ALYMSYS- bevacizumab-maly injection, solution
Amneal Pharmaceuticals LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALYMSYSsafely and effectively. See full prescribing information for ALYMSYS. ALYMSYS® (bevacizumab-maly) injection, for intravenous use Initial U.S. Approval: 2022 ALYMSYS (bevacizumab-maly) is biosimilar* to AVASTIN (bevacizumab)

INDICATIONS AND USAGE

Alymsys is a vascular endothelial growth factor inhibitor indicated for the treatment of: (1)

- 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 bevacizumab product-containing regimen. (1.1)

Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer. (1.1) (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 paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (1.6)

DOSAGE AND ADMINISTRATION

Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys for 28 days following major surgery and until adequate wound healing. (2.1) (2)
Metastatic colorectal cancer (2.2) (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 bevacizumab product-containing regimen

First-line non−squamous non−small cell lung cancer (2.3) (2)

- 15 mg/kg every 3 weeks with carboplatin and paclitaxel
  Recurrent glioblastoma (2.4) (2)
- 10 mg/kg every 2 weeks
  Metastatic renal cell carcinoma (2.5) (2)
- 10 mg/kg every 2 weeks with interferon alfa
  Persistent, recurrent, or metastatic cervical cancer (2.6) (2)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan
  Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7) (2)
- 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

Administer as an intravenous infusion (2.9) (2)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None (4) (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: In patients who experience wound healing complications during Alymsys treatment, withhold Alymsys until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of bevacizumab products after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis. (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 Alymsys 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, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2) (8)

See 17 for PATIENT COUNSELING INFORMATION. (8)

***Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of ALYMSYS has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information. (8)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

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

Alymsys, 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 bevacizumab product-containing regimen.

Limitations of Use: Alymsys 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

Alymsys, 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

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

1.4 Metastatic Renal Cell Carcinoma

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

1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Alymsys, 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

Alymsys, 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys until at least 28 days following major surgery and until adequate wound healing.

2.2 Metastatic Colorectal Cancer

The recommended dosage when Alymsys 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 bevacizumab product-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

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).

2.8 Dosage Modifications for Adverse Reactions

Table 1 describes dosage modifications for specific adverse reactions. No dose reductions for Alymsys 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 • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Alymsys
		Withhold Alymsys until adequate wound healing. The safety of

Wound Healing Complications *[see Warnings and Precautions (5.2)]*.	• Any	resumption of bevacizumab products after resolution of wound healing complications has not been established.
	• Necrotizing fasciitis	Discontinue Alymsys
Hemorrhage *[see Warnings and Precautions (5.3)]*.	• Grade 3 or 4	Discontinue Alymsys
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Alymsys
Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*.	• Arterial thromboembolism, severe	Discontinue Alymsys
	• Venous thromboembolism, Grade 4	Discontinue Alymsys
Hypertension *[see Warnings and Precautions (5.6)]*.	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Alymsys
	• Hypertension, severe	Withhold Alymsys if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*.	• Any	Discontinue Alymsys
Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.	• Nephrotic syndrome	Discontinue Alymsys
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Alymsys until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.	• Severe	Discontinue Alymsys
	• 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 Alymsys

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 Alymsys 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 Alymsys solution at 2°C to 8°C (36°F to 46°F) for up to 12 hours.
- No incompatibilities between Alymsys 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 bevacizumab products 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 bevacizumab products 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 Alymsys 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 bevacizumab 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 bevacizumab and 4% in patients who did not receive bevacizumab. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received bevacizumab and 0.7% in patients who did not receive bevacizumab *[see Adverse Reactions (6.1)]*.

In patients who experience wound healing complications during Alymsys treatment, withhold Alymsys until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following major surgery and until adequate wound healing. The safety of resumption of bevacizumab products after resolution of wound healing complications has not been established *[see Dosage and Administration (2.8)]*.

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

5.3 Hemorrhage

Bevacizumab products 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 bevacizumab compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3 to 5 hemorrhagic events ranged from 0.4% to 7% in patients receiving bevacizumab *[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 bevacizumab with chemotherapy compared to none of the patients receiving chemotherapy alone.

Do not administer Alymsys to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3 to 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 bevacizumab compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3 - 5 ATE was 5% in patients receiving bevacizumab 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 bevacizumab products 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 to 4 VTE occurred in 11% of patients receiving bevacizumab with chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grades 3 to 4 VTE was 5% in patients receiving bevacizumab with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Alymsys in patients with a Grade 4 VTE, including pulmonary embolism.

5.6 Hypertension

Severe hypertension occurred at a higher incidence in patients receiving bevacizumab products 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 Alymsys. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Alymsys - induced or -exacerbated hypertension after discontinuing Alymsys. Withhold Alymsys 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 Alymsys in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing bevacizumab products, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating bevacizumab products 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 bevacizumab 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 bevacizumab. 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 bevacizumab 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 bevacizumab 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 to 4 proteinuria resolved in 74% of patients. Bevacizumab was reinitiated in 42% of patients. Of the 113 patients who reinitiated bevacizumab, 48% experienced a second episode of Grades 2 to 4 proteinuria.

Nephrotic syndrome occurred in <1% of patients receiving bevacizumab 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 5,805 patients who received bevacizumab with chemotherapy and 3,713 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 bevacizumab. Serum creatinine levels did not return to baseline in approximately one-third of patients who received bevacizumab.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Alymsys 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, bevacizumab

products 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 Alymsys 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 bevacizumab with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing bevacizumab, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving bevacizumab. 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 bevacizumab products on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Alymsys *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

5.12 Congestive Heart Failure (CHF)

Alymsys is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab arm compared to 82% in the placebo arm. Discontinue Alymsys 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 bevacizumab in 4,463 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),

or other cancers at the recommended dose and schedule for a median of 6 to 23 doses. The most common adverse reactions observed in patients receiving bevacizumab 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, bevacizumab 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 bevacizumab was evaluated in 392 patients who received at least one dose of bevacizumab in a double-blind, active-controlled study (AVF2107g), which compared bevacizumab (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, bevacizumab with bolus-IFL, or bevacizumab 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 Bevacizumabvs. Placebo in Study AVF2107g

Adverse Reaction[a]	**Bevacizumabwith 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%

a NCI-CTC version 3

In Combination with FOLFOX4

The safety of bevacizumab 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, bevacizumab (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or bevacizumab alone (10 mg/kg every 2 weeks). Bevacizumab 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 to 5 hematologic occurring at a higher incidence (≥ 2%) in patients receiving bevacizumab 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 bevacizumab was evaluated as first-line treatment in 422 patients with

unresectable NSCLC who received at least one dose of bevacizumab 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 bevacizumab (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive bevacizumab continued to receive bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab and are considered safety evaluable *[see Clinical Studies (14.4)]*. Patients were randomized (2:1) to receive bevacizumab (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 bevacizumab with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving bevacizumab with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

The safety of bevacizumab was evaluated in 337 patients who received at least one dose of bevacizumab in a multicenter, double-blind study (BO17705) in patients with mRCC. Patients who had undergone a nephrectomy were randomized (1:1) to receive either bevacizumab (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 Bevacizumabvs. Placebo with Interferon Alfa in Study BO17705

Adverse Reaction[a]	**Bevacizumabwith 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%
a NCI-CTC version 3		

The following adverse reactions were reported at a 5-fold greater incidence in patients receiving bevacizumab 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 bevacizumab was evaluated in 218 patients who received at least one dose of bevacizumab 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 bevacizumab (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without bevacizumab (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 bevacizumab 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 Bevacizumabwith Chemotherapy vs. Chemotherapy Alone in Study GOG-0240

Adverse Reaction[a]	**Bevacizumabwith 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%
a NCI-CTC version 3		

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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

The safety of bevacizumab was evaluated in 179 patients who received at least one dose of bevacizumab in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 Bevacizumabwith Chemotherapy vs. Chemotherapy Alone in Study MO22224

Adverse Reaction[a]	**Bevacizumabwith 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%
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 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 bevacizumab products. 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 Alymsyson Other Drugs

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when bevacizumab was administered in combination with these drugs; however, 3 of the 8 patients receiving bevacizumab 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 their mechanism of action *[see Clinical Pharmacology (12.1)]*, bevacizumab products may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of bevacizumab products 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 to 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 products 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 from bevacizumab products, advise women not to breastfeed during treatment with Alymsys and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Bevacizumab products 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 Alymsys and for 6 months after the last dose.

Infertility

Females

Bevacizumab products increase 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 Alymsys. Long-term effects of bevacizumab products on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without bevacizumab, the incidence of ovarian failure was higher in patients who received bevacizumab with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing bevacizumab 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 bevacizumab products 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 received bevacizumab. Bevacizumab products are 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 bevacizumab 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 1,745 patients from five randomized, controlled studies, 35% of patients were ≥65 years old. The overall incidence of ATE was increased in all patients receiving bevacizumab 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-maly is a vascular endothelial growth factor inhibitor. Bevacizumab-maly is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab-maly has an approximate molecular weight of 149 kDa. Bevacizumab-maly is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Alymsys (bevacizumab-maly) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Alymsys contains bevacizumab-maly 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-maly, 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 products bind VEGF and prevent 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 bevacizumab 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 of bevacizumab 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 bevacizumab as compared to females and patients with low tumor burden.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

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

Bevacizumab products 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

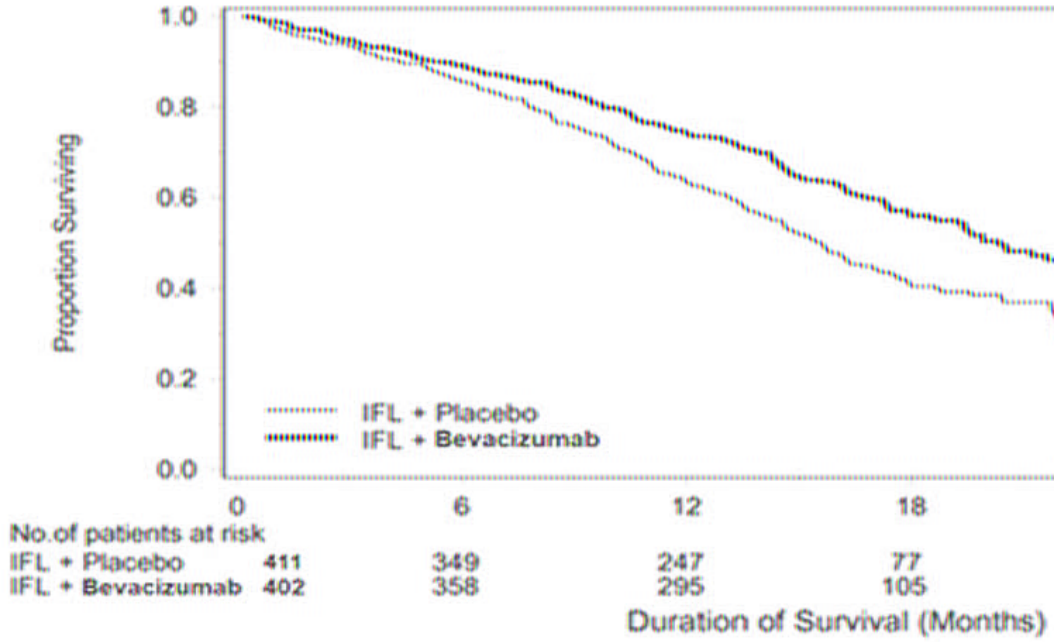
The safety and efficacy of bevacizumab was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2, fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), bevacizumab (5 mg/kg every 2 weeks) with bolus-IFL, or bevacizumab (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the bevacizumab with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Bevacizumab 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 bevacizumab improved survival across subgroups defined by age (< 65 years, ≥65 years) and sex. Results are presented in Table 6 and Figure 1.

Table 6: Efficacy Results in Study AVF2107g		
Efficacy Parameter	**Bevacizumab 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 χ^2 test		

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



Among the 110 patients randomized to bevacizumab 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 bevacizumab 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), bevacizumab

(10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or bevacizumab alone (10 mg/kg every 2 weeks). Bevacizumab was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The bevacizumab 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 bevacizumab 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 bevacizumab with FOLFOX4.

Study TRC-0301

The activity of bevacizumab 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 bevacizumab 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 bevacizumab-containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received bevacizumab for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing bevacizumab as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without bevacizumab (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 bevacizumab as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of bevacizumab 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 7 and Figure 2.

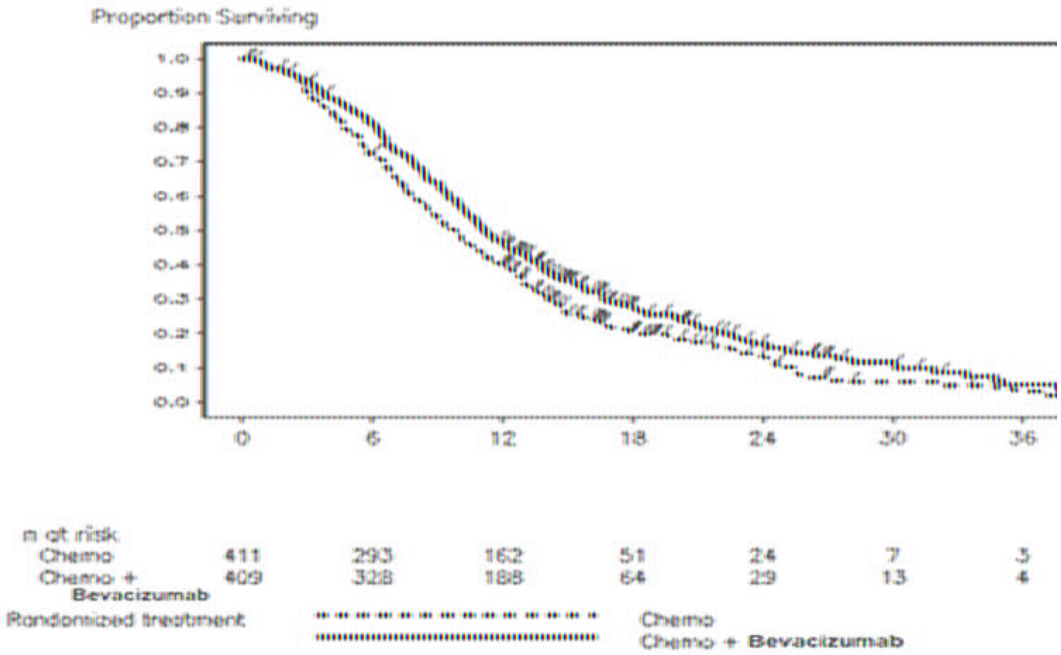
Table 7: Efficacy Results in Study ML18147

Efficacy Parameter	**Bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for bevacizumab with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for bevacizumab 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 bevacizumab with FOLFOX4 versus FOLFOX4 alone and bevacizumab with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the bevacizumab-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 bevacizumab 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 bevacizumab to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

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

Study E4599

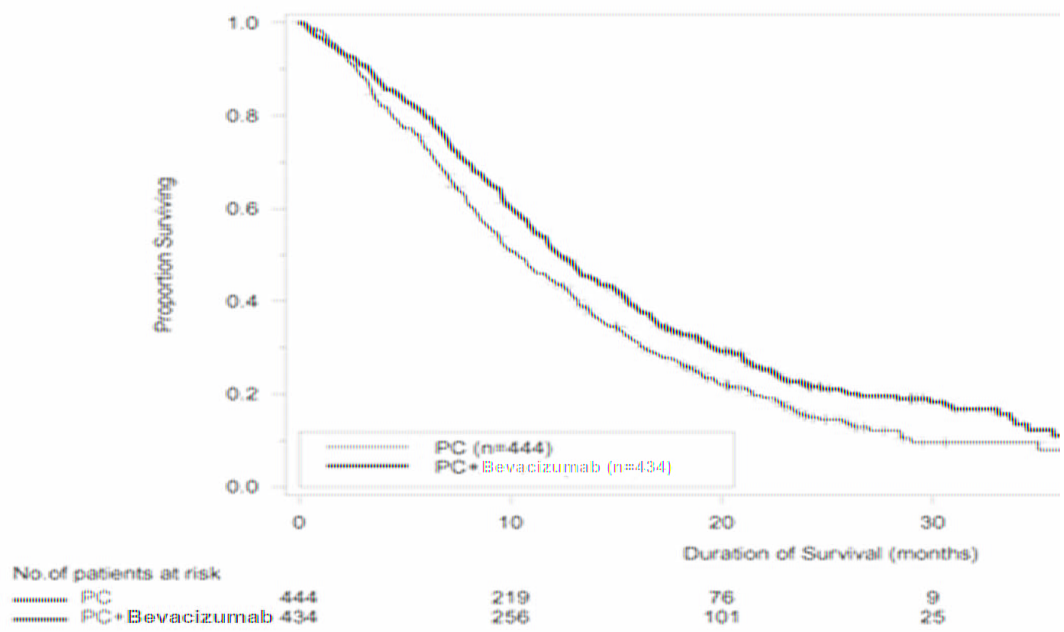
The safety and efficacy of bevacizumab as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large,

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 bevacizumab 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive bevacizumab continued to receive bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 1,043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, bevacizumab 7.5 mg/kg or bevacizumab 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 bevacizumab-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for bevacizumab 7.5

mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for bevacizumab 15 mg/kg]. The addition of bevacizumab 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 bevacizumab 7.5 mg/kg and HR 1.03 (95%

CI: 0.86, 1.23), p-value of 0.761 for bevacizumab 15 mg/kg].

14.4 Recurrent Glioblastoma

Study EORTC 26101

The safety and efficacy of bevacizumab 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 bevacizumab (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 bevacizumab 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 bevacizumab 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 bevacizumab with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the bevacizumab 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 bevacizumab with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E

The efficacy and safety of bevacizumab 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 bevacizumab were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and bevacizumab versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either bevacizumab (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.

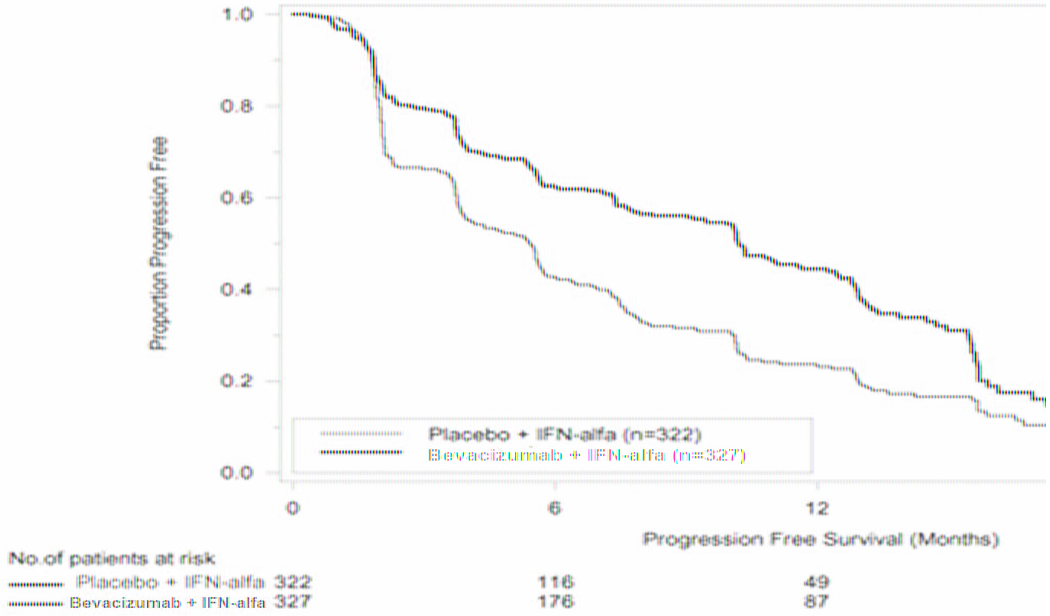
The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3 to 5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving bevacizumab 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 bevacizumab 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 bevacizumab were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing bevacizumab 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 bevacizumab, or paclitaxel and topotecan with or without bevacizumab.

The dosing regimens for bevacizumab, 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 bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with bevacizumab, Days 1 to 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 8.

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

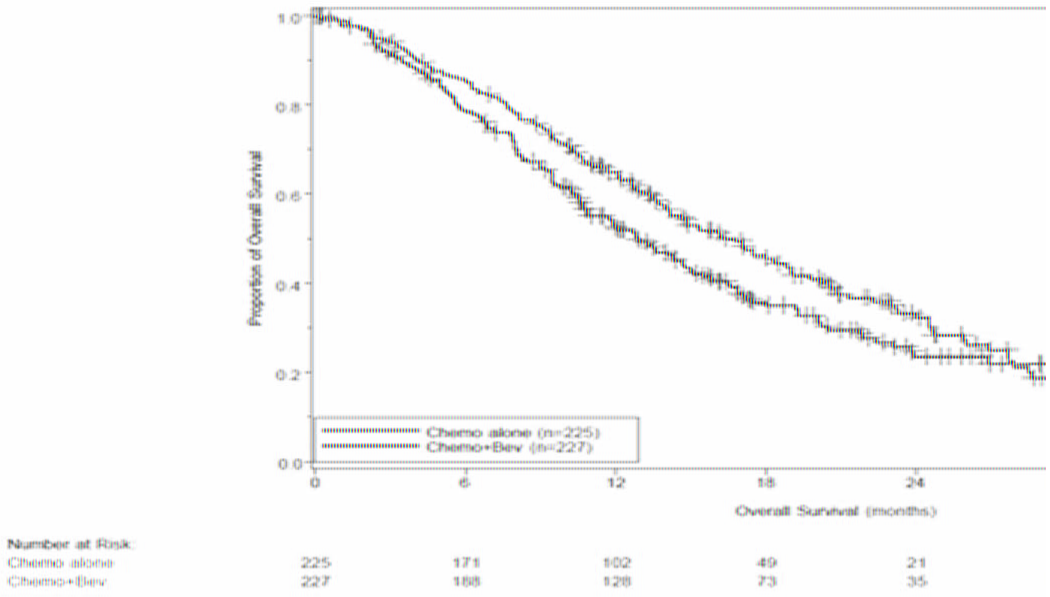


Table 8: Efficacy Results in Study GOG-0240		
Efficacy Parameter	**Bevacizumab with Chemotherapy (N=227)**	**Chemotherapy (N=225)**
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	
[a] Kaplan-Meier estimates.		
[b] log-rank test (stratified).		

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

Table 9: Efficacy Results in Study GOG-0240		
Efficacy Parameter	**Topotecan and Paclitaxel with or without Bevacizumab (N=223)**	**Cisplatin and Paclitaxel with or without Bevacizumab (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 bevacizumab 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 bevacizumab with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

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

Study MO22224

The safety and efficacy of bevacizumab were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing bevacizumab 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 bevacizumab 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 bevacizumab 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 10 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 11.

Table 10: Efficacy Results in Study MO22224

Efficacy Parameter	**Bevacizumabwith 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 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224

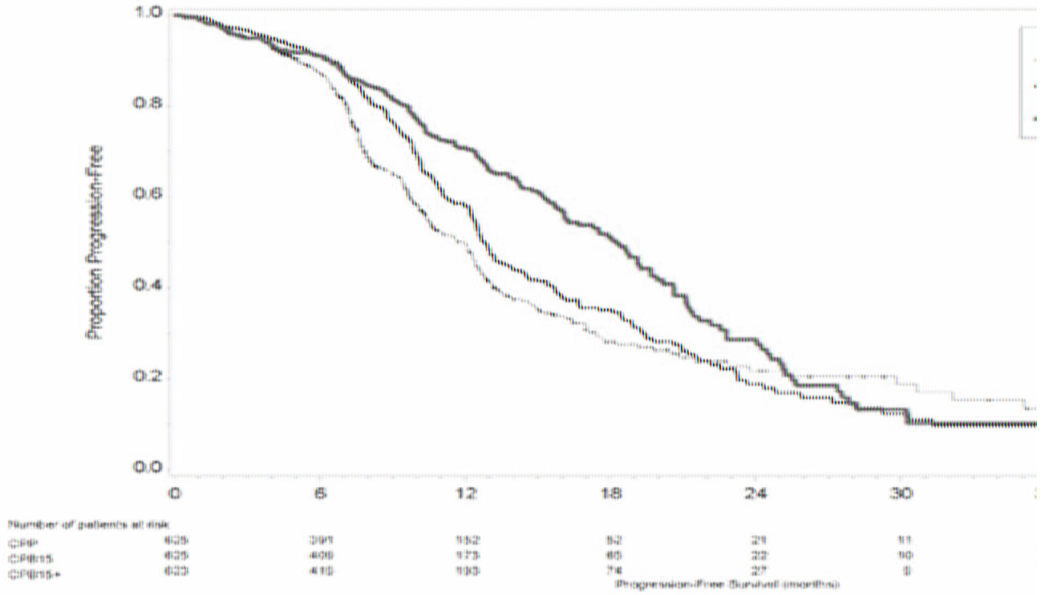


Table 11: Efficacy Results in Study MO22224 by Chemotherapy						
Efficacy Parameter	**Paclitaxel**		**Topotecan**		**Pegylated Liposomal Doxorubicin**	
	Bevacizumabwith Chemotherapy (N=60)	**Chemotherapy (N=55)**	**Bevacizumabwith Chemotherapy (N=57)**	**Chemotherapy (N=63)**	**Bevacizumabwith Chemotherapy (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						

16 HOW SUPPLIED

Alymsys (bevacizumab-maly) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied in a carton containing single-dose vial in the following strengths and packaging configurations:

- 100 mg/4 mL (25 mg/mL): carton of one vial (NDC 70121-1754-1); carton of 10 vials (NDC 70121-1754-7).
- 400 mg/16 mL (25 mg/mL): carton of one vial (NDC 70121-1755-1); carton of 10

vials (NDC 70121-1755-7).

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: Bevacizumab products 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: Bevacizumab products can increase the risk of wound healing complications. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Bevacizumab products 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: Bevacizumab products increase 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: Bevacizumab products can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their health care 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 bevacizumab products 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: Bevacizumab products increase the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Alymsys 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: Bevacizumab products can cause infusion-related reactions. Advise patients to contact their health care provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

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

Embryo-Fetal Toxicity: Advise female patients that bevacizumab products may cause fetal harm and to inform their health care 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 Alymsys and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Bevacizumab products 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 Alymsys and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:

Amneal Pharmaceuticals LLC

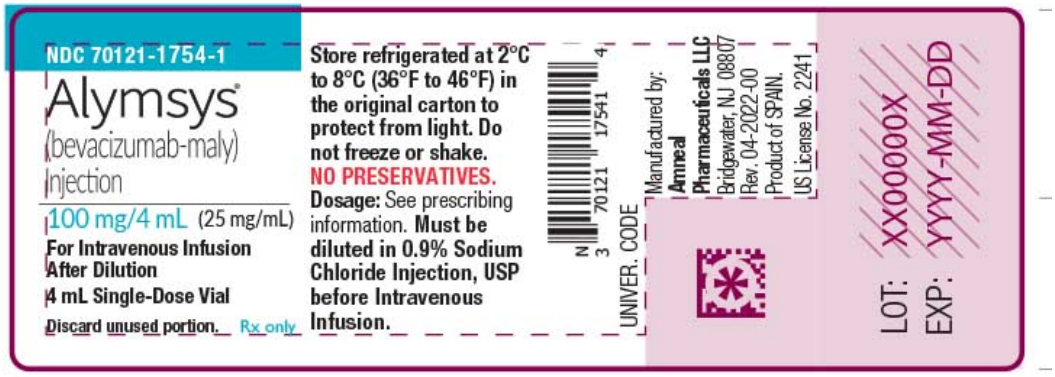
Bridgewater, NJ 08807

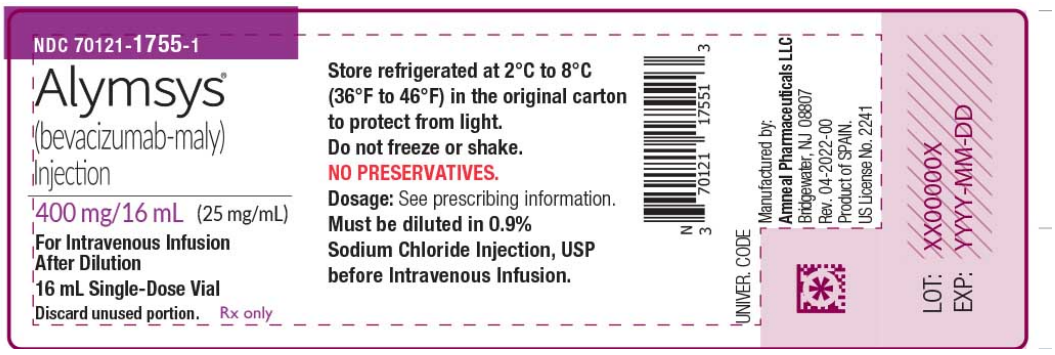
Product of Spain

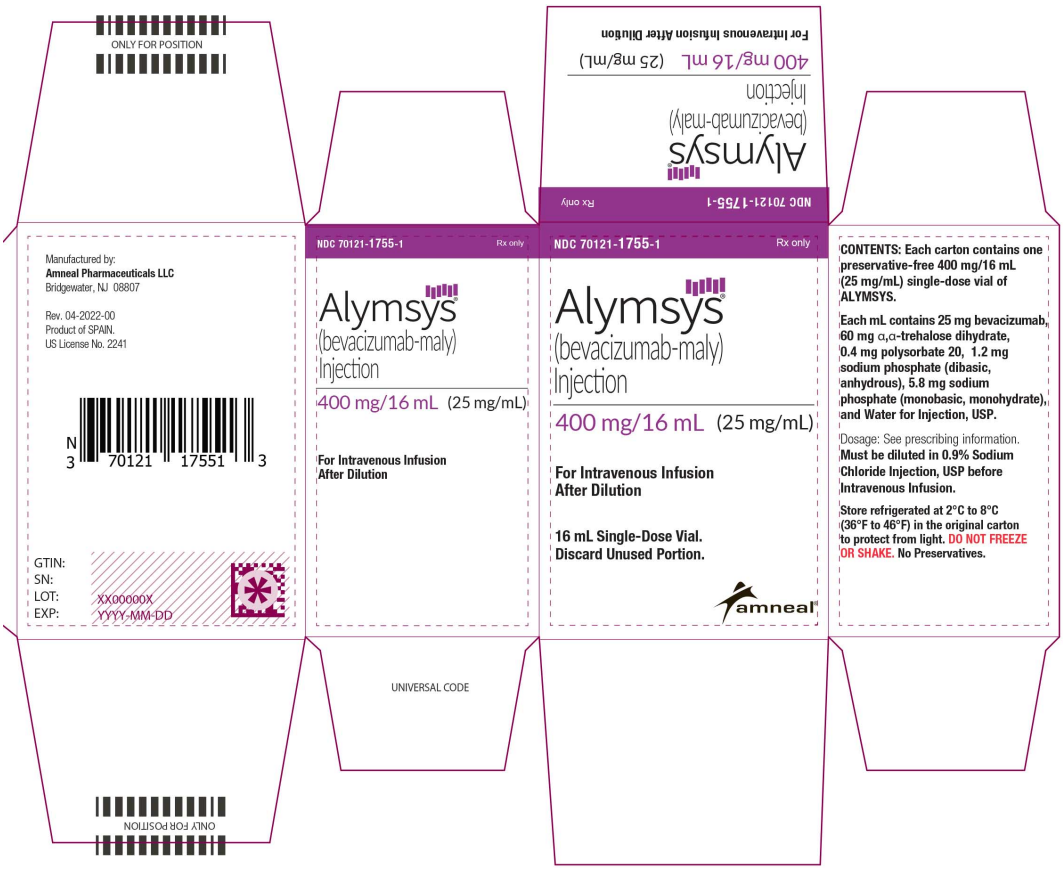
US License No. 2241

Rev. 04-2022-01

PRINCIPAL DISPLAY PANEL







ALYMSYS

bevacizumab-maly injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70121-1754
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BEVACIZUMAB (UNII: 2S9ZZM9Q9V) (BEVACIZUMAB - UNII:2S9ZZM9Q9V)	BEVACIZUMAB	100 mg in 4 mL

Inactive Ingredients	
Ingredient Name	**Strength**
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	240 mg in 4 mL
POLYSORBATE 20 (UNII: 7T1F30V5YH)	1.6 mg in 4 mL
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	4.8 mg in 4 mL
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	23.2 mg in 4 mL
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70121-1754-7	10 in 1 CARTON	04/15/2022	04/15/2023
1		4 mL in 1 VIAL; Type 0: Not a Combination Product		
2	NDC:70121-1754-1	1 in 1 CARTON	04/15/2022	
2		4 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761231	04/15/2022	10/31/2028

ALYMSYS

bevacizumab-maly injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70121-1755
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BEVACIZUMAB (UNII: 2S9ZZM9Q9V) (BEVACIZUMAB - UNII:2S9ZZM9Q9V)	BEVACIZUMAB	400 mg in 16 mL

Inactive Ingredients

Ingredient Name	Strength
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	960 mg in 16 mL
POLYSORBATE 20 (UNII: 7T1F30V5YH)	6.4 mg in 16 mL
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	19.2 mg in 16 mL
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	92.8 mg in 16 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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1		16 mL in 1 VIAL; Type 0: Not a Combination Product		
2	NDC:70121-1755-1	1 in 1 CARTON	04/15/2022	
2		16 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761231	04/15/2022	10/31/2028

Labeler - Amneal Pharmaceuticals LLC (827748190)

Establishment

Name	Address	ID/FEI	Business Operations
Universal Farma SL		468272833	analysis(70121-1754, 70121-1755) , manufacture(70121-1754, 70121-1755) , sterilize(70121-1754, 70121-1755)