For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

BEVAKALP

1. GENERIC NAME
Bevacizumab Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
BEVACIZUMAB 400
Each vial of 16ml contains:
Bevacizumab….400 mg
Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic anhydrous, α, α-trehalose dihydrate, Polysorbate 80, Water for injection.

BEVACIZUMAB 100
Each vial of 4ml contains:
Bevacizumab….100 mg
Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic anhydrous, α, α-trehalose dihydrate, Polysorbate 80, Water for injection.

3. DOSAGE FORM AND STRENGTH
Dosage form: Concentrate for solution for intravenous infusion.
Strength: 100mg/4ml and 400mg/16ml

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication
Metastatic Colorectal Cancer
Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients w with mCRC (metastatic colorectal cancer).

Non-Squamous Non-Small Cell Lung Cancer
Bevacizumab in combination with platinum-based chemotherapy is indicated for the treatment to patient for the first-line treatment of unrespectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer.
Bevacizumab in combination with erlotinib, is indicated to patients for the first-line treatment of unrespectable, advanced, recurrent or metastatic non-squamous non-small cell lung cancer bearing EGFR activating mutations.

Glioblastoma
Bevacizumab is indicated as a single agent therapy for the treatment of glioblastoma with progressive disease in adult patients following prior therapy.

Metastatjc Breast Cancer

Bevacizumab in combination with capecitabine is indicated for the first line treatment of those metastatic breast cancer patients where other chemotherapy options such as taxanes or anthracyclines are not considered appropriate. This therapy should not be given to those patients who in the prior one year have been given taxanes and anthracyclines in an adjuvant setting.

Bevacizumab in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer patients.

Metastatic Renal Cell Carcinoma

Bevacizumab in combination with interferon alpha is indicated for the treatment of advanced and/or metastatic renal cell carcinoma.

Persistent Recurrent or Metastatic Carcinoma of the Cervix

Bevacizumab in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan is indicated for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix.

Epithelial Ovarian Fallopian Tube or Primarv Peritoneal Cancer

Bevacizumab in combination with carboplatin and paclitaxel is indicated for the front-line treatment of patients with advanced FIGO (International Federation of Gynecology and Obstetrics) stages i.e., Ill 8, 111 C and IV, of epithelial ovarian, fallopian tube or primary peritoneal cancer.

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.

Bevacizumab either in combination with carboplatin and paclitaxel or in combination 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.

4.2 Posology and method of administration

Method of Administration:

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Bevacizumab must be administered under the supervision of a physician experienced in the use of medicinal products.

- 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:

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

Metastatic carcinoma of the colon or rectum:

The recommended dose of Bevacizumab is either 5 mg per kg or 10 mg per kg of body weight administered once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight administered once every 3 weeks.

Metastatic breast cancer*:*

The recommended doses of Bevacizumab are 10 mg/kg of body weight administered once every 2 weeks or 15 mg/kg of body weight administered once every 3 weeks.

Non-squamous non-small cell lung cancer*:*

First-line treatment of non-squamous non-small cell lung cancer in combination with platinum based chemotherapy:

Bevacizumab should be administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Bevacizumab as a single agent until disease progression. The recommended dose of Bevacizumab is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

First-line treatment of non-squamous non-small cell lung cancer with EGFR activating mutations in combination with erlotinib:

EGFR mutation testing should be performed prior to initiation of the treatment. To avoid false negative or false positive determinations, it is important to choose a methodology which is well-validated and robust. When given in addition to erlotinib, the recommended dose of Bevacizumab is 15 mg/kg of body weight administered once every 3 weeks.

Glioblastoma:

The recommended dose Bevacizumab is 10 mg/kg of body weight administered once every 2 weeks.

Advanced and/or metastatic renal cell cancer*:*

The recommended dose of Bevacizumab is 10 mg/kg of body weight administered once every 2 weeks.

Cervical Cancer*:*

Bevacizumab should be administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.

The recommended dose of Bevacizumab is 15 mg/kg of body weight administered once every 3 weeks.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

***Front-line treatment*:**

Bevacizumab should be administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of Bevacizumab is 15 mg/kg of body weight given once every 3 weeks.

Treatment of platinum-sensitive recurrent disease:

Bevacizumab should be administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Bevacizumab as single agent until

progression of disease. The recommended dose of Bevacizumab is 15 mg/kg of body weight administered once every 3 weeks.

Treatment of platinum-resistant recurrent disease:

Bevacizumab should be administered in combination with paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin.

The recommended dose of Bevacizumab is 10 mg/kg of body weight administered once every 2 weeks. When Bevacizumab is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Bevacizumab is 15 mg/kg of body weight administered once every 3 weeks.

- In Elderly patients, no dose adjustments are required.
- The safety and efficacy of Bevacizumab in children less than 18 years old have not been established. No recommendations on posology can be made.
- The safety and efficacy have not been studied in patients with renal or hepatic impairment.
- If the patient misses a dose of Bevacizumab the doctor will decide when the patient should be given the next dose of Bevacizumab.

Dose Modifications:

There are no recommended dose reductions for Bevacizumab.

Bevacizumab should be discontinued in case of:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ.
- Wound dehiscence and wound healing complications requiring medical intervention.
- Serious hemorrhage (i.e., requiring medical intervention).
- Severe arterial thromboembolic events.
- Life-threatening venous thromboembolic events, including pulmonary embolism.
- Hypertensive crisis or hypertensive encephalopathy.
- Posterior Reversible Encephalopathy Syndrome (PRES).
- Nephrotic syndrome.

Bevacizumab should be suspended temporarily for:

- At least 4 weeks prior to elective surgery.
- Severe hypertension not controlled with medical management.
- Moderate to severe proteinuria.
- Severe infusion reactions.

Dose Reduction

During the clinical study carried out with Bevacizumab dose reduction was not recommended.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

4.3 Contraindications

Bevacizumab is contraindicated in patients with the following conditions:

- Hypersensitivity to Bevacizumab (active ingredient) or any of the excipients
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies

- Pregnancy

4.4 Special warnings and precautions for use

Gastrointestinal (GI) perforations and Fistulae:

Patients treated with Bevacizumab, may be at an increased risk for the development of GI perforation and gall bladder perforation. In patients with metastatic carcinoma of the colon or rectum, intra-abdominal inflammatory process may be a risk factor for GI perforations; hence, caution should be taken while treating such patients. Typical presentation may include abdominal pain, nausea, emesis, constipation and fever. Perforations can be complicated by intra-abdominal abscess, fistula formation and the need for diverting ostomies. Use of Bryxta™ should be avoided in patients with ovarian cancer who have previous history of recto-sigmoid involvement by pelvic examination or bowel involvement or bowel obstructions. 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 GI 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 (Gastrointestinalvaginal 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-GI Fistulae:

Higher incidence of serious and sometimes fatal fistula formations involving tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites have been reported with use of Bevacizumab. Bevacizumab should be discontinued permanently in patients with tracheoesophageal fistula or any grade 4 fistula or fistula formation involving an internal organ.

Wound healing and Surgery complications:

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Bevacizumab should not be initiated 28 days following any surgery or until wounds are fully healed. Suspend Bevacizumab for at least 28 days prior to any elective surgery.

Hypertension:

The dose dependent incidence of hypertension is likely to occur during Bevacizumab therapy. Pre-existing hypertension should be properly controlled before starting treatment with Bevacizumab. No information is there on the effect of Bevacizumab in patients with uncontrolled hypertension at the time of initiating the treatment. Regular monitoring of blood pressure is generally recommended during Bevacizumab therapy.

In case of pre-existing hypertension, it should be controlled properly using standard antihypertensive drugs appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not recommended for patients receiving 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):
Rare incidences of PRES are reported. PRES, a rare neurobiological disorder can present with headache, seizure, lethargy, confusion, blindness, visual and other neurological disturbances and mild to severe hypertension. Brain imaging preferably MRI is required to confirm the diagnosis of PRES. Bevacizumab should be discontinued with patients developing PRES.

Proteinuria:
Patients having pre-existing hypertension are at risk of developing proteinuria during Bevacizumab treatment. Prior to starting the Bevacizumab therapy and also during the treatment, it is recommended to monitor proteinuria by dipstick urine analysis. Nephrotic syndrome is reported in patients treated with Bevacizumab. Bevacizumab should be permanently discontinued in patients who develop nephrotic syndrome.

Arterial Thromboembolism:
Patients receiving Bevacizumab therapy are at increased risk of developing serious and sometimes fatal arterial thromboembolic events (ATEs) including cerebral infarction, transient ischemic attacks, myocardial infarctions, angina and other ATEs. Patients receiving Bryxta™ and chemotherapy, with a history of arterial thromboembolism, diabetes or aged above 65 years are at increased risk of developing ATEs. Bevacizumab should be discontinued in patients who have experienced ATE.

Venous thromboembolism:
Patients may develop venous thromboembolic reactions, including pulmonary embolism during Bevacizumab treatment. Patients undergoing treatment for persistent, recurrent, or metastatic cervical cancer with Bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events. Close monitoring is required for patients with < Grade 3 thromboembolic reactions. Bevacizumab should be discontinued in patients with life threatening (Grade 4) thromboembolic reactions, including pulmonary embolism.

Hemorrhage:
Increased risks of hemorrhage, especially tumor-associated hemorrhage are related with Bevacizumab therapy. Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Bevacizumab therapy.
The risk of CNS hemorrhage in patients with untreated CNS metastases was not studied during Bevacizumab treatment. Hence, caution should be taken while initiating treatment with Bevacizumab in such patients. Patients should be monitored for signs and symptoms of CNS

bleeding, and Bevacizumab treatment discontinued in cases of intracranial bleeding. Relevant information is not available 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.
Hence, caution should be taken before starting the treatment in such 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 hemorrhage/hemoptysis:
Patients with non-small cell lung cancer under Bevacizumab treatment may be at risk of serious, and in some cases fatal, pulmonary hemorrhage/hemoptysis. Patients with recent pulmonary hemorrhage/ hemoptysis (> 2.5 ml of red blood) should not be treated with Bevacizumab.

Congestive heart failure (CHF):
Incidences of CHF have been reported with Bevacizumab treatment. Bevacizumab treatment may lead to asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization. Therefore, caution should be exercised while treating patients with history of clinically significant cardiovascular disease such as coronary artery disease, or CHF with Bevacizumab. Occurrence of CHF Grade 3 or higher reactions was more frequent among patients receiving Bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone.

Neutropenia and infections:
Patients treated with Bevacizumab in combination with some myelotoxic chemotherapy regimens had increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) in comparison to chemotherapy alone. It has been mainly seen in therapies involving combination with platinum- or taxane in the treatment of non-small cell lung cancer, metastatic breast cancer 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 is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody for patients undergoing Bevacizumab treatment. In case of reaction, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Systemic effects following intravitreal use:
A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systematic adverse reactions including non-ocular hemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors. Bevacizumab is not formulated for intravitreal use.

Eye Disorder:
Reactions including infectious endophthalmitis, intraocular inflammation such as steril endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, increased intraocular hemorrhage such as viterious hemorrhage or retinal hemorrhage and conjunctival hemorrhage have been reported following unapproved intravitreal use of Bevacizumab compounded from vials approved for intravenous administration in cancer patients. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

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. Therefore, caution should be taken 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.

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

4.5 Drugs 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.

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 clinical trials of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in patients treated with Bevacizumab and sunitinib malate combination.

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 non-small cell lung cancer and metastatic breast cancer.

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 metastatic colorectal cancer in combination with Bevacizumab containing chemotherapy.

4.6 Use in special populations

Women of childbearing potential

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

Pregnancy

There are no clinical trial data on the use of Bevacizumab in pregnant women. Bevacizumab may cause fetal harm based on findings from animal studies and the drug's mechanism of action. In the post-marketing setting, cases of fetal abnormalities have been reported in women treated with Bevacizumab alone or in combination with known embryotoxic chemotherapeutics. Bevacizumab is contraindicated in pregnancy.

Nursing Mothers

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

Fertility

Repeat dose toxicity studies in animals have shown that Bevacizumab may have an adverse effect on female fertility long term effects of Bevacizumab treatment on fertility are unknown.

4.7 Effects On Ability to Drive and Use Machine

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.

4.8 Undesirable Effects

Summary of the safety profile

The overall safety profile of Bevacizumab is based on data from over 5,700 patients with various malignancies, predominantly treated with Bevacizumab in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

- Gastrointestinal perforations.
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non- small cell lung cancer patient.
- Arterial thromboembolism.

The most frequently observed adverse reactions across clinical trials in patients receiving Bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Bevacizumab therapy are likely to be dose-dependent.

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

List adverse reactions associated with the use of Bevacizumab in combination with different chemotherapy regimens in multiple indications.

Table: provides all adverse reactions by frequency that were determined to have a causal relationship with Bevacizumab through:

- comparative incidences noted between clinical trial treatment arms (with at least a 10% difference compared to the control arm for NCI-CTCAE Grade 1-5 reactions or at least a 2% difference compared to the control arm for NCI-CTCAE Grade 3-5 reactions,
- post-authorisation safety studies,
- spontaneous reporting,
- epidemiological studies\non-interventional or observational studies,
- or through an evaluation of individual case reports.

Table: 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 also includes adverse reactions which are considered by the MAH to be clinically significant or severe.

Post-marketing adverse reactions are included in both Tables, where applicable. Detailed information about these post-marketing reactions are provided in table below.

Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication.

Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, Bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

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 neuropathi[c], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalo-pathy syndrome [a,b,d]	Hypertensive encephalo-pathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					

Cardiac disorders		Congestive heart failure[b, d], Supraventricular tachycardia				
Vascular disorders	Hypertension[d], Thrombo-embolism (venous)[b,d]	Thrombose-embolism (arterial)[b,d], Haemorrhage[d], Deep vein thrombosis				Renal thrombotic microangiopathy[a,b]
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis Epistaxis Cough	Pulmonary haemorrhage/ Haemoptysis[b, d, d], Pulmonary embolism, Hypoxia, Dysphonia				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[d,] Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythrodysaesthesia syndrome				

Musculoskeletal and connective tissue disorders	Arthralgia Myalgia	Fistula[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[b,c,d]	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 '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 sub study 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: 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 Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome [a,b,c,] Hypertensive encephalopathy[c]
Cardiac disorders		Congestive heart failure[a, b], Supraventricular tachycardia				
Vascular disorders	Hypertension[a, b]	Thromboembolism arterial[a, b], Haemorrhage[a, b], Thromboembolism (venous)[a,b] Deep vein thrombosis				Renal thrombotic microangiopathy[b,c]

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[b, d], Palmar-plantar erythrodysaesthesia 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						Foetal abnormalities[a, b]

genetic disorder						
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal Inflammation				

Table: 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 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 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 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 refers below within section "Further information on selected serious adverse reactions"

[c] for further information please refer to Table 'Adverse reactions reported in post-marketing setting.'

[d] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and Fistulae

Bevacizumab has been associated with serious cases of gastrointestinal perforation.

Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation

was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all Bevacizumab treated patients.

In Bevacizumab clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

GI-vaginal Fistulae in study GOG-0240

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Bevacizumab tin-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with Bevacizumab+ chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistulae

Bevacizumab use has been associated with serious cases of fistulae including reactions resulting in death.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of Bevacizumab tin-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon ($\geq 0.1\%$ to $< 1\%$) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Reactions were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Bevacizumab tin, with most reactions occurring within the first 6 months of therapy.

Wound healing

As Bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials.

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting Bevacizumab tin. An increased incidence of post-operative bleeding or wound healing complication occurring within 60 days of major surgery was observed if the patient was being treated with Bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome.

In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving Bevacizumab compared with up to 0.9% of patients in the control arms (NCI-CTCAE v.3).

In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.8% of patients in the Bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension

In reported clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the Bevacizumab containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertensions in patients receiving Bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Bevacizumab and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received Bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with Bevacizumab in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

Hypertension was generally adequately controlled with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of Bevacizumab treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal.

The risk of Bevacizumab tin-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome

There have been rare reports of Bevacizumab tin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurological disorder. Presentation may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The clinical presentation of PRES is often nonspecific, and therefore the diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

In patients developing PRES, early recognition of symptoms with prompt treatment of specific symptoms including control of hypertension (if associated with severe uncontrolled hypertension) is recommended in addition to discontinuation of Bevacizumab therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although

some patients have experienced some neurologic sequelae. The safety of reinitiating Bevacizumab therapy in patients previously experiencing PRES is not known.

Across clinical trials, 8 cases of PRES have been reported. Two of the eight cases did not have radiological confirmation via MRI.

Proteinuria

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving Bevacizumab tin.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of Bevacizumab therapy. In most clinical trials urine protein levels of $\geq$ 2g/24 hrs led to the holding of Bevacizumab until recovery to < 2g/24 hrs.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTCAE v.3 Grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in Bevacizumab treated patients, compared with up to 4.5% of patients in the chemotherapy control group.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with Bevacizumab in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan.

The haemorrhagic reactions that have been observed in clinical trials were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with ant rheumatic/anti-inflammatory substances, treatment with anticoagulants, prior radiotherapy, Bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent phase III trials, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade reactions were seen with a frequency of up to 9.3% when treated with Bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions have been observed in up to 2.3% of patients treated with Bevacizumab plus chemotherapy as compared with < 1% with chemotherapy alone (NCI-CTCAE v.3). Major or massive

pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal cancer patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving Bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with Bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to Bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with Bevacizumab (1.2%) at the time of interim safety analysis (NCI-CTCAE v.3).

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of Bevacizumab tin-treated patients. These were most commonly NCI-CTCAE v.3 Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the Bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common reactions of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Thromboembolism

Arterial thromboembolism: An increased incidence of arterial thromboembolic reactions was observed in patients treated with Bevacizumab across indications, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic reactions.

In clinical trials, the overall incidence of arterial thromboembolic reactions ranged up to 3.8% in the Bevacizumab containing arms compared with up to 2.1% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Bevacizumab compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.7% of patients treated with Bevacizumab in combination with chemotherapy compared to up to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in up to 1.4% of patients treated with Bevacizumab in combination with chemotherapy compared to up to 0.7% of patients treated with chemotherapy alone.

In one clinical trial evaluating Bevacizumab in combination with 5-fluorouracil/folinic acid, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment

with irinotecan were included. In this trial arterial thromboembolic reactions were observed in 11% (11/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

Venous thromboembolism: The incidence of venous thromboembolic reactions in clinical trials was similar in patients receiving Bevacizumab in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic reactions include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic reactions ranged from 2.8% to 17.3% of Bevacizumab tin-treated patients compared with 3.2% to 15.6% in the control arms.

Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus Bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with Bevacizumabin combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin.

Patients who have experienced a venous thromboembolic reaction may be at higher risk for a recurrence if they receive Bevacizumabin combination with chemotherapy versus chemotherapy alone.

Congestive heart failure (CHF)

In clinical trials with Bevacizumabtin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In four phase III trials (AVF2119g, E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer CHF Grade 3 (NCI-CTCAE v.3) or higher was reported in up to 3.5% of patients treated with Bevacizumabin combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with Bevacizumab, the incidences of Grade 3 or higher CHF for the respective Bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + Bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all Grade CHF were similar between the anthracycline + Bevacizumab (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Bevacizumabtin, patients with pre-existing CHF of NYHA (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF.

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving Bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus Bevacizumab to R-CHOP without Bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus Bevacizumab arm. These results suggest that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m^2 when combined with Bevacizumab.

Hypersensitivity reactions/infusion reactions

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Bevacizumabin combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials of Bevacizumab is common (up to 5% in Bevacizumab-treated patients).

Infections

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 infections have been reported in up to 24% of patients treated with Bevacizumabin combination with paclitaxel and topotecan compared with up to 13% of patients treated with paclitaxel and topotecan.

Ovarian failure/fertility

In NSABP C-08, a phase III trial of Bevacizumabin adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test, has been evaluated in 295 premenopausal women. New cases of ovarian failure were reported in 2.6% patients in the mFOLFOX-6 group compared to 39% in the mFOLFOX-6 + Bevacizumab group. After discontinuation of Bevacizumab treatment, ovarian function recovered in 86.2% of these evaluable women. Long term effects of the treatment with Bevacizumab on fertility are unknown.

Laboratory abnormalities

Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Bevacizumab treatment.

Across clinical trials, the following Grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with Bevacizumabwith at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR).

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of Bevacizumabtin. The observed increase in serum creatinine was not associated with a higher

incidence of clinical manifestations of renal impairment in patients treated with Bevacizumabtin.

Other special populations

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with Bevacizumab (see sections 4.4 and 4.8 under *Thromboembolism*). In one clinical trial, the incidence of hypertension of grade ≥ 3 was twofold higher in patients aged > 65 years than in the younger age group (<65 years). In a study of platinum-resistant recurrent ovarian cancer patients, alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were also reported and occurred at a rate at least 5% higher in the CT + BV arm for Bevacizumab-treated patients ≥ 65 years of age compared with Bevacizumab-treated patients aged < 65 years.

No increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure, and haemorrhage was observed in elderly patients (> 65 years) receiving Bevacizumab as compared to those aged ≤ 65 years treated with Bevacizumab

Paediatric population

The safety and efficacy of Bevacizumab in children less than 18 years old have not been established.

In study BO25041 of Bevacizumab added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with Bevacizumab.

In study BO20924 of Bevacizumab with current standard of care in rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, the safety profile of Bevacizumab treated children was comparable with that observed in adults treated with Bevacizumab.

Bevacizumab is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with Bevacizumab.

Post-marketing experience

Table: 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) (see also section 4.4)
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 (see also section 4.4 and *Hypersensitivity reactions/infusion reactions* above)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and *Hypertension* in section 4.8) Posterior Reversible Encephalopathy Syndrome (PRES), (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use. For further information on proteinuria see section 4.4 and *Proteinuria* in section 4.8.
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 in, 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 (see also section 4.4)
	Cases of non-mandibular osteonecrosis have been observed in Bevacizumab treated paediatric patients (see section 4.8, Paediatric population).
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 (see section 4.6)

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

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic and immunomodulation agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01X C07

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. Neutralizing the biological activity of VEGF regresses the vascularization of tumours, normalizes remaining tumors vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumor growth.

5.3 Pharmacokinetic Properties

The pharmacokinetic data for Bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, Bevacizumab was administered as an IV infusion. 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 (V_c) 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 (V_p) 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 V_c (+ 20%) than female patients.

Biotransformation

Assessment of Bevacizumab metabolism in rabbits following a single IV dose of ^{125}I-Bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. 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.

Pharmacokinetics in special populations

The population pharmacokinetics were analysed in adult and pediatric patients to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of Bevacizumab in relation to age.

Renal impairment

No trials have been conducted to investigate the pharmacokinetics of Bevacizumab in renally impaired patients since the kidneys are not a major organ for Bevacizumab metabolism or excretion.

Hepatic impairment

No trials have been conducted to investigate the pharmacokinetics of Bevacizumab in patients with hepatic impairment since the liver is not a major organ for Bevacizumab metabolism or excretion.

Paediatric population

The pharmacokinetics of Bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of Bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of Bevacizumab when body weight was taken into account.

The pharmacokinetics of Bevacizumab was well characterized by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, Bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, Bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, Bevacizumab exposure trended lower as body weight decreased.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Preclinical studies for Bevacizumab were performed as per GLP standards. Toxicological studies included independent acute toxicity studies in mice and rats by intended intravenous route of administration as well as repeated dose toxicity studies (comparative) by intravenous route comprising biweekly dosing schedule over a period of four weeks was performed in rats

and rabbits. Local tolerance evaluation was a part of repeated dose toxicity studies and by an independent skin sensitization study in guinea pigs.
In acute toxicity studies, Bevacizumab revealed a good safety margin in terms of (Totality over the acute dose of 625 mg/kg in mice & 500 mg/kg in rats by intravenous route and were approximately 5X (in mice) and 8X (in rats) of the human equivalent dose. No mortality, apparent signs of toxicity, adverse changes in body weights and gross pathological lesions were noticed in both mice and rats when compared to vehicle control groups. BEVACIZUMAB did not induce any dermal sensitization in guinea pigs. No adverse local tolerance effects were noticed at the site of injection in both rats and rabbits.

Comparative studies with repeated biweekly intravenous administration with Bevacizumab was conducted over a period of four weeks at dose levels of 62, 155 and 310 mg/kg in rats and 31, 77.5 and 155 mg/kg in rabbits. The selected dose levels in respective species were 1X, 2.5X & 5X of the human equivalent dose. A recovery group was maintained for a period of two weeks at 5X dose to determine delayed or persistence of toxicity, if any. Vehicle treated control groups were maintained in these studies. An approved reference medicinal product as used at 1X of the human equivalent dose in these repeated dose toxicity studies. No mortality occurred either in rats or rabbits. No adverse changes were noticed during detailed clinical examination, body weight and feed intake determinations, haematological, biochemical, organ weight estimations, bone marrow examination and gross or histopathological evaluation. No differences were noticed in these studies in comparison to reference medicinal product, in both acts and rabbits. No delayed toxicity was noticed during treatment of recovery period of wo weeks. The immunogenic response in Bevacizumab treated groups was comparable to that of reference medicinal product treated group. No immunogenicity titers were noticed against host cell proteins (HCP) which also demonstrates that the product has extremely low levels of HCP contaminants. The no observed adverse effect level (NOAEL) of similar biologic of Bevacizumab was considered to be more than 5X of human equivalent dose (310 mg/kg in rats and 155 mg/ kg in rabbits) by intravenous administration.
Thus, the overall pre-clinical profile of Bevacizumab seems to be comparable with the reference medicinal product and considered to be safe at the recommended dose in human.

7. DESCRIPTION

Bevacizumab is a recombinant humanized monoclonal antibody (containing 1334 amino acids produced in Chinese hamster ovary cell line. It binds with high affinity to vascular endothelial growth factor A (VEGF-A). VEGF is a signal protein which stimulates vasculogenesis and angiogenesis. Bevacizumab binds to VEGF, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological activity of VEGF regresses the vascularization of tumours, normalizes remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Bevacizumab is Colorless to pale brown liquid solution. The molecular formula is $C_{6538}H_{10000}N_{1716}O_{2032}S_{44}$ (based on amino acid residues) and Each glycosylated heavy-chain has a molecular weight of 51 kDa (approx.) and each light-chain has a molecular weight of 23

kDa (approx.). The intact molecular mass of Bevacizumab is 149 kDa (approximately) including the glycosylated moieties.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

No incompatibilities between Bevacizumab and polyvinylchloride or polyolefin bags have been observed.

Dextrose (5%) solution should not be used since it causes aggregation of the protein.

8.2 Shelf-life

Do not use later than the date of expiry

8.3 Packaging information

Bevacizumab injection is available in vial.

8.4 Storage and Handing Instructions

Store between +2°C to 8°C. Do not freeze and shake. Protect from light. Prior to infusion, Bevacizumab solution is diluted in 0.9 % sodium chloride infusion solution. Bevacizumab solution does not contain any preservative; therefore, care has been taken to ensure the sterility of the prepared solution. Microbiologically, the prepared 'infusion solution containing Bevacizumab should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at +2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability of Bevacizumab in infusion solution has been demonstrated for 72 hours.

Special Instruction for Use, Handing and Disposal

Adequate aseptic techniques should be used. Bevacizumab should be prepared by experienced healthcare personnel. Prior to administration, Bevacizumab should be inspected visually for particulate matter and discolouration. Bevacizumab is for single-use only, as the product contains no preservatives. Any unused medicinal product should be disposed as per biologics disposable guidelines of local body.

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 final concentration should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. Bevacizumab can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 mi.

9. PATIENT COUNSELLING INFORMATION

BEVAKALP

BEVACIZUMAB Injection

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1. What BEVAKALP is and what it is used for

BEVAKALP contains the active substance Bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection and cancer). Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once BEVAKALP is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour. BEVAKALP is a medicine used for the treatment of adult patients with advanced cancer in the large bowel, i.e., in the colon or rectum. BEVAKALP will be administered in combination with chemotherapy treatment containing a fluoropyrimidine medicine.

BEVAKALP is also used for the treatment of adult patients with metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy medicinal product called paclitaxel or Capecitabine.

BEVAKALP is also used for the treatment of adult patients with advanced non-small cell lung cancer. BEVAKALP will be administered together with a chemotherapy regimen containing platinum. BEVAKALP is also used for the treatment of adult patients with advanced non-small cell lung cancer when cancer cells have specific mutations of a protein called epidermal growth factor receptor (EGFR).

BEVAKALP will be administered in combination with erlotinib. BEVAKALP is also used for treatment of adult patients with advanced kidney cancer. When used for patients with kidney cancer, it will be administered with another type of medicine called interferon. BEVAKALP is also used for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. When used for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, it will be administered in combination with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back at least 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, BEVAKALP will be

administered in combination with carboplatin and gemcitabine or with carboplatin and paclitaxel. When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back before 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, BEVAKALP will be administered in combination with paclitaxel, or topotecan, or pegylated liposomal doxorubicin. BEVAKALP is also used for the treatment of adult patients with persistent, recurrent or metastatic cervical cancer. BEVAKALP will be administered in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy.

9.2. What you need to know before you use BEVAKALP

Do not use BEVAKALP if:

- you are allergic (hypersensitive) to Bevacizumab or to any of the other ingredients of this medicine.
- you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you are pregnant.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using BEVAKALP:

- It is possible that BEVAKALP may increase the risk of developing holes in the gut wall. If you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), please discuss this with your doctor.
- BEVAKALP may increase the risk of developing an abnormal connection or passageway between two organs or vessels. The risk of developing connections between the vagina and any parts of the gut can increase if you have persistent, recurrent or metastatic cervical cancer.
- This medicine can increase the risk of bleeding or increase the risk of problems with wound
- healing after surgery. If you are going to have an operation, if you have had major surgery
- within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine.
- BEVAKALP may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing.
- BEVAKALP can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting BEVAKALP treatment.
- This medicine increases the risk of having protein in your urine especially if you already have high blood pressure.
- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries. Please talk to your doctor since blood clots can lead to heart attack and stroke.

- BEVAKALP can also increase the risk of developing blood clots in your veins (a type of blood vessel).
- This medicine may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.
- It is possible that BEVAKALP may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.
- It is possible that BEVAKALP can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.
- BEVAKALP can increase the risk of developing a weak heart. It is important that your doctor knows if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease.
- This medicine may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).
- It is possible that BEVAKALP can cause hypersensitivity and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.
- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with BEVAKALP treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

Please consult your doctor, even if these above statements were only applicable to you in the past. Before you are given BEVAKALP or while you are being treated with BEVAKALP.

- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with BEVAKALP, in particular when you are also receiving or have received an injection of bisphosphonate into your blood.

You may be advised to have a dental check-up before you start treatment with BEVAKALP.

Children and adolescents

BEVAKALP use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations. Death of bone tissue (osteonecrosis) in bones other than the jaw have been reported in patients under 18 years old when treated with BEVAKALP.

Other medicines and BEVAKALP

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Combinations of BEVAKALP with another medicine called sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects. Discuss with your doctor to make sure that you do not combine these medicine.
Tell your doctor if you are using platinum- or taxane-based therapies for lung or metastatic breast cancer. These therapies in combination with BEVAKALP may increase the risk of severe side effects.
Please tell your doctor if you have recently received, or are receiving, radiotherapy.

Pregnancy, breast feeding and fertility
You must not use this medicine if you are pregnant. BEVAKALP may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with BEVAKALP and for at least 6 months after the last dose of BEVAKALP.
Tell your doctor straightaway if you are pregnant, become pregnant during treatment with this medicine, or plan to become pregnant in the near future.
You must not breast-feed your baby during treatment with BEVAKALP and for at least 6 months after the last dose of BEVAKALP, as this medicine may interfere with the growth and development of your baby.
BEVAKALP may impair female fertility. Please consult your doctor for more information.
Ask your doctor, pharmacist or nurse for advice before taking any medicine.

Driving and using machines
BEVAKALP has not been shown to reduce your ability to drive or to use any tools or machines. However, sleepiness and fainting have been reported with BEVAKALP use. If you experience symptoms that affect your vision or concentration, or your ability to react, do not drive and use machines until symptoms disappear.

9.3. How to use BEVAKALP
Dosage and frequency of administration
The dose of BEVAKALP needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5 mg, 7.5 mg, 10 mg or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of BEVAKALP that is right for you. You will be treated with BEVAKALP once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until BEVAKALP fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration
BEVAKALP is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the BEVAKALP vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted BEVAKALP solution by intravenous infusion (a drip into your vein). The first infusion will be given to you over 90

minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

The administration of BEVAKALP should be temporarily discontinued

- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,
- if you undergo surgery.

The administration of BEVAKALP should be permanently discontinued if you develop

- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- an abnormal tube-like connection or passage between the windpipe and the gullet, between
- internal organs and skin, between the vagina and any parts of the gut or between other tissues that are not normally connected (fistula), and are judged by your doctor to be severe, serious infections of the skin or deeper layers under the skin,
- a blood clot in your arteries,
- a blood clot in the blood vessels of your lungs,
- any severe bleeding.

If too much BEVAKALP is given

- you may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

If a dose of BEVAKALP is missed

- your doctor will decide when you should be given your next dose of BEVAKALP. You should discuss this with your doctor.

If you stop treatment with BEVAKALP

Stopping your treatment with BEVAKALP may stop the effect on tumour growth. Do not stop treatment with BEVAKALP unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. The side effects listed below were seen when BEVAKALP was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by BEVAKALP.

Allergic reactions

If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include: difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, chills and shivering, feeling sick (nausea) or being sick (vomiting).

You should seek help immediately if you suffer from any of the below mentioned side effects.

Severe side effects, which may be **very common** (affects more than 1 user in 10), include:

- high blood pressure,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- feeling weak and having no energy,
- tiredness,
- diarrhoea, nausea, vomiting and abdominal pain.

Severe side effects, which may be **common** (affects 1 to 10 users in 100), include:

- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,
- blocking of the veins by a blood clot,
- blocking of the blood vessels of the lungs by a blood clot,
- blocking of the veins of the legs by a blood clot,
- heart failure,
- problems with wound healing after surgery,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- decreased number of red cells in the blood,
- lack of energy,
- stomach and intestinal disorder,
- muscle and joint pain, muscular weakness,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing,
- pain, including headache, back pain and pain in the pelvis and anal regions,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- sleepiness,
- nose bleed,
- increase in heart rate (pulse),

- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood,
- infections of the skin or deeper layers under the skin,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer.

Severe side effects of **unknown** frequency (frequency cannot be estimated from the available data), include:
- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- allergic reactions (the signs may include difficulty breathing, facial redness, rash, low blood
- pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting),
- a negative effect on a woman's ability to have children (see the paragraphs below the list of side effects for further recommendations),
- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure,
- clogging of a very small blood vessel(s) in the kidney,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,
- a hole in the stomach or intestines,
- an open sore or hole in the lining of the stomach or small intestine (the signs may include
- abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit),
- bleeding from the lower part of the large bowel,
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue (see the paragraphs below the list of side effects for further recommendations),
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and
- nausea/vomiting).

You should seek help as soon as possible if you suffer from any of the below mentioned side effects.

Very common (affects more than 1 user in 10) side effects, which were not severe, include:
- constipation,
- loss of appetite,
- fever,

- problems with the eyes (including increased production of tears),
- changes in speech,
- change in the sense of taste,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- loss of body weight,
- nose bleeds.

Common (affects 1 to 10 users in 100) side effects, which were not severe, include:
- voice changes and hoarseness.

Patients older than 65 years have an increased risk of experiencing the following side effects:
- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,
- fatigue,
- high blood pressure.

BEVAKALP may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen),which may be severe.
Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.
Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.
BEVAKALP has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way.
When BEVAKALP is injected directly into the eye (unapproved use), the following side effects may occur:
- Infection or inflammation of the eye globe,
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,

- Bleeding in the eye.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5. How to store BEVAKALP
Store between +2°C to 8°C. Do not freeze and shake. Protect from light. Prior to infusion, BEVAKALP solution is diluted in 0.9 % sodium chloride infusion solution. BEVAKALP solution does not contain any preservative; therefore, care has been taken to ensure the sterility of the prepared solution. Microbiologically, the prepared 'infusion solution containing BEVAKALP should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at +2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability of BEVAKALP in infusion solution has been demonstrated for 72 hours.

9.6. Contents of the pack and other information
What BEVAKALP contains
- 16 mL solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of Bevacizumab.
- 4 mL solution in a vial (Type I glass) with a stopper {butyl rubber) containing 100mg of Bevacizumab.

Each pack contains 1 vial.

SPECIAL PRECAUTIONS FOR DISPOSAL
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via waste water and disposal through household waste should be avoided.

10. DETAILS OF MANUFACTURER
Manufactured by:
Cadila Healthcare Limited
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H. No-8A, Opp. Ramdev Masala, Village – Changodar, Tal: Sanand, Dist-Ahmedabad- 382213

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Mfg Lic No. G/28D/BIO/02 issued on 16.05.2017

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/BEVAKALP 400 mg/16 mL, 100 mg/4 ml /APR-21/01/PI