SUMMARY OF PRODUCT CHARACTERISTICS[SmPC]

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1.0 Name of the Medicinal Product

Bevacizumab

2.0 Qualitative and Quantitative Composition

Bevacizumab in vials is a sterile, clear, colorless and preservative-free solution, available in following dose strengths and its compositions are as follows:

3.0 Pharmaceutical Form

Concentrate for solution in 4 ml and 16 ml single use vials for intravenous (IV) infusion.

4.0 Clinical Particulars

4.1 Therapeutic indications

Metastatic Colorectal Cancer (mCRC):

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

Bevacizumab, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Bevacizumab -containing regimen.

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

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

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

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

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.

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.
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.

4.2 Posology and method of administration

Metastatic carcinoma of the colon or rectum (mCRC):
Bevacizumab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.
Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC):
The recommended doses are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with
intravenous 5-FU-based chemotherapy.
Administer 5 mg/kg when used in combination with bolus-IFL.
Administer 10 mg/kg when used in combination with FOLFOX4.
Administer 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks when used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen in patients who have progressed on a first-line Bevacizumab -containing regimen.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC):
The recommended dose is 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel.

Glioblastoma:
The recommended dose is 10 mg/kg every 2 weeks.
Metastatic Renal Cell Carcinoma (mRCC)
The recommended dose is 10 mg/kg every 2 weeks in combination with interferon alfa.

Cervical Cancer:
The recommended dose of Bevacizumab is 15 mg/kg every 3 weeks as an intravenous infusion administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin, or paclitaxel and topotecan.

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.

Administration:

- Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.
- Do not initiate bevacizumab until at least 28 days following major surgery. Administer bevacizumab after the surgical incision has fully healed.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.
- Do not administer or mix with dextrose solution.

Preparation for Administration:

- Use appropriate aseptic technique. Parenteral drug products should be inspected visually for 90 particulate matter and discoloration prior to administration, whenever solution and container permit.
- Withdraw necessary amount of Bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

4.3 Contraindications

Bevacizumab is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients in formulation
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies.
- Pregnancy

4.4 Special warnings and precautions for use

Gastrointestinal (GI) 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.

Non-GI 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 [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. 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 necrotizing 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. There is evidence suggesting that all Grade (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. 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 (NCI-CTCAE v.3).

Arterial thromboembolism

Incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic 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 (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3).

Haemorrhage

Patients treated with bevacizumab have an increased risk of hemorrhage, especially tumour-associated hemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy (NCI-CTCAE v.3).

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 (NCI-CTCAE v.3).

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.

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 hospitalization. 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.

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 humanized 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.

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.

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 hemorrhage such as vitreous hemorrhage or retinal hemorrhage and conjunctival hemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

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.

Embryo-fetal Toxicity

Bevacizumab may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Pregnant women should be advised about potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with and for 6 months after the last dose of bevacizumab.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on bevacizumab pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of bevacizumab in patients receiving

bevacizumab monotherapy compared to patients receiving bevacizumab in combination with interferon alfa-2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

- There is no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38 as reported earlier.
- There is no significant effect of bevacizumab on the pharmacokinetics of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum in metastatic colorectal cancer patients.
- There is no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a in renal cancer patients as reported earlier.
- There is no significant effect of bevacizumab on the pharmacokinetics of cisplatin and gemcitabine in non-squamous NSCLC patients as reported earlier.

Combination of bevacizumab and sunitinib malate

Microangiopathic haemolytic anaemia (MAHA) was reported in 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. 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.

4.6 Usage in special populations

Pregnancy:

Bevacizumab may cause fetal harm based on findings from animal studies and the drug's mechanism of action. Limited post marketing reports describe cases of fetal malformations with use of bevacizumab in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Pregnant women should be advised of the potential risk to a fetus. The background risk of major birth defects and miscarriage is unknown.

Animal Data

Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6-18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30

mg/kg dose, and 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hind limb phalanges.

2. Nursing Mothers

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, advise a nursing woman that breastfeeding is not recommended during treatment with bevacizumab.

3. Pediatric Use

The safety, effectiveness and pharmacokinetic profile of bevacizumab in pediatric patients have not been established. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received bevacizumab. Bevacizumab is not approved for use in patients under the age of 18 years.

Animal Data

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

4. Geriatric Use

Severe adverse events that occurred at a higher incidence in patients aged ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration,

hypokalemia, and hyponatremia. The effect of bevacizumab on overall survival was similar in elderly patients as compared to younger patients.

Patients aged ≥ 65 years receiving bevacizumab plus FOLFOX-4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue. Patients aged ≥ 65 years receiving carboplatin, paclitaxel, and bevacizumab had a greater relative risk for proteinuria as compared to younger patients.

Adverse events of dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration were observed in patients aged ≥ 65 when compared with younger patients.

The overall incidence of arterial thromboembolic events was increased in all patients receiving bevacizumab with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years as compared to those < 65 years.

5. Renal Impairment

The safety and efficacy of bevacizumab have not been studied in patients with renal impairment.

6. Hepatic Impairment

The safety and efficacy of bevacizumab has not been studied in patients with hepatic impairment.

4.7 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.

4.8 Undesirable effects

The following summary safety profile of Bevacizumab is based on clinical trial data from patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy.

The most serious adverse reactions were:

- Gastrointestinal perforations

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

The most frequently observed adverse reactions 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.

Below table lists adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications during clinical trial and post marketing experience.

Adverse Events Associated with Bevacizumab Use

System organ class	***Adverse event***
Immune system	Hypersensitivity infusion reactions
Infections and infestations	Sepsis, Abscess, cellulitis, infection, urinary tract infection and necrotising fasciitis
Blood and the lymphatic system	Febrile neutropenia, Leucopenia, Thrombocytopenia, Neutropenia, Anaemia and Lymphopenia
Metabolism and nutrition disorders	Dehydration, Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Cerebrovascular accident, Syncope, Dizziness, Somnolence, Headache, Dysguesia, Dysarthria, Posterior Reversible Encephalopathy Syndrome, Hypertensive
Eye disorders	Eye disorder, Lacrimation increased
Cardiac disorders	Supraventricular tachycardia and Congestive heart failure and Intra-Abdominal Thrombosis and Hypotension
Vascular disorders	Hypertension, Thromboembolism (arterial & venous), Deep vein thrombosis, Haemorrhage, Renal thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	Pulmonary haemorrhage/ Haemoptysis, Pulmonary embolism, Epistaxis, Dysphonia, Dyspnoea, Hypoxia, Rhinitis, Nasal septum perforation, Pulmonary hypertension and Voice Alteration
Gastrointestinal disorders	Diarrhoea, Dry Mouth, Colitis, Nausea, Vomiting, Gastrointestinal perforation, Intestinal perforation, Ileus Intestinal obstruction, Abdominal pain, Gastrointestinal disorder, Constipation, Stomatitis, Rectal haemorrhage, Gastrointestinal ulcer, Recto-vaginal fistula and

System organ class	***Adverse event***
Hepatobiliary disorders	Gall bladder perforation
Skin and subcutaneous tissue disorders	Wound healing complications, Palmar-plantar erythrodysaesthesia syndrome, Exfoliative dermatitis, Dry skin, Alopecia, skin ulcer and
Musculoskeletal, connective tissue and bone disorders	Muscular weakness, Myalgia, Arthralgia, osteonecrosis of the jaw, Non-mandibular osteonecrosis, Fistula and Back pain
Renal and urinary disorders	Proteinuria
General disorders and administration site conditions	Asthenia, Fatigue, Pain, Lethargy, Mucosal inflammation, Pyrexia
Reproductive system and breast disorders	Ovarian failure and Pelvic Pain
Congenital, familial, and genetic disorder	Foetal abnormalities
Special Senses	Taste Disorder
Investigations	Weight decreased

Bevacizumab in Combination with FOLFOX-4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment were observed. The most frequent adverse events (selected Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events) occurring at a higher incidence (≥ 2%) in patients receiving FOLFOX-4 plus bevacizumab compared to patients receiving FOLFOX-4 alone were fatigue, diarrhea, sensory neuropathy, nausea, vomiting, dehydration, hypertension, abdominal pain, hemorrhage, other neurological, ileus and headache.

Bevacizumab in Combination with Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin Based Chemotherapy in Second-line mCRC Patients who have progressed on a Bevacizumab Containing Regimen in First-line mCRC:

No new safety signals were observed when bevacizumab was administered in second line mCRC patients who progressed on an bevacizumab containing regimen in first line mCRC. The safety data was consistent with the known safety profile established in first and second line mCRC.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to Bevacizumab. Based on clinical data, some subjects tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. These subjects tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab with the incidence of antibodies to other products may be misleading.

Laboratory abnormalities

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

The following Grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with bevacizumab with 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).

There were observed 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 bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

Other adverse event which includes, Recto-vaginal fistulae also observed with bevacizumab treatment.

Adverse effects reported during post-approval use of bevacizumab

The following adverse reactions have been identified during post-approval use of bevacizumab.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, PRES, mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; endophthalmitis (infectious and sterile); intraocular inflammation; retinal detachment; increased intraocular pressure; hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; vitreous floaters; ocular hyperemia; ocular pain or discomfort

Gastrointestinal: Gastrointestinal ulcer, intestinal necrosis, anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Hepatobiliary disorders: Gallbladder perforation

Infections and infestations: Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation

Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw; non-mandibular osteonecrosis (cases have been observed in pediatric patients who have received bevacizumab)

Neurological: Posterior Reversible Encephalopathy Syndrome (PRES) and Hypertensive encephalopathy

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory thoracic and mediastinal disorders: Nasal septum perforation, dysphonia and Pulmonary hypertension

Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, hypertension, gastrointestinal perforation, hemorrhage

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

Congenital, familial, and genetic disorder: Foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed

4.9 Overdose

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

5.0 Pharmacological Properties

5.1 Pharmacodynamics properties

Mechanism of Action

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanized murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149 000 daltons.

Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor 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.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to Bevacizumab. Based on clinical data, some subjects tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. These subjects tested positive for neutralizing antibodies

against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab with the incidence of antibodies to other products may be misleading.

5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab is presented based on clinical trials conducted on patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability; with initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Absorption

Based on a population pharmacokinetic analysis, the estimated half-life of bevacizumab was approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days.

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.

5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks.

6.0 Pharmaceutical Particulars

6.1 List of excipients

S. No.	Ingredients	Function
1	α , α-Trehalose dihydrate	Tonicity agent
2	Sodium phosphate (monobasic, monohydrate)	Buffering agent
3	Sodium phosphate (dibasic, anhydrous)	Buffering agent
4	Polysorbate 20	Stabilizing agent
5	Water for Injection	Solvent

6.2 Incompatibilities

Do not administer Bevacizumab injection in conjunction with other drug solutions.

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefine bags or infusion sets have been observed. A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

6.3 Shelf life

2 years from the date of manufacture.

Chemical and physical infusion stability has been demonstrated for 48 hours at 2°C to 8°C and at room temperature in sodium chloride 9 mg/ml (0.9%) solution for injection.

From a microbiological point of view, the product 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Keep the container in the outer carton in order to protect from light. Keep out of reach of children. Do not freeze or shake.

6.5 Nature and contents of container

The following presentations are available:

S. No.	Strengths / Dosages
1.	**Bevacizumab: 100 mg/ 4ml** Bevacizumab injection 4 ml single dose vial. Each 4 ml contains 100 mg of Bevacizumab (concentration: 25mg/ml).

2.	**Bevacizumab: 400 mg/ 16ml** Bevacizumab injection 16 ml single dose vial Each 16 ml contains 400 mg of Bevacizumab (concentration: 25mg/ml).

Container closure system is the primary packaging item of the Bevacizumab drug product. 6 ml and 20 ml clear pre sterilized glass vial: neutral (USP Type 1, make: Schott Kaisha Pvt. Ltd.) with 20mm butyl rubber stopper is used to fill Bevacizumab drug product. The rubber stopper is formulated with elastomer butyl coated with FluroTec® (make: West Pharmaceutical service), which doesn't affect the product quality and using 20mm flip off seals (make: West Pharmaceutical service) for sealing. Upon filling of the drug product into the glass vial, the vial is stoppered with a elastomeric butyl rubber stopper and sealed with flip-off seal. The approved vial label with batch details is affixed on the glass vial. The labeled glass vial is placed into the carton box along with one package insert.

6.6 Special precautions for disposal

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 discoloration prior to administration.

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.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

7.0 Marketing Authorisation / Prequalification Holder

Manufactured by:

Hetero Biopharma Limited,
Sy. No. 458 (Part), TSIIC-Formulation SEZ,
Polepally Village, Jadcherla Mandal
Mahaboobnagar District – 509 301,
Telangana State, India.

8.0 Marketing Authorization Number(s)

05500/07341/NMR/2019

9.0 Date of first authorisation / renewal of the authorisation

Nov 20, 2020