SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bevamab 100 for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single use vial contains 100 mg of bevacizumab (humanized anti-VEGF monoclonal antibody) in 4 mL (25 mg/mL)

3 PHARMACEUTICAL FORM

Concentrate for solution in single use vial for intravenous (IV) infusion.

Clear to slightly opalescent, colorless to pale brown solution.

Sterile/radioactive statement

Sterile

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bevacizumab is indicated for the treatment of:

1. In addition to platinum-based chemotherapy, indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
2. Metastatic carcinoma of the colon or rectum in adult patients in combination with fluoropyrimidine-based chemotherapy.
3. Advanced and/or metastatic renal cell cancer in adult patients as first line treatment in combination with Interferon alfa-2a.
4. Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients as the front-line treatment in combination with carboplatin and paclitaxel. For treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer and naïve to VEGF receptor-targeted agents including bevacizumab
5. Platinum -resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients in combination with paclitaxel, topotecan or pegylated doxorubicin who received only up to two prior chemotherapy regimens and naïve to VEGF receptor-targeted agents including bevacizumab.
6. Persistent, recurrent, or metastatic carcinoma of the cervix in adult

patients in combination with paclitaxel and cisplatin/topotecan who cannot receive platinum therapy.

7. Glioblastoma with progressive disease in adult patients following prior therapy as a single agent.
8. Metastatic breast cancer as first line treatment in combination with capecitabine in adult patients in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Metastatic breast cancer as first line treatment in adult patients in combination with paclitaxel.

4.2 Posology and Method of Administration

Posology

Bevacizumab was administered at the dose level of 7.5 mg/kg of body weight every 3 weeks as an IV infusion in addition to platinum-based chemotherapy during clinical trial in patients with unresectable or metastatic NSCLC.

Information provided below is based on the innovator data.

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy

Bevacizumab is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by bevacizumab as a single agent until disease progression.

The recommended dose of bevacizumab is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an IV infusion. Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of bevacizumab, administered as an IV infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an IV infusion. It is recommended that treatment be

continued until progression of the underlying disease or until unacceptable toxicity.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment: Bevacizumab is 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 as an IV infusion.

Treatment of platinum-sensitive recurrent disease: Bevacizumab is 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 disease progression. The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

Treatment of platinum-resistant recurrent disease: Bevacizumab is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an IV infusion. 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 given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.

Cervical Cancer

Bevacizumab is 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 given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Glioblastoma

The recommended dose of bevacizumab is 10 mg/kg every 2 weeks as an IV infusion.

Metastatic breast cancer (mBC)

The recommended dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks or 15mg/kg of body weight given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Special populations

Elderly patients

No dose adjustment is required in the elderly.

Patients with renal impairment

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

Patients with hepatic impairment

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

Paediatric population

The safety and efficacy of bevacizumab in children less than 18 years old have not been established. There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of bevacizumab in children with glioblastoma.

Method of administration

The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

It should not be administered as an IV push or bolus.

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Precautions to be taken before handling or administering the medicinal product:

For instructions on dilution of the medicinal product before administration, see section 6.6. Bevacizumab infusions should not be administered or mixed with glucose solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Information provided in this section is based on the innovator data.

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.

GI-vaginal Fistulae

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

Non-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. 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.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension

An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen.

Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all Grade 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.

Arterial thromboembolism

In clinical trials, the 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. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.

Haemorrhage

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

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating

therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly.

Pulmonary haemorrhage/haemoptysis

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

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.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all Grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment.

Neutropenia and infections

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. This

has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions/infusion reactions

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic 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 IV bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when bevacizumab and IV 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 IV bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Bevacizumab is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for IV administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

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.

4.5 Interactions with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

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

Combination of bevacizumab and sunitinib malate

In two clinical trials of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate.

Combination with platinum- or taxane-based therapies

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

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and bevacizumab have not been established.

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the two randomised phase III studies in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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. Studies in animals have shown reproductive toxicity including malformations. IgGs are known to cross the placenta, and bevacizumab is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed.

Bevacizumab is contraindicated in pregnancy.

Breast-feeding

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

Fertility

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

bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

4.7 Effects on Ability to Drive and Use Machines

Information provided in this section is based on the innovator data.

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

Information provided below is based on the study conducted with Bevacizumab.

In a prospective, randomized, open label, multicentre, comparative, parallel-group, active controlled phase III study, 129 Indian patients with unresectable or metastatic NSCLC were administered with 7.5 mg/kg Intas Bevacizumab drug product or Avastin™ (F. Hoffman-La Roche Limited, Switzerland) every 3 weeks, in combination with cisplatin (80 mg/m2 on day 1 of each cycle) and gemcitabine (1250 mg/m2 on day 1 and 8 of each cycle), for four cycles. Of 129 patients, 87 received Intas Bevacizumab drug product and 42 received Avastin™. A total of 419 adverse events (AEs) were reported by 99 patients during the conduct of study: 312 in patients treated with Intas Bevacizumab and 107 in patients treated with Avastin™. Of these adverse events, 258 AEs were grade 1 (mild), 118 AEs were grade 2 (moderate), 38 AEs were grade 3 (severe) and 4 AEs were grade 5 (death) in nature. Majority of AEs were judged unlikely to be related to the administered drug and were recovered completely. Total 10 deaths were reported in the study: 4 in patients receiving Intas Bevacizumab drug product and 6 in patients receiving Avastin™.

The most frequently reported AEs with incidence of more than 4% during the study were nausea, vomiting, hypertension, asthenia, anaemia, leukopenia, neutropenia, thrombocytopenia, tachycardia, constipation, diarrhoea, abdominal pain, hypochlorhydria, pyrexia, mucosal ulceration, loss of appetite, pain, fatigue, respiratory distress, dizziness, alopecia, dyspnoea and cough, hypokalaemia, hyponatremia, headache and back pain. These were the expected AEs reported with the use of Bevacizumab and other chemotherapy agents used during the conduct of the study. Overall, Intas Bevacizumab drug product and Avastin™ were well tolerated in patients with NSCLC.

Information provided below is based on the innovator data.

a. ***Summary of the safety profile***

The overall safety profile of bevacizumab is based on data from over 5,400 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 NSCLC patients.
- 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.

b. ***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).

Table 1 and 2 list adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications.

Table 1 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 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference

compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered to be clinically significant or severe.

Post-marketing adverse reactions (innovator data) are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions are provided in Table 3.

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.

For those events presented in the Table 1 below, for which grade was 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 was unadjusted for the differential time on treatment.

Table 1: Adverse Reactions by Frequency

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis[a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombocytopenia	Anaemia, Lymphopenia				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]				
Metabolism and nutrition disorders	Anorexia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalopathy syndrome[a,b,d]	Hypertensive encephalopathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thromboembolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Epistaxis, Hypoxia,				

		Dysphonia[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				
Hepatobiliary disorders						Gallbladder perforation[a,b]

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia	Fistula[b,d], Myalgia, 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				Foetal abnormalitie[a,b]
Congenital, familial, and genetic disorder						
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased decreased					

[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

[b] Terms represent a group of events that describe a medical

concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a 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 paediatric population only.

Table 2: Severe Adverse Reactions by Frequency

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising Fasciitis[c]
Blood and lymphatic	Febrile neutropenia,	Anaemia, Lymphopenia				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
system disorders	Leucopenia, Neutropenia[a], Thrombocytopenia					
Immune system disorders						Hypersensitivity, Infusion reactions[a,b,c]
Metabolism and nutrition disorders		Dehydration				
Nervous system disorders	Peripheral sensory Neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible 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 ulcerc, Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation[b,c]
Skin and		Wound healing				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
subcutaneous tissue disorders		complications[a,b], 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 genetic disorder						Foetal abnormalities [a,c]
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal Inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the postmarketing setting, therefore, the frequency

and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled "Frequency Not Known."

[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

[b] For additional information refer below within section "Further information on selected serious adverse reactions"

[c] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

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

Safety profile of bevacizumab in treatment of glioblastoma was assessed in 163 patients who received bevacizumab alone or bevacizumab plus irinotecan. All patients received prior radiotherapy and temozolomide. Bevacizumab was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Bevacizumab was discontinued due to adverse events in 4.8% of patients treated with bevacizumab alone.

In patients receiving bevacizumab alone (N = 84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to bevacizumab: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving bevacizumab alone or bevacizumab plus irinotecan (N = 163), the incidence of bevacizumab-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and PRES (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

d) 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 receiving front-line treatment, 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-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 recurrence outside 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-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥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, 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 postoperative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting bevacizumab. 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 1.2% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension

In 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 hypertension 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 hospitalization.

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

The risk of bevacizumab-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-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.

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 8.1% 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 ≥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 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 antirheumatic/anti-inflammatory substances, and treatment with anticoagulants, prior radiotherapy, and 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-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-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 bevacizumab in 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 bevacizumab in combination with chemotherapy versus chemotherapy alone.

Congestive heart failure (CHF)

In clinical trials with bevacizumab, 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 bevacizumab in 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 bevacizumab, 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/m2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to RCHOP 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/m2 when combined with bevacizumab.

Hypersensitivity reactions/infusion reactions

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in 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 bevacizumab in 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 bevacizumab in 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 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).

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 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.

Immunogenicity

As with all therapeutic proteins, there is a potential for immune response to bevacizumab. The detection of antibody formation is highly dependent on the sensitivity and specificity of assay. Additionally, observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to bevacizumab in studies described below with incidence of

antibodies in other studies or other products may be misleading.

In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab (innovator product) using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Information provided below is based on the study conducted with Intas Bevacizumab.

Immunogenicity of Intas Bevacizumab was evaluated during a prospective, randomized, open-label, multicenter, parallel-group, active-controlled study in 129 Indian patients with unresectable or metastatic NSCLC. Patients were administered with Intas Bevacizumab drug product (N=87) or Avastin™ (N=42) at the dose level of 7.5 mg/kg every 3 weeks, in combination with cisplatin and gemcitabine, for four cycles. Pre-dose (baseline) and post- dose (end of 4 cycles) samples were analyzed from 20 patients from Intas Bevacizumab arm. No incidence of anti-drug antibodies against bevacizumab was observed in any patient.

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. In one clinical trial, the incidence of hypertension of grade ≥3 was two-fold 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.

*e) **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 nonrhabdomyosarcoma 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 (innovator data)

Table 3: Adverse Reactions Reported in Post-marketing Setting

System organ class (SOC)	**Reactions (frequency*)**
Infections and Infestations	Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare)
Immune system disorders	Hypersensitivity reactions and infusion reactions (not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.
Nervous system disorders	Hypertensive encephalopathy (very rare) Posterior Reversible Encephalopathy Syndrome (PRES), (rare)

System organ class (SOC)	Reactions (frequency*)
Vascular disorders	Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been reported in patients treated with Bevacizumab, most of which occurred in patients who had identified risk factors for
	ONJ, in particular exposure to IV bisphosphonates and/or a history of dental disease requiring invasive dental procedures
	Cases of non-mandibular osteonecrosis have been observed in Bevacizumab treated paediatric patients.
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed.

- If specified, frequency has been derived from clinical trial data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Information provided in this section is based on the innovator data.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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. 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.

Pharmacodynamic effects

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.

Clinical efficacy

Information provided in this section is based on the study conducted with Intas Bevacizumab.

Efficacy and safety profile of Intas Bevacizumab drug product and Avastin™ (F. Hoffman-La Roche Limited, Switzerland) was evaluated during a prospective, randomized, open label, multicenter, comparative, parallel-group, active controlled, phase III study in 129 Indian patients with unresectable or metastatic NSCLC. Chemotherapy-naïve male or female patients with histologically or cytologically confirmed NSCLC were randomized (2:1) to receive IV cisplatin 80 mg/m² on day 1 and IV gemcitabine 1250 mg/m² on day 1 and 8 of each cycle in combination with either Intas Bevacizumab (n=87) or Avastin™ (n=35) at a dose of 7.5 mg/kg every three weekly for total of four cycles. Patients with predominant squamous histology, brain metastasis, gross haemoptysis (≥1/2 tsp of bright red blood), unstable angina, or receiving anticoagulant therapy were excluded. The primary efficacy parameter was best overall response (best response recorded across all time points from start of treatment until end of treatment; complete response [CR] + partial response [PR]) at the end of 4th chemotherapy cycle. Other efficacy parameters included disease control rate (CR + PR + stable disease) and overall response rate (CR + PR) at the end of 4th chemotherapy cycle. Out of 129 patients enrolled and dosed, 110 patients (n=75 for Intas Bevacizumab and n=35 for Avastin™) were included in per protocol population.

Efficacy results at the end of study (4th cycle) as measured by best overall response rate, disease control rate and overall response rate are summarized in below Table 4. Overall, efficacy profile of Intas Bevacizumab and Avastin™ was found to be similar.

Table 4: Efficacy Results of Intas Bevacizumab in NSCLC (Per Protocol Population)

Response	Per-protocol Population, N (%)		Difference of Treatments [95% CI]
	Intas Bevacizumab (N=75)	Avastin™ (N=35)	
Best overall response rate (CR + PR)	31 (41.33%)	14 (40.00%)	1.33% [-18.35, 21.02%]
Disease control rate (CR + PR + SD)	71 (94.67%)	33 (94.29%)	0.38% [-8.84, 9.60%]
Overall response rate (CR + PR)	27 (36.00%)	12 (34.29%)	1.71% [-17.40, 20.83%]

5.2 Pharmacokinetic properties

Information provided in this section is based on the study conducted with Intas Bevacizumab.

Pharmacokinetic (PK) profile of Intas Bevacizumab was evaluated in subset of patients during comparative, open-label, randomized, multicenter phase III study in patients with unresectable or metastatic NSCLC. In each 21-day cycle, patients were administered Intas Bevacizumab or Avastin™ as IV infusion at 7.5 mg/kg dose in combination with cisplatin and gemcitabine, for total four cycles. Serum samples were collected from 10 patients each from Intas Bevacizumab and Avastin™ arm during cycle 1. Descriptive statistics were used to report the PK parameters of Intas Bevacizumab and Avastin™ (Table 5).

Table 5: Pharmacokinetic Parameters of Intas Bevacizumab in NSCLC patients (Cycle 1)

Parameters (Units)	Mean ± SD (Untransformed data)	
	Intas Bevacizumab(N=09)	Avastin™ (N=10)
AUC_{0-480} (µg*h/mL)	1805.912 ± 293.6909	2155.212 ± 577.5223
C_{max} (µg/mL)	29.038 ± 4.3307	35.790 ± 4.2238
T_{max} (h)*	1.750 (1.500 – 2.000)	1.750 (1.500 – 2.000)

*Median value reported for T_{max}

Information provided in this section is based on the innovator data.

The PK 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 PK of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

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

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of 125I-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.

<u>Pharmacokinetics in special populations</u>

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

Paediatric population

The PK 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 PK model. The PK results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalized by body weight, with exposure trending lower as body weight decreased. Age was not associated with the PK of bevacizumab when body weight was taken into account.

The PK 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.

Renal impairment

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

5.3 Preclinical safety data

Information provided below is based on the studies conducted with Intas Bevacizumab.

In acute toxicity studies, maximum tolerated dose of Intas Bevacizumab was found to be 1845 mg/kg and 915 mg/kg in mice and rats, respectively when administered by IV route. In 28-day repeat-dose toxicity studies, no observed adverse effect level of Intas Bevacizumab was found to be 91.5 and 192 mg/kg/week in rats and rabbits, respectively when administered by IV route. In local tolerance studies, Intas Bevacizumab was found to be non-irritant and non-sensitizer in rabbits and guinea pigs, respectively.

Information provided below is based on the innovator 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. Information on foetal malformations observed in the post marketing setting are provided in section on Fertility, Pregnancy and Lactation and Undesirable Effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate

Mono-Sodium dihydrogen phosphate monohydrate

di-Sodium hydrogen phosphate anhydrous

Polysorbate 20

Ortho phosphoric acid

Sodium hydroxide

Water for injection

6.2 Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride and polyolefin bags have been observed.

6.3 Shelf life

Vial (unopened)

24 months when stored under recommended storage conditions

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C 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 25 ± 2°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Bevacizumab should not be used after the expiry date shown on pack.
Store vials in a refrigerator at 2°C to 8°C.
Do not freeze. Do not shake.
Keep the vial in the outer carton in order to protect from light.
Keep out of reach and sight of children.
The product doesn't contain any anti-microbial preservative; therefore, care must be taken to ensure sterility of the prepared solution.

6.5 Nature and contents of container

Intas Bevacizumab 100mg/4mL: 4 mL solution in a vial (Type-I glass) with a stopper (flurotec coated) containing 100 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for administration, disposal and other handling

Bevacizumab infusions should not be administered or mixed with dextrose

or glucose solutions. Do not administer as IV push or bolus.

It should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 to 16.5 mg/mL.

Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

7 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Intas Pharmaceuticals Limited

Plot No. 423/P/A, Sarkhej - Bavla

Highway, Village: Moraiya, Taluka:

Sanand, District: Ahmedabad 382 213,

Gujar

8. Marketing Authorisation Number
H2026/CTD11020/23313

9. Date of First Authorisation / Renewal of Authorisation
2026 March 14

10. Date of Revision of The Text
2026 March 14