenia	70	74	73
Myalgia	7	8	15
Pain	55	61	62
Thrombocytopenia	0	5	5

► **Mucocutaneous hemorrhage:** Both serious and nonserious hemorrhagic events occurred at a higher incidence in patients receiving bevacizumab (see Warnings). In the 309 patients in which grade 1 to 4 events were collected, epistaxis was common and reported in 35% of patients receiving bolus-IFL plus bevacizumab compared with 10% of patients receiving bolus-IFL plus placebo. These events were generally mild in severity (grade 1) and resolved without medical intervention. Other mild to moderate hemorrhagic events reported more frequently in patients receiving bolus-IFL plus bevacizumab when compared with those receiving bolus-IFL plus placebo included GI hemorrhage (24% vs 6%), minor gum bleeding (2% vs 0%), and vaginal hemorrhage (4% vs 2%).

► **Thromboembolism:** In a clinical study, 18% of patients receiving bolus-IFL plus bevacizumab and 15% of patients receiving bolus-IFL plus placebo experienced a grade 3 to 4 thromboembolic event. The incidence of the following grade 3 and 4 thromboembolic events were higher in patients receiving bolus-IFL plus bevacizumab compared with patients receiving bolus-IFL plus placebo: Cerebrovascular events (4 vs 0 patients), deep venous thrombosis (34 vs 19), intra-abdominal thrombosis (13 vs 5), and myocardial infarction (6 vs 3). In contrast, the incidence of pulmonary embolism was higher in patients receiving bolus-IFL plus placebo (16 vs 20).

In the same study, 14% of patients who received bolus-IFL plus bevacizumab and 8% of patients who received bolus-IFL plus placebo had a thromboembolic event and received full-dose warfarin. Two patients in each treatment arm (4 total) developed bleeding complications. In the 2 patients treated with full-dose warfarin and bevacizumab, these events were associated with marked elevations in their international normalized ratio. Twenty-one percent of patients receiving bolus-IFL plus bevacizumab and 3% of patients receiving bolus-IFL developed an additional thromboembolic event.

► **Other adverse events:** The following other serious adverse events are considered unusual in cancer patients receiving cytotoxic chemotherapy and occurred in at least 1 subject treated with bevacizumab in clinical studies.

**GI** – Anastomotic ulceration, intestinal necrosis, intestinal obstruction, mesenteric venous occlusion.

**Miscellaneous** – Hyponatremia, pancytopenia, polyserositis, ureteral stricture.

**Overdosage**

The maximum tolerated dose of bevacizumab has not been determined. The highest dose tested in humans (20 mg/kg IV) was associated with headache in 9 of 16 patients and with severe headache in 3 of 16 patients.

**Patient Information**

Counsel all patients regarding the potential risk of bevacizumab to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving bevacizumab, apprise her of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Also counsel patients who discontinue bevacizumab concerning the prolonged exposure following discontinuation of therapy (half life of approximately 20 days) and the possible effects of bevacizumab on fetal development.