**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

Bevacizumab 100 Equity, concentrate for solution for infusion

Bevacizumab 400 Equity, 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 recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

Sugar free.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear or slightly opalescent from colourless to light brown liquid.

The solution is free of visible particulate matter.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Metastatic Colorectal Cancer: Bevacizumab Equity in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic adenocarcinoma of the colon or rectum.
- Locally recurrent or metastatic Breast Cancer: Bevacizumab Equity in combination with paclitaxel is indicated for first-line treatment of patients with locally recurrent or metastatic adenocarcinoma of the breast.
- Advanced, metastatic or recurrent adenocarcinoma of the lung: Bevacizumab Equity, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent adenocarcinoma of the lung.
- Advanced and/or metastatic Renal Cell Cancer (mRCC): Bevacizumab Equity in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

### 4.2 Posology and method of administration

Bevacizumab Equity must be prepared and administered under the supervision of a healthcare provider experienced in the use of antineoplastic medicines.

**Posology**

*Metastatic carcinoma of the colon or rectum (mCRC)*

The recommended dose of Bevacizumab Equity, administered as an intravenous infusion, is as follows:

First-line treatment: 5 mg/kg of body weight given once every 2 weeks or 7,5 mg/kg of body weight given once every 3 weeks.

Second-line treatment: 10 mg/kg of body weight given every 2 weeks 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.

*Metastatic Breast Cancer (mBC)*

The recommended dose of Bevacizumab Equity is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

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

*Adenocarcinoma of the lung*

Bevacizumab Equity is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Bevacizumab Equity as a single agent until disease progression. The recommended dose of Bevacizumab Equity when used in addition to cisplatin-based chemotherapy is 7,5 mg/ kg of body weight given once every 3 weeks as an intravenous infusion. The recommended dose of Bevacizumab Equity when used in addition to carboplatin-based chemotherapy 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.

*Advanced and/or metastatic Renal Cell Cancer (mRCC)*

The recommended dose of Bevacizumab Equity 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.

**Special populations**

Analyses of demographic data suggest that no dose adjustments are necessary for age or sex.

*Elderly*: No close adjustment for Bevacizumab Equity is required in the patients ≥ 65 years of age.

*Renal impairment:* The safety and efficacy of Bevacizumab Equity have not been studied in patients with renal impairment (see section 5.2).

*Hepatic impairment*: The safety and efficacy of Bevacizumab Equity has not been studied in patients with hepatic impairment (see section 5.2).

**Paediatric population**

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

**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. The initial dose of Bevacizumab Equity should be administered following chemotherapy, all subsequent doses can be given before or after chemotherapy.

Bevacizumab Equity 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 medicine*

For instructions on dilution of the medicine before administration, see section 6.6.

Bevacizumab Equity infusions should not be administered or mixed with glucose solutions. This medicine must not be mixed with other medicines except those mentioned in section 6.6.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy and lactation (see section 4.6)
- Patients with untreated Central Nervous System (CNS) metastases (see section 4.4).
- Concomitant use with sunitinib (see section 4.5).

- Intravitreal use.

## 4.4 Special warnings and precautions for use

*Traceability*

In order to improve the traceability of biological medicines, the name and the batch number of the administered product should be clearly recorded.

*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 Equity. 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 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*

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 Equity. Permanently discontinue Bevacizumab Equity 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 Equity in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Bevacizumab Equity should be considered.

*Wound healing complications* (see section 4.8)

Bevacizumab Equity 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 less frequently been reported in patients treated with Bevacizumab Equity. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab Equity therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

*Hypertension (see section 4.8)*

An increased incidence of hypertension was observed in Bevacizumab Equity-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 Equity treatment.

There is no information on the effect of Bevacizumab Equity 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 Equity 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 reports of Bevacizumab Equity-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 Equity. The safety of reinitiating Bevacizumab Equity 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 Equity. 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 Equity. 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 Equity in combination with chemotherapy compared to those who received chemotherapy alone.

Patients receiving Bevacizumab Equity 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 Equity.

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 Equity treatment.

Patients treated with Bevacizumab Equity in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Bevacizumab Equity should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3).

*Haemorrhage*

Patients treated with Bevacizumab Equity have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab Equity should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Bevacizumab Equity therapy (NCI-CTCAE v.3) (see section 4.8).

Patients with untreated CNS metastases were routinely excluded from clinical trials with Bevacizumab Equity, 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 (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Bevacizumab Equity treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of Bevacizumab Equity 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 Equity 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 Equity concomitantly (NCI-CTCAE v.3).

*Pulmonary haemorrhage/haemoptysis*

Patients with non-small cell lung cancer treated with Bevacizumab Equity 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 Equity.

*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 Equity, 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 hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Bevacizumab Equity.

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 Equity 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 (NCI-CTCAE v.3) (see section 4.8).

*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 Equity in comparison to chemotherapy alone.

*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 Equity is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

*Osteonecrosis of the jaw (ONJ)* (see section 4.8)

Cases of ONJ have been reported in cancer patients treated with Bevacizumab Equity, 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 Equity 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 Equity. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

*Intravitreal use*

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

*Ovarian failure/fertility*

Bevacizumab Equity may impair female fertility (see sections 4.6 and 4.8). Therefore, fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Bevacizumab Equity.

## 4.5 Interaction with other medicines 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 Equity monotherapy compared to patients receiving Bevacizumab Equity 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 medicines*

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

*Combination of bevacizumab and sunitinib malate*

In clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in patients treated with Bevacizumab Equity (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 Equity and sunitinib malate (see *Hypertension, Proteinuria, PRES* in section 4.4).

*Combination with platinum- or taxane-based therapies* (see sections 4.4 and 4.8)

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 ort taxane-based therapies in the treatment of NSCLC and mBC.

*Radiotherapy*

The safety and efficacy of concomitant administration of radiotherapy and Bevacizumab Equity 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 clinical studies in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with Bevacizumab Equity plus chemotherapy, is associated with decreased progression free survival (PFS) and/or overall survival (OS), and with increased toxicity compared with Bevacizumab Equity 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 Equity in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Bevacizumab Equity 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 (see section 4.8). Bevacizumab Equity is contraindicated in pregnancy (see section 4.3).

### Breastfeeding

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 (see section 5.3), women must discontinue breastfeeding during therapy and not breastfeed for at least six months following the last dose of Bevacizumab Equity (see section 4.3).

### Fertility

Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3). In the adjuvant treatment of patients with colon cancer,

premenopausal women have shown a higher incidence of new cases of ovarian failure in the Bevacizumab Equity group compared to the control group. After discontinuation of Bevacizumab Equity treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with Bevacizumab Equity on fertility are unknown.

## 4.7 Effects on ability to drive and use machines

Bevacizumab Equity has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with Bevacizumab Equity use (see Table 1 in section 4.8). If patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

## 4.8 Undesirable effects

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

*Summary of the safety profile*

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 Equity 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 Equity therapy are likely to be dose-dependent.

Tables 1 and 2 list adverse reactions associated with the use of Bevacizumab Equity in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class.

Table 1 provides all adverse reactions by frequency that were determined to have a causal relationship with Bevacizumab Equity 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 includes 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 are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions is 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 frequently seen with chemotherapy; however, Bevacizumab Equity may exacerbate these reactions when combined with chemotherapeutic medicines. 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** | **Frequent** | **Less frequent** | **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, leukopenia, neutropenia[b], | | |

| | | | |
|---|---|---|---|
| | thrombocytopenia, anaemia, lymphopenia | | |
| **Immune system disorders** | Hypersensitivity, infusion reactions[a,b,d] | | |
| **Metabolism and nutrition disorders** | Anorexia, hypomagnesaemia, hyponatraemia, dehydration | | |
| **Nervous system disorders** | Peripheral sensory neuropathy[b], dysarthria, headache, dysguesia, cerebrovascular accident, syncope, somnolence | Posterior reversible encephalopathy syndrome[a,b,d], hypertensive encephalopathy[a] | |
| **Eye disorders** | Eye disorder, increased lacrimation | | |
| **Cardiac disorders** | Congestive heart failure[b,d], supraventricular tachycardia | | |
| **Vascular disorders** | Hypertension[b,d], thromboembolism (venous)[b,d], thromboembolis[m] | | Renal thrombotic |

| | | | |
|---|---|---|---|
| | (arterial)[b,d], haemorrhage[b,d], deep vein thrombosis | | microangio-pathy[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 | | Gastrointes-tinal ulcer[a] |
| **Hepato-biliary** | | | Gallbladder |

| | | | |
|---|---|---|---|
| **disorders** | | | perforation[a],[b] |
| **Skin and subcutaneous tissue disorders** | Wound healing complications[b,d], exfoliative dermatitis, dry skin, skin discoloration, palmar-plantar erythrondys-aesthesia 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 | | |

[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 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** | **Frequent** | **Less frequent** | **Frequency Not Known** |
|---|---|---|---|
| **Infections and infestations** | Sepsis, cellulitis, abscess[a,b], infection, urinary tract, infection | | Necrotising fasciitis[c] |
| **Blood and lymphatic system disorders** | Febrile neutropenia, leukopenia, neutropenia[a], thrombocytopenia, anaemia, lymphopenia | | |
| **Immune system** | | | Hypersensitivity, |

| | | | |
|---|---|---|---|
| **disorders** | | | infusion reactions[a,b,c] |
| **Metabolism and nutrition disorders** | Dehydration, hyponatraemia | | |
| **Nervous system disorders** | Peripheral sensory neuropathy[a], cerebrovascular accident, syncope, somnolence, headache | | Posterior reversible encephalopathy syndrome [a,b,c], hypertensive encephalopathy[c] |
| **Cardiac disorders** | Congestive heart failure[a,b], supraventricular tachycardia | | |
| **Vascular disorders** | Hypertension[a,b], thromboembolism arterial[a,b], haemorrhage[a,b], thromboembolism (venous)[a,b], deep vein thrombosis | | Renal thrombotic microangiopathy[b,c], aneurysms and artery dissections |
| **Respiratory, thoracic and mediastinal disorders** | Pulmonary haemorrhage/ haemoptysis[a,b], pulmonary embolism, epistaxis, dyspnoea, hypoxia | | Pulmonary hypertension[c], nasal septum perforation[c] |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Diarrhoea, nausea, vomiting, abdominal pain, intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae[c,d], gastrointestinal disorder, stomatitis, proctalgia | | Gastrointestinal perforation[a,b], gastrointestinal ulcer[c], rectal haemorrhage |
| **Hepatobiliary disorders** | | | Gallbladder perforation[b,c] |
| **Skin and subcutaneous tissue disorders** | Wound healing complications[a,b], Palmar-plantar 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,** | | | Foetal |

| | | | |
|---|---|---|---|
| **familial, and genetic disorder** | | | 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 post-marketing 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 adverse events**

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

Bevacizumab Equity 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 metastatic adenocarcinoma of the lung, 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.

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 Equity-treated patients.

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 frequently in patients with other types of cancer.

*Non-GI Fistulae* (see section 4.4)

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

Less frequent 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 Equity, with most reactions occurring within the first 6 months of therapy.

*Wound healing* (see section 4.4)

As Bevacizumab Equity may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in 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 Equity. 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 Equity at the time of surgery. The incidence varied between 10 % and 20 %.

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 Equity and paclitaxel and in none of the patients receiving pac!itaxel alone.

*Hypertension* (see section 4.4)

In clinical trials, the overall incidence of hypertension (all grades) ranged up to 42,1 % in patients receiving Bevacizumab Equity. The overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving Bevacizumab Equity ranged from 0,4 % to 17,9 %. Grade 4 hypertension (hypertensive crisis) occurred in up to 1,0 % of patients treated with Bevacizumab Equity and chemotherapy compared to up to 0,2 % of patients treated with the same chemotherapy alone.

In patients who received Bevacizumab Equity in combination with erlotinib as first-line treatment for adenocarcinoma of the lung with EGFR activating mutations, all grade hypertension was observed in 77,3 % of the patients, compared to 14,3 % of patients treated with erlotinib alone. Grade 3 hypertension was 60,0 % in patients treated with Bevacizumab Equity 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 less frequently resulted in discontinuation of Bevacizumab Equity treatment or hospitalisation.

Cases of hypertensive encephalopathy have been reported less frequently, some of which were fatal.

The risk of Bevacizumab Equity-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 reports of Bevacizumab Equity-treated patients developing signs and symptoms that are consistent with PRES, a 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 Equity therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of reinitiating Bevacizumab Equity therapy in patients previously experiencing PRES is not known.

*Proteinuria* (see section 4.4)

Proteinuria has been reported within the range of 0,7 % to 54,7 % of patients receiving Bevacizumab Equity.

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 Equity therapy. In most clinical trials urine protein levels of ≥ 2 g/24 hrs led to the holding of Bevacizumab Equity until recovery to < 2 g/24 hrs.

*Haemorrhage* (see section 4.4)

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 Equity-treated patients, compared with up to 4,5 % of patients in the chemotherapy control group.

The haemorrhagic reactions that have been observed 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 Equity 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 Equity 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 Equity 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 Equity 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 less frequently in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.4).

In an exploratory retrospective analysis of clinical data in patients with various tumour types, 3,3 % with brain metastases experienced CNS bleeding (all Grade 4) when treated with Bevacizumab Equity, compared to 1 % (Grade 5) that were not exposed to Bevacizumab Equity. In patients with treated brain metastases, one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with Bevacizumab Equity (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 Equity-treated patients. These were most frequently 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 Equity 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 frequent 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 Equity 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 Equity containing arms compared with up to 2,1 % in the chemotherapy control arms. Fatal outcome was reported in 0,8 % of patients receiving Bevacizumab Equity 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 Equity 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 Equity in combination with chemotherapy compared to up to 0,7 % of patients treated with chemotherapy alone.

In patients with metastatic colorectal cancer receiving Bevacizumab Equity in combination with 5-fluorouracil/folinic acid, arterial thromboembolic reactions were observed in 11 % of patients compared to 5,8 % in the chemotherapy control group.

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

Across indications, the overall incidence of venous thromboembolic reactions ranged from 2,8 % to 17,3 % of Bevacizumab Equity-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 Equity compared with up to 4,9 % in patients treated with chemotherapy alone.

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

*Congestive heart failure (CHF)*

Congestive heart failure (CHF) was observed in all cancer indications but occurred predominantly in patients with metastatic breast cancer. 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 Equity in combination with chemotherapy compared with up to 0,9 % in the control arms. For patients who received anthracyclines concomitantly with Bevacizumab Equity, the incidences of Grade 3 or higher CHF for the respective Bevacizumab Equity and control arms were similar to those in the other studies in metastatic breast cancer: 2,9 % in the anthracycline + Bevacizumab Equity arm and 0 % in the anthracycline + placebo arm. In addition, the incidences of all Grade CHF were similar between the anthracycline + Bevacizumab Equity (6,2 %) and the anthracycline + placebo arms (6,0 %).

Most patients with metastatic breast cancer who developed CHF showed improved symptoms and/or left ventricular function following appropriate medical therapy.

No information is available on the risk of CHF in patients with pre-existing CHF of NYHA (New York Heart Association) II-IV.

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 patients with diffuse large B-cell lymphoma when receiving Bevacizumab Equity with a cumulative doxorubicin dose greater than 300 mg/m$^2$. 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 Equity.

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

Anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Bevacizumab Equity in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions is frequent (up to 5 % in Bevacizumab Equity-treated patients).

*Ovarian failure/fertility* (see sections 4.4 and 4.6)

In a study of Bevacizumab Equity 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, were reported in 2,6 % patients in the mFOLFOX-6 group compared to 39 % in the mFOLFOX-6 + Bevacizumab Equity group. After discontinuation of Bevacizumab Equity treatment, ovarian function recovered in 86,2 % of these evaluable women. Long term effects of the treatment with Bevacizumab Equity on fertility are unknown.

*Laboratory abnormalities*

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

Across clinical trials, the following Grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with Bevacizumab Equity 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

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

**Other special populations**

*Elderly patients*

In 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 leukopenia 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 Equity (see sections 4.4 and 4.8 under Thromboembolism). 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 Equity as compared to those aged ≤ 65 years treated with Bevacizumab Equity.

*Paediatric population*

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

**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 (less frequent) (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 (less frequent) (see also section 4.4 and Hypertension in section 4.8)<br>Posterior Reversible Encephalopathy Syndrome (PRES), (less frequent) (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)<br>Pulmonary hypertension (not known)<br>Dysphonia (frequent) |
| **Gastrointestinal disorders** | Gastrointestinal ulcer (not known) |
| **Hepato-biliary disorders** | Gall bladder perforation (not known) |
| **Musculoskeletal and** | Cases of Osteonecrosis of the Jaw (ONJ) have been |

| | |
|---|---|
| **connective tissue disorders** | reported in patients treated with Bevacizumab Equity, 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 Equity-treated paediatric patients |
| **Congenital, familial, and genetic disorder** | Cases of foetal abnormalities in women treated with Bevacizumab Equity alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.6) |

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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

## 4.9 Overdose

The highest dose tested (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

A. 26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01XC07

Bevacizumab Equity is a biosimilar medicine.

*Mechanism of action*

Bevacizumab Equity (bevacizumab) is a recombinant humanised monoclonal antibody, that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab Equity inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.

*Pharmacodynamics*

Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

### 5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab are available from patients with solid tumours, where it was administered as an IV infusion. The rate of infusion was based on tolerability, with initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab are linear at doses ranging from 1 to 10 mg/kg.

*Distribution:*

The typical value for central volume (Vc) was 2,73 L and 3,28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (Vp) was 1,69 L and 2,35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger Vc (+ 20 %) than female patients.

*Biotransformation:*

Assessment of bevacizumab metabolism in rabbits following a single IV dose of $^{125}$I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

*Elimination:*

The value for clearance is, on average, equal to 0,188 and 0,220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+

17 %) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30 % faster in patients with low levels of serum albumin and 7 % faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

**Pharmacokinetics in special populations:**

The population pharmacokinetics of bevacizumab were analysed 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 studies 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 studies 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.

*Children and Adolescents:*

The pharmacokinetics of bevacizumab have been studied in a limited number of paediatric patients. The resulting pharmacokinetic data suggest that the volume of distribution and clearance of bevacizumab were comparable to that of adults with solid tumours.

**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 and 4.8.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

α, α-trehalose dihydrate

Sodium dihydrogen phosphate monohydrate

Disodium phosphate anhydrous

Polysorbate 20

Water for injections

### 6.2 Incompatibilities

This medicine 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

Vial (unopened)

2 years

Diluted medicine

Chemical and physical in-use stability has been demonstrated for 48 hours at 2 °C to 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 a refrigerator (2 °C – 8 °C).

Do not freeze.

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

For storage conditions after dilution of the medicine, see section 6.3.

## 6.5 Nature and contents of container

4 mL solution in a clear, colourless vial (Type I glass) with a grey stopper (butyl rubber) and aluminium seal with white plastic flip-off cap containing 100 mg of bevacizumab.

16 mL solution in a clear, colourless vial (Type I glass) with a grey stopper (butyl rubber) and aluminium seal with white plastic flip-off cap containing 400 mg of bevacizumab.

Pack of 1 vial.

## 6.6 Special precautions for disposal and other handling

Bevacizumab Equity should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution. A sterile needle and syringe should be used to prepare Bevacizumab Equity.

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 Equity can be diluted with 0,9 % sodium chloride solution for injection to a total volume of 100 mL.

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

No incompatibilities between Bevacizumab Equity and polyvinyl chloride or polyolefine bags or infusion sets have been observed.

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

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## 8. REGISTRATION NUMBER(S)

56/26/0466/7

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 February 2025

## 10. DATE OF REVISION OF THE TEXT