SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Gyvexia 25 mg/mL concentrate for solution for infusion

2. Qualitative and Quantitative Composition

Each mL of concentrate contains 25 mg of bevacizumab*

Each 4 mL vial contains 100 mg of bevacizumab

Each 16 mL vial contains 400 mg of bevacizumab

For dilution and other handling recommendations, see section 6.6

*Bevacizumab is a recombination humanized monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Concentrate for solution for infusion

Sterile clear to slightly opalescent liquid, colorless to pale yellow

4. Clinical Particulars

4.1 Therapeutic Indication

In combination with other agents for:

- Metastatic Colorectal Cancer (mCRC)
- Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)
- Advanced and/or metastatic Renal Cell Cancer (mRCC)
- Malignant Glioma (WHO grade IV) - Glioblastoma
- Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer
- Cervical Cancer

Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer other than predominantly squamous cell histology.

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

Bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.

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

Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

4.2 Posology and method of administration

Gyvexia must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Posology

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Gyvexia, administered as an intravenous 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.

Non-small cell lung cancer (NSCLC)

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

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

The recommended dose of Gyvexia is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous 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.

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib

EGFR mutation testing should be performed prior to initiation of treatment with the combination of Gyvexia and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determination.

The recommended dose of Gyvexia when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that the treatment with Gyvexia in addition to erlotinib is continued until disease progression.

For the posology and method of administration of erlotinib, please refer to the full erlotinib prescribing information.

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of Gyvexia is 10 mg/kg of body weight given once every 2 weeks as an intravenous 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: Gyvexia is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Gyvexia as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

The recommended dose of Gyvexia is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

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

Treatment of platinum-resistant recurrent disease: Gyvexia is administered in combination with one of the following agents - paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Gyvexia is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Gyvexia is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Gyvexia is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.

Cervical Cancer

Gyvexia is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.

The recommended dose of Gyvexia is 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.

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. Current available data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made.

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.

Method of administration

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

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

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in section 4.4.

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. Gyvexia infusion 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 excipient listed in section 6.1.

- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal (GI) perforations and Fistulae (see section 4.8)

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 (see section 4.8)

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 therapy should be considered.

Wound healing complications (see section 4.8)

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 (see section 4.8)

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) (see section 4.8)

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 (see section 4.8)

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 (see section 4.8)

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 (see section 4.8)

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).

Hemorrhage

Patients treated with bevacizumab have an increased risk of hemorrhage, especially tumor-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 signals 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 hemorrhage/hemoptysis

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

Aneurysms and artery dissections

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

Congestive heart failure (CHF) (see section 4.8)

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.

Neutropenia and infections (see section 4.8)

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 (see section 4.8)

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) (see section 4.8)

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, lf possible.

Intravitreal use

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

Systemic effects after 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/fertillty

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

4.5 Interaction 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 (see Hypertension, Proteinuria, PRES in section 4.4).

Combination with platinum- or taxane-based therapies

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

Radiotherapy

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

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomized phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no clinical trial data on the use of bevacizumab in pregnant women. 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

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

4.8 Undesirable effects

Summary of the safety profile

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

The most serious adverse reactions were:

- Gastrointestinal perforations (see section 4.4)
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non-small cell lung cancer patients (see section 4.4)
- Arterial thromboembolism (see section 4.4)

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

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

Tabulated list of adverse reactions

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

Tables 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-authorization 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 by the MAH to be clinically significant or severe.

Post-marketing adverse reactions 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.

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		Necrotizing fasciitis[a]		
Blood and	Febrile	Anaemia,				

lymphatic system disorders	neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Lymphopenia				
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]				
Metabolism and nutrition disorders	Anorexia Hypomagnesaemia Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysgeusia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalo-pathy syndrome[a,b,d]	Hypertensive encephalo-pathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorder		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				Renal thrombotic microangiopathy[a,b] Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal Disorder, Proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				

Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b] Non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic Pain				
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

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

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

[c]Based on a substudy from NSABP C-08 with 295 patients

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

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

[f]Observed in pediatric population only

Table 2: Severe adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotizing fasciitis[c]
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders						Hypersensitivity, infusion reactions[a,b,c]
Metabolism and nutrition disorders		Dehydration, Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome[a,b,c],

						Hypertensive encephalopathy[c]
Cardiac disorder		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] Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Epistaxis, Dysphoea, Hypoxia,				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal Disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b] Gastrointestinal ulcer[c], Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation[b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar 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 by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the postmarketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled "Frequency Not Known."

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

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

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

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

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and Fistulae (see section 4.4)

Bevacizumab has been associated with serious cases of gastrointestinal perforation.

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

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

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

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

GI-vaginal Fistulae in study GOG-0240

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

Non-GI Fistulae (see section 4.4)

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 (see section 4.4)

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

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

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

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

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

Hypertension (see section 4.4)

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 (see section 4.4)

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 (see section 4.4)

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 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical trials urine protein levels of ≥ 2g/24 hrs led to the holding of bevacizumab until recovery to < 2g/24 hrs.

Haemorrhage (see section 4.4)

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

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

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

Tumour-associated haemorrhage (see section 4.4)

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, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent phase III trials, while patients with unknown tumour histology were included. In patients with NSCLC excluding predominant squamous histology, all Grade reactions were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with < 1% with chemotherapy alone (NCI-CTCAE v.3). Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.4).

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomized clinical trials. In an exploratory retrospective analysis of data from 13 completed randomized 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 (see section 4.4)

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

Hypersensitivity reactions/infusion reactions (see section 4.4 and Post-marketing experience below)

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 (see sections 4.4 and 4.6)

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 normalized 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.

Other special populations

Elderly patients

In randomized clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see sections 4.4 and 4.8 under Thromboembolism). In one clinical trial, the incidence of hypertension of grade ≥ 3 was 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.

Paediatric population

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

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

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

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

Post-marketing experience

Table 3: Adverse reactions reported in post-marketing setting

System organ class (SOC)	Reactions (frequency*)
Infections and infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see also section 4.4)
Immune system disorders	Hypersensitivity reactions and infusion reactions (not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see also section 4.4 and Hypersensitivity reactions/infusion reactions above)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and Hypertension in section 4.8) Posterior Reversible Encephalopathy Syndrome (PRES) (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use. For further information on proteinuria see section 4.4 and Proteinuria in section 4.8
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with bevacizumab, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)
	Cases of non-mandibular osteonecrosis have been observed in bevacizumab-treated paediatric patients (see section 4.8, Paediatric population)
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.6)

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

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. Pharmacological properties:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agent, 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 tumors, 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.

5.2 Pharmacokinetic properties:

The pharmacokinetic data for bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability, with an

initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value of peripheral volume (V_p) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is co-administered with antineoplastic agents. After correcting for body weight, male patients had a large 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 blind 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 of 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 patient with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

Pharmacokinetics in special populations

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

Renal impairment

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

Hepatic impairment

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

Paediatric population

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

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. Information on foetal malformations observed in the post marketing setting are provided in section 4.6 Fertility, Pregnancy and Lactation and 4.8 Undesirable Effects.

6. Pharmaceutical particulars

6.1 List of excipients

α,α-Trehalose dihydrate, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, polysorbate 20, water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

6.3 Shelf life

Unopened vial

2 years

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C- 8°C and 30°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 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in refrigerator (2°C - 8°C)

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

4 ml solution in a vial (Type I glass) with a stopper (chlorobutyl rubber) containing 100 mg of bevacizumab.

16 ml solution in a vial (Type I glass) with a stopper (chlorobutyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Gyvexia should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be

kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of bevacizumab can be diluted with 0.9 % sodium chloride solution for injection to a total volume of 100 mL.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

No incompatibilities between bevacizumab and polyvinyl chloride (PVC) or polyolefine (PO) bags or infusion sets have been observed.

Bevacizumab is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. Marketing authorization holder

Exeltis (Thailand) Co.,Ltd., Bangkok, Thailand

(Manufactured by Sinergium Biotech S.A., Buenos Aires, Argentine Republic, released by mAbxience S.A.U., Buenos Aires, Argentine Republic)

8. Marketing authorization number

On registration process

9. Date of first authorization/Renewal of the authorization

Draft version

10. Date of revision of the text

Draft version