

BEVASTIM

Bevacizumab Injection

Concentrate for Solution for IV Infusion

COMPOSITION

Bevastim Injection: Each vial contains Bevacizumab INN 100 mg (25 mg/ml).

DESCRIPTION

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 contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

CLINICAL PHARMACOLOGY

Mode of Action

Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces tumour angiogenesis, thereby inhibiting tumour growth. Administration of Bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

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). The estimated half-life of Bevacizumab was approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

The clearance of Bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. 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. In Study, 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. The relationship between Bevacizumab exposure and clinical outcomes has not been explored.

INDICATIONS

Metastatic Colorectal Cancer (mCRC)

Bevacizumab is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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

Metastatic Renal Cell Carcinoma (mRCC)

Bevacizumab is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

Glioblastoma

Bevacizumab as a single agent is indicated for the treatment of patients with Glioblastoma.

DOSAGE AND ADMINISTRATION

Administration

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.

- Do not initiate Bevacizumab until at least 28 days following major surgery. Administer Bevacizumab after the surgical incision has fully healed.
- 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 infusion over 60 minutes is tolerated.

Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC): The recommended doses are 5 mg/kg in combination with bolus IFL or 10 mg/kg in combination with FOLFOX 4 every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks when used in combination with intravenous 5-FU-based chemotherapy.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC): The recommended dose is 7.5 mg or 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel. Bevacizumab is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Bevacizumab as a single agent until disease progression.

Metastatic Renal Cell Carcinoma (mRCC): The recommended dose is 10 mg/kg every 2 weeks.

Glioblastoma: The recommended dose is 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks.

Dose Modifications

There are no recommended dose reductions.

Discontinue Bevastim for: Gastrointestinal perforations, wound dehiscence and wound healing complications requiring medical interventions, serious hemorrhage, severe arterial thromboembolic events, hypertensive crisis or hypertensive encephalopathy, reversible posterior leukoencephalopathy syndrome (RPLS), nephrotic syndrome.

Temporarily suspend Bevastim for at least 4 weeks prior to elective surgery or severe hypertension not controlled with medical management or moderate to severe proteinuria pending further or severe infusion reactions.

Special dosage instructions

Children and adolescents: The safety and efficacy of Bevacizumab in children and adolescents have not been established.

Elderly: No dose adjustment is required in the elderly.

Renal impairment: The safety and efficacy of Bevacizumab have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of Bevacizumab have not been studied in patients with hepatic impairment.

Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of Bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection. Discard any unused portion left in a vial, as the product contains no preservatives. Diluted Bevacizumab solutions for infusion may be stored at 2°C-8°C for up to 8 hours. No incompatibilities between Bevacizumab and polyvinylchloride or polyolefin bags have been observed. **DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.**

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Non-Gastrointestinal Fistula Formation:** Discontinue Bevacizumab if fistula formation occurs.
- Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction):** Discontinue Bevacizumab for severe ATE.
- Hypertension:** Monitor blood pressure and treat hypertension. Temporarily suspend Bevacizumab if not medically controlled. Discontinue Bevacizumab for hypertensive crisis or hypertensive encephalopathy.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Discontinue Bevacizumab
- Proteinuria:** Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend Bevacizumab for moderate proteinuria.
- Infusion Reactions:** Stop for severe infusion reactions.
- Ovarian Failure:** Inform females of reproductive potential of the risk of ovarian failure with Bevacizumab.

ADVERSE EFFECTS

Most common adverse reactions are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder and exfoliative dermatitis.

DRUG INTERACTIONS

Effect of antineoplastic agents on Bevacizumab pharmacokinetics: No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on Bevacizumab pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of Bevacizumab in patients receiving Bevacizumab monotherapy compared to patients receiving Bevacizumab in combination with interferon alfa-2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of Bevacizumab on the pharmacokinetics of other antineoplastic agents: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of Bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38. No significant effect of Bevacizumab on the pharmacokinetics of capecitabine and its metabolites and on the pharmacokinetics of oxaliplatin as determined by measurement of free and total platinum.

Results from one trial in renal cancer patients demonstrated no significant effect of Bevacizumab on the pharmacokinetics of interferon alfa-2a. The potential effect of Bevacizumab on the pharmacokinetics of cisplatin and gemcitabine was investigated in non-squamous NSCLC patients. Trial results demonstrated no significant effect of Bevacizumab on the pharmacokinetics of cisplatin.

Combination of Bevacizumab and sunitinib malate: Combinations of Bevacizumab with another medicine sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects.

Combination with platinum- or taxane-based therapies: Increased rates of severe neutropenia, febrile neutropenia or infection with or without severe neutropenia have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

Radiotherapy: The safety and efficacy of concomitant administration of radiotherapy and Bevacizumab has not been established.

EGFR monoclonal antibodies in combination with Bevacizumab chemotherapy regimens: No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with Bevacizumab-containing chemotherapy. In patients with mCRC the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS and with increased toxicity compared with Bevacizumab plus chemotherapy alone.

USE IN SPECIFIC POPULATIONS

Women of childbearing potential

Women of childbearing potential have to use effective contraception during (and up to 6 months after) treatment.

Pregnancy

Pregnancy Category C. Bevacizumab is contraindicated in pregnancy.

Breast-feeding: It is not known whether Bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and Bevacizumab could harm infant growth and development, women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of Bevacizumab.

Fertility: Bevacizumab increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Bevacizumab. After discontinuation of Bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with Bevacizumab on fertility are unknown.

OVERDOSE

The highest dose tested in humans (20 mg/kg body weight, IV) was associated with severe migraine in several patients. Treatment of overdose should consist of general supportive measures.

PHARMACEUTICAL INFORMATION

Storage condition

Store the vial in original carton at 2°C to 8°C. Protect from light. Do not freeze or shake. Keep out of the reach of children.

Infusion solutions should be used immediately after dilution. Diluted Bevastim solutions may be stored at 2°C - 8°C for up to 8 hours.

Presentation and Packaging

Bevastim Injection: Each commercial box contains 1 vial of 4 ml solution.

Manufactured By
**BEACON**
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LF14801