Bevec®

بی ویک

(Bevacizumab)

COMPOSITION:
Bevec® 400mg/16ml
Active Ingredient:
Bevacizumab 25mg per ml

Bevec® 100mg/4ml
Active Ingredient:
Bevacizumab 25mg per ml

Concentrate for solution for infusion
(As per innovator's specs.)

DESCRIPTION
Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

CLINICAL PHARMACOLOGY

Mechanism of Action
Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamics
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
Bevacizumab was administered as an IV infusion according to clinical trials data. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution
The typical value for central volume (Vc) was 2.73 L and 3.28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (Vp) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger Vc (+ 20%) than female patients.

Metabolism
The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

Elimination
The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.
Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

INDICATIONS

Metastatic Colorectal Cancer
Bevacizumab, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with metastatic colorectal cancer (mCRC). Bevacizumab, 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 containing regimen.
Limitations of Use: Bevacizumab is not indicated for adjuvant treatment of colon cancer.

First-Line treatment of Non-Squamous Non–Small Cell Lung Cancer
Bevacizumab, 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).

Metastatic breast cancer (mBC)
Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Bevacizumab in combination with capecitabine.

Recurrent Glioblastoma
Bevacizumab is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

Metastatic Renal Cell Carcinoma
Bevacizumab, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

Persistent, Recurrent, or Metastatic Cervical Cancer
Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Bevacizumab, in combination with carboplatin and paclitaxel, followed by Bevacizumab as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
Bevacizumab, 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.
Bevacizumab, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Bevacizumab as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Persistent, Recurrent, or Metastatic Carcinoma of the Cervix
Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

Hepatocellular Carcinoma
Bevacizumab, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

DOSAGE AND ADMINISTRATION

Adult dosage

Metastatic Colorectal Cancer
The recommended dosage when Bevacizumab 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-containing regimen.

First-Line treatment of Non-Squamous Non-Small Cell Lung Cancer
The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

Metastatic breast cancer (mBC)
The recommended dose of Bevacizumab is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

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

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

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.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Stage III or IV Disease Following Initial Surgical Resection
The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Bevacizumab 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Hepatocellular Carcinoma
The recommended dosage is 15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Recurrent Disease

Platinum Resistant
The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).
The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive
Bevacizumab is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Bevacizumab as single agent until disease progression. The recommended dose of Bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Dosage Adjustment in Specific population

Pediatric dosage
The safety and effectiveness of Bevacizumab in pediatric patients have not been established.

Dosage adjustment in Renal impairment
The safety and efficacy have not been studied in patients with renal impairment

Dosage adjustment in Hepatic impairment
The safety and efficacy have not been studied in patients with hepatic impairment.

Administration requirements
Do not administer Bevacizumab until at least 28 days following surgery and the wound is fully healed.
The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
It should not be administered as an intravenous push or bolus. Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Precautions to be taken before handling or administering the medicinal product
Bevacizumab infusions should not be administered or mixed with glucose solutions.

Special precautions for disposal and other handling
Bevacizumab should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.
The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions, the necessary amount of Bevacizumab can be diluted with 0.9 % sodium chloride solution for injection to a total volume of 100 ml.
Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.
No incompatibilities between Bevacizumab and polyvinyl chloride or polyolefine bags or infusion sets have been observed.
Bevacizumab is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Dosage Modifications for Adverse Reactions
There are no recommended dose reductions.

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae	Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Bevacizumab
Wound Healing Complications	Any	Withhold Bevacizumab until adequate wound healing.The safety of resumption of Bevacizumab after resolution of wound healing complications has not been established.
	Necrotizing fasciitis	Discontinue Bevacizumab
Hemorrhage	Grade 3 or 4	Discontinue Bevacizumab
	Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Bevacizumab
Thromboembolic Events	Arterial thromboembolism, severe	Discontinue Bevacizumab
	Venous thromboembolism, Grade 4	Discontinue Bevacizumab
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Bevacizumab
	• Hypertension, severe	Withhold Bevacizumab if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES)	Any	Discontinue Bevacizumab
Renal Injury and Proteinuria	Nephrotic syndrome	Discontinue Bevacizumab
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Bevacizumab until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions	Severe	Discontinue Bevacizumab
	Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	Mild, clinically insignificant	Decrease infusion rate

CONTRAINDICATIONS
• Hypersensitivity to the active substance or to any of the excipients.
• Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
• Pregnancy

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforations and Fistulae
Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal Fistulae
Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-Gastrointestinal Fistulae
Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue Bevacizumab in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Bevacizumab should be considered.

Wound Healing Complications
Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.
Necrotizing fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension
An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Proteinuria
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4$ of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome.

Arterial thromboembolism
In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.
Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with Bevacizumab.
Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions.

Venous thromboembolism
Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under Bevacizumab treatment.
Patients treated for persistent, recurrent, or metastatic cervical cancer with Bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.
Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.

Haemorrhage
Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Bevacizumab therapy.
Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomized clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and Bevacizumab treatment discontinued in cases of intracranial bleeding.
There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly.

Pulmonary haemorrhage/haemoptysis
Patients with non-small cell lung cancer treated with bevacizumab may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 ml of red blood) should not be treated with Bevacizumab.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Congestive heart failure (CHF)
Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Bevacizumab. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.
CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment.

Neutropenia and infections
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions/infusion reactions
Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of Bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (ONJ)
Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use
Bevacizumab is not formulated for intravitreal use.

Eye disorders
Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab

compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use
A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.
A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

Ovarian failure/fertility
Bevacizumab may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Bevacizumab.

Effects on ability to drive and use machines
Bevacizumab has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with Bevacizumab use. If patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

ADVERSE REACTIONS

Table 1: Adverse Reactions by Frequency

System organ class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis [a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]				
Metabolism and nutrition disorders	Anorexia Hypomagnesaemia Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysgeusia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalo-pathy syndrome [a,b,d]	Hypertensive encepha-lopathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d] Deep vein thrombosis				Renal thrombotic microangiopathy[a,b] Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Epistaxis, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal Disorder, Proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b] Non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure	Pelvic Pain				
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.
[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients.
[d] For additional information refer below within section "Further information on selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in pediatric population only.

Table 2: Severe Adverse Reactions by Frequency

System organ class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising fasciitis[c]
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders						Hypersensitivity, infusion reactions[a,b,c]
Metabolism and nutrition disorders		Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalo-pathy syndrome [a,b,c], Hypertensive encephalopathy[c]
Cardiac disorders		Congestive heart failure[a,b], Supraventri-cular tachycardia				
Vascular disorders	Hypertension[a,b]	Thromboembo-lism arterial[a,b], Haemorrhage[a,b], Thromboem-bolism (venous)[a,b] Deep vein thrombosis				Renal thrombotic microangiopathy[b], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b], Gastrointestinal ulcer[c], Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation [b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b],Palmar-plantar erythrodysaes-thesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular weakness, Back Pain				Osteonecrosis of the jaw[b,c]
Renal and urinary disorders		Proteinuria[a,b]				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure[a,b]
Congenital, familial, and genetic disorder						Foetal abnormalities[a,c]
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal Inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the postmarketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled “Frequency Not Known.”
[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[b] For additional information refer below within section "Further information on selected serious adverse reactions"
[c] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[d] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Post-marketing experience
Table 3 Adverse reactions reported in post-marketing setting

System organ class (SOC)	Reactions (frequency*)
Infections and Infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare)
Immune system disorders	Hypersensitivity reactions and infusion reactions (not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting
Nervous system disorders	Hypertensive encephalopathy (very rare) Posterior Reversible Encephalopathy Syndrome (PRES), (rare)
Vascular disorders	Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been reported in patients treated with Bevacizumab, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures
	Cases of non-mandibular osteonecrosis have been observed in Bevacizumab treated paediatric patients
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed

* if specified, the frequency has been derived from clinical trial data

DRUG INTERACTIONS

Effect of antineoplastic agents on bevacizumab pharmacokinetics
No clinically relevant interaction of co-administered chemotherapy on bevacizumab pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There were neither statistically significant nor clinically relevant differences in bevacizumab clearance in patients receiving Bevacizumab monotherapy compared to patients receiving Bevacizumab in combination with interferon alfa-2a, erlotinib or chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents
No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alpha 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate
In two clinical trials of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.
MAHA is a haemolytic disorder, which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate.

Combination with platinum- or taxane-based therapies
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) 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. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that 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 SPECIAL POPULATIONS

Pregnancy
There are no clinical trial data on the use of bevacizumab in pregnant women. Studies in animals have shown reproductive toxicity including malformations. IgGs are known to cross the placenta, and bevacizumab is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed. Bevacizumab is contraindicated in pregnancy.

Nursing mother
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.

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

Geriatric Use
No dose adjustment is required in the patients ≥ 65 years of age.

Females of Reproductive Potential
Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility. In a phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. 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.

OVER DOSAGE
The highest dose tested in humans (20 mg/kg of body weight, intravenous every 2 weeks) was associated with severe migraine in several patients.

PRESENTATION
One vial of Bevec® 100/4ml.
One vial of Bevec® 400/16ml.

INSTRUCTIONS
Do not freeze. Store at 2–8°C.
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.

For suspected adverse drug reaction, email us at reports@pharmevo.biz
For more information on our products call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

ہدایات:
دوا کو بچنے سے بچائیں ۔
دوا کو ۲ °C سے ۸°C پر رکھیں ۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
دوا کے ممکنہ منفی اثرات کے متعلق reports@pharmevo.biz پر مطلع کریں۔
ہماری ادویات کی مزید معلومات کے لئے فارماسسٹ کی
ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
پیر تا جمعہ صبح 9:00 سے شام 6:00 بجے
یا ہمیں pharmassist@pharmevo.biz پر ای میل کریں

Marketed by:
PharmEvo®
Our dream, a healthier society
PharmEvo (Pvt.) Ltd.
Plot # A-29, North Western Industrial Zone, Port Qasim, Karachi-75020, Pakistan.
www.pharmevo.biz

Manufactured by:
BIOCAD
Biotechnology Company
JSC «BIOCAD»,
Petrovo-Dalnee Village, Krasnogorsky District, Moscow region, 143422, Russia.