PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Avastin® 100 Concentrate solution for Infusion (Parenteral)
Avastin® 400 Concentrate solution for Infusion (Parenteral)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Avastin contains bevacizumab as the active substance.

Each single-use vial contains bevacizumab 25 mg/mL:

Avastin 100 contains 100 mg bevacizumab per 4 mL

Avastin 400 contains 400 mg bevacizumab per 16 mL

Contains sugar (α, α trehalose dihydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Single-use, preservative free, clear glass vials with grey rubber stoppers, containing clear to slightly opalescent, colourless to pale brown, sterile liquid concentrate. The concentrate must be diluted before use.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metastatic Colorectal Cancer:

Avastin 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:

Avastin in combination with paclitaxel is indicated for first-line treatment of patients with locally recurrent or metastatic adenocarcinoma of the breast.

Avastin in combination with capecitabine, is indicated for first-line treatment of adult patients with metastatic adenocarcinoma of the breast in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.

Advanced, metastatic or recurrent adenocarcinoma of the lung:

Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent adenocarcinoma of the lung.

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

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

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer:

Avastin, in combination with carboplatin and paclitaxel is indicated for the first-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

Cervical Cancer:

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

Malignant Glioma (WHO Grade IV) - Glioblastoma:

Avastin in combination with radiotherapy and temozolomide is indicated for the treatment of adult patients with newly diagnosed glioblastoma.

Avastin, as a single agent, or in combination with irinotecan, is indicated for the treatment of patients with glioblastoma after relapse or disease progression.

4.2 Posology and method of administration

General instructions:

Avastin must be prepared and administered under the supervision of a healthcare professional experienced in the use of antineoplastic medicines. It is recommended that Avastin be continued until progression of the underlying disease.

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

The safety and efficacy of alternating or switching between Avastin and products that are biosimilar but not deemed interchangeable have not been established. Therefore, the benefit-risk of alternating or switching need to be carefully considered.

The initial Avastin 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 Avastin should be administered following chemotherapy; all subsequent doses can be given before or after chemotherapy.

Dose reduction of Avastin for side effects is not recommended. If indicated, Avastin should either be discontinued or temporarily suspended, see sections 4.4 and 4.8. It is recommended that Avastin treatment be continued until progression of the underlying disease.

Withdraw the necessary amount of Avastin and dilute to the required administration volume with 0,9 % sodium chloride solution. The concentration of the final bevacizumab solution should be

kept within the range of 1,4 - 16,5 mg/mL. For recommendations on the storage of Avastin before and after dilution, please refer to section 6.4.

Incompatibilities: see section 6.2

Avastin infusions should not be administered or mixed with glucose solutions.

Do not administer as an intravenous push or bolus.

Metastatic Colorectal Cancer (mCRC):

The recommended dose of Avastin, 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:

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

Metastatic Breast Cancer (mBC):

The recommended dose of Avastin 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.

Adenocarcinoma of the lung:

First-line treatment of Non-Small Cell Lung Cancer (NSCLC) in combination with platinum-based chemotherapy.

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

The recommended dose of Avastin 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 Avastin when used in addition to carboplatin-based chemotherapy is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

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

The recommended dose of Avastin 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 Avastin in addition to erlotinib is continued until disease progression.

Please refer to the full professional information for erlotinib patient selection and dosage.

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

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion.

Malignant Glioma (WHO Grade IV) - Glioblastoma

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

Newly diagnosed glioblastoma: Avastin (10 mg/kg of body weight given once every 2 weeks) is administered in combination with temozolomide and radiotherapy for 6 weeks. Following a 4 week treatment break, Avastin (10 mg/kg of body weight given once every 2 weeks) is re-initiated in combination with temozolomide for up to 6 cycles of 4 week duration. After administration of up to 6 cycles of combined Avastin and temozolomide, Avastin (15 mg/kg of body weight given once every 3 weeks) is continued as a single agent until disease progression.

Treatment of recurrent disease: 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer:

First-line treatment: Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent for 15 months or until disease progression, whichever occurs earlier.

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

Treatment of recurrent disease:

Platinum sensitive:

Avastin is administered in combination with carboplatin and gemcitabine for six cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression.

The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion when administered in combination with Carboplatin and paclitaxel for 6

cycles and up to 8 cycles followed by continued use of Avastin as a single agent until disease progression.

Alternatively, 15 mg/kg every 3 weeks when administrated in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression.

Platinum resistant:

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin.

Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks.

It is recommended that treatment be continued until disease progression.

Cervical Cancer:

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

The recommended dose of Avastin 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.

Special dosage instructions

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

Paediatric use: The safety and efficacy of Avastin in children and adolescents (< 18 years) have not been established (see section 4.4).

Elderly use: No dose adjustment for Avastin is required in patients ≥ 65 years of age.

***Renal impairment*:** The safety and efficacy of Avastin have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of Avastin have not been studied in patients with hepatic impairment.

4.3 Contraindications

Avastin is contraindicated in patients with known hypersensitivity to:

- Bevacizumab or any components of the product.
- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.
- Avastin must not be used during pregnancy. Women must not breastfeed during Avastin treatment and for at least six months after the last dose of Avastin (see section 4.6).
- Concomitant use with sunitinib (see section 4.5).
- Intravitreal use.

4.4 Special warnings and precautions for use

Gastro-intestinal perforations and Fistulae:

Patients with metastatic carcinoma of the colon or rectum may be at increased risk for the development of gastro-intestinal perforation and gallbladder perforation when treated with Avastin and chemotherapy. Therefore, caution should be exercised when treating these patients with Avastin. Avastin should be permanently discontinued in patients who develop gastro-intestinal perforation.

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin are at increased risk of fistulae between the vagina and any part of the GI tract (GI-vaginal fistulae) (see section 4.8).

Wound healing complications*:*

Avastin may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported.

Avastin therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during Avastin treatment, Avastin should be withheld until the wound is fully healed. Avastin therapy should be withheld for elective surgery.

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

Non-GI Fistulae:

Patients are at increased risk for the development of fistulae when treated with Avastin.

Permanently discontinue Avastin in patients with TE (tracheoesophageal) fistula or any grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.

Hypertension:

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

Monitoring of blood pressure is essential during Avastin 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. Avastin should be permanently discontinued, if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES):

There have been reports of Avastin-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (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 Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

Proteinuria:

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 proteinuria may be related to Avastin dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during Avastin therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1,4 % of patients treated with Avastin. Avastin should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Arterial thromboembolism:

In five clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents (CVA), transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Avastin should be permanently discontinued in patients who develop arterial thromboembolic events. A history of arterial thromboembolic events, or age greater than 65, was associated with an increased risk of arterial thromboembolic events during Avastin therapy. Patients receiving Avastin plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Diabetes mellitus patients are particularly liable to develop arterial thromboembolism. Caution should be taken when treating these patients with Avastin.

Venous thromboembolism:

Patients are at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin are at increased risk of venous thromboembolic events (see section 4.8).

Avastin should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤ Grade 3 need to be closely monitored.

Haemorrhage:

The risk of CNS haemorrhage in patients with CNS metastases receiving Avastin could not be fully evaluated, as these patients were excluded from clinical trials. Patients with metastatic cancer of the colon or rectum have an increased risk of tumour-associated haemorrhage. Avastin should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Avastin therapy. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating Avastin therapy in these patients. However, patients who developed venous thrombosis while receiving Avastin therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and Avastin, concomitantly.

Pulmonary Haemorrhage/Haemoptysis:

Patients with adenocarcinoma of the lung treated with Avastin are at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see section 4.8, Haemorrhage). Patients with recent pulmonary haemorrhage/haemoptysis (> 2,5 mL red blood) should not be treated with Avastin.

Congestive Heart Failure (CHF)/Cardiomyopathy:

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating Avastin therapy in patients with these risk factors.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin (see section 4.8).

Neutropenia:

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone.

Ovarian Failure / Fertility

Avastin may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin (see sections 4.4, 4.6 and 4.8).

Paediatric use

Avastin is not approved for use in patients under the age of 18 years. The safety and efficacy of Avastin in this population have not been established. Addition of Avastin to standard of care did not demonstrate clinical benefit in paediatric patients in two phase II clinical trials: one in paediatric high grade glioma and one in paediatric metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to Avastin.

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

4.5 Interaction with other medicines and other forms of interaction

Combination use of Avastin and sunitinib malate*:*

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

Effect of antineoplastic agents on Avastin pharmacokinetics*:*

No clinically relevant interaction of co-administered chemotherapy on Avastin pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There was no difference in clearance of Avastin in patients treated with single-agent Avastin compared to patients receiving Avastin in combination with interferon alpha 2a, erlotinib or chemotherapies (IFL, 5-FU-LV, carboplatin-paclitaxel, capecitabine, doxorubicin or cisplatin-gemcitabine).

Effect of Avastin on the pharmacokinetics of other antineoplastic agents:

No clinically relevant interaction of Avastin 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 Avastin on gemcitabine pharmacokinetics cannot be drawn.

Radiotherapy*:*

The safety and efficacy of concomitant administration of radiotherapy and Avastin was evaluated in a study of 921 patients with newly diagnosed glioblastoma.

No new adverse events associated with Avastin were reported in this study.

The safety and efficacy of concomitant administration of radiotherapy and Avastin has not been established in other indications.

4.6 Fertility, pregnancy and lactation

Pregnancy

Avastin is contraindicated during pregnancy (see section 4.3).

Avastin has been shown to be embryotoxic and teratogenic when administered to rabbits. Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of Avastin could result in an adverse outcome of pregnancy. IgGs are known to cross the placental barrier, and Avastin may inhibit angiogenesis in the foetus.

In the post-marketing setting, cases of foetal abnormalities in women treated with Avastin alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). Avastin may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with Avastin.

Contraception

In women with childbearing potential, appropriate contraceptive measures must be used during Avastin therapy and for at least six months following the last dose of Avastin.

Lactation

As maternal IgG is excreted in milk and Avastin could harm infant growth and development, women must discontinue breastfeeding during Avastin therapy and not breastfeed for at least six months following the last dose of Avastin (see section 4.3).

Fertility

Repeat dose safety studies in animals have shown that Avastin may have an adverse effect on female fertility (see “Ovarian failure/fertility” under sections 4.4 and 4.8). A sub-study with 295 premenopausal women has shown a higher incidence (32/82 patients) of new cases of ovarian failure in the Avastin group compared to the control group (2/78 patients). After discontinuation of Avastin treatment, ovarian function recovered in the majority of patients (25/29). Long term effects of the treatment with Avastin on fertility are unknown.

Ovarian failure was defined as the presence of all of the following for females who were premenopausal at randomisation: a negative serum β-HCG pregnancy test, ≥ 3 months of amenorrhea, and serum follicle-stimulating hormone (FSH) of ≥ 30 MIU/mL.

4.7 Effects on ability to drive and use machines

There is evidence that Avastin treatment may result in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

4.8 Undesirable effects

a. Summary of the safety profile:

Clinical Trials

The overall safety profile of Avastin is based on data from approximately 5 500 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials (see section 4.4 as well).

The most serious side effects were:

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

The most frequently observed side effects across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin therapy are likely to be dose-dependent.

b. Tabulated summary of adverse drug reactions from clinical trials

Table 1 lists side effects associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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). These reactions had occurred either with at least a 2 % difference compared to the control arm (NCI-CTC [common toxicity criteria] Grade 3-5 reactions) or with at least a 10 % difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials.

Side effects are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping side effects are presented in the order of decreasing seriousness. Some of the side effects are reactions commonly seen with chemotherapy, however, Avastin 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: Very Common and Common Side effects

System Organ Class (SOC)	***NCI-CTC Grade 3 - 5 Reactions (≥ 2 % difference between the study arms in at least one clinical trial)***		***All Grade Reactions (≥ 10 % difference between the study arms in at least one clinical trial)***
	Very common	***Common***	***Very common***
Infections and infestations		Sepsis Abscess Cellulitis Infection	Paronychia
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Thrombocytopenia Neutropenia	Anaemia Lymphopenia	
Metabolism and nutrition disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria

Eye disorders			Eye disorder Increased lacrimation
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis Cough
Gastro-intestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal perforation Ileus Intestinal obstruction Recto-vaginal fistulae** Gastro-intestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea

Endocrine disorders			Ovarian failure**
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthaenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthaenia Pain Mucosal inflammation
Reproductive System and Breast		Pelvic pain	
Investigations			Decreased weight

** *Based on a substudy from AVF3077s (NSABP C-08) with 295 patients.*

** *Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.*

Table 2: Side effects reported in the post-marketing setting

System Organ Class (SOC)	Reactions
Congenital, familial and genetic disorders	Cases of foetal abnormalities in women treated with Avastin alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.5).
Immune system disorders	Hypersensitivity reactions and infusion reactions: 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 hypersensitivity, infusion reactions below).
Nervous system disorders	Hypertensive encephalopathy. Posterior Reversible Encephalopathy Syndrome (PRES) (see section 4.4).
Vascular disorders	Renal thrombotic microangiopathy, clinically manifested as proteinuria. (For further information on proteinuria see section 4.4)
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation Pulmonary hypertension Dysphonia
Gastrointestinal disorders	Gastrointestinal ulcer
Hepatobiliary disorders	Gallbladder perforation

Musculoskeletal, connective tissue and bone disorders	Cases of osteonecrosis of the jaw (ONJ) have been observed in Avastin treated patients mainly in association with prior or concomitant use of bisphosphonates (see section 4.4). Cases of osteonecrosis at sites other than the jaw, have been observed in Avastin treated paediatric patients (see section 4.4).
Infections and Infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (see section 4.4).

Osteonecrosis observed in paediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.

c. Further information on selected serious side effects:

Gastro-intestinal perforations and Fistulae (also refer to section 4.4):

Avastin has been associated with serious cases of gastro-intestinal (GI) perforation or fistulae (see also below, under heading *Fistulae*). Gastro-intestinal perforation have been reported in clinical trials with an incidence of less than 1 % in patients with metastatic adenocarcinoma of the breast or lung, up to 2,0 % in metastatic renal cell cancer, newly diagnosed glioblastoma, or ovarian cancer and up to 2,7 % (including gastrointestinal fistula and abscess) in patients with metastatic colorectal adenocarcinoma. Cases of GI perforations have also been observed in patients with relapsed glioblastoma.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, GI perforations, (all grades) were reported in 3,2 % of patients, all of whom had a history of prior pelvic radiation.

Fatal outcome was reported in approximately a third of serious cases of gastro-intestinal perforations, which represents between 0,2 – 1 % of all Avastin treated patients.

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.

Non-GI Fistulae (see section 4.4*):*

Avastin use has been associated with serious cases of fistulae including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 1,8 % of Avastin-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 other types of fistulae that involve areas of the body other than the gastro-intestinal tract (e.g. bronchopleural, and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most events occurring within the first 6 months of therapy.

Wound healing (see section 4.4):

As Avastin 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 adenocarcinoma 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 Avastin. 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 Avastin at the time of surgery. The incidence varied between 10 % (4/40) and 20 % (3/15). Cases of serious wound healing complications have been reported during Avastin use, some of which had a fatal outcome (see section 4.4). In trials in locally recurrent and metastatic

adenocarcinoma of the breast, Grade 3 - 5 wound healing complications were observed in 1,1 % of patients receiving Avastin compared with up to 0,9 % of patients in the control arms.

In a study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (including craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3,6 % in patients treated with single-agent Avastin.

In patients with newly diagnosed glioblastoma the incidence of Grade 3-5 post-operative wound healing complications (including complications following craniotomy) was 3,3 % when treated with Avastin in combination with chemotherapy and radiotherapy, compared with 1,6 % when treated with chemotherapy and radiotherapy alone.

Nasal Septum Perforations:

Cases of nasal septum perforations have been reported in patients treated with Avastin (see section 4.4).

Hypertension:

In clinical trials, the overall incidence of hypertension (all grades) ranged up to 42,1 % in Avastin-treated patients in clinical trials compared with up to 14 % in those treated with comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medication) in patients receiving Avastin ranged from 0,4 % to 17,9 %. Grade 4 hypertension (hypertensive crisis) occurred in up to 1,0 % of patients treated with Avastin and chemotherapy compared to up to 0,2 % of patients treated with the same chemotherapy alone.

In a study on patients who received Avastin in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, all grade hypertension was observed in 77,3 % compared to 14,3 % of patients treated with erlotinib alone. Grade 3 hypertension was 60,0 % in patients treated with Avastin 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 Avastin treatment or hospitalisation.

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

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

Posterior Reversible Encephaolopathy Syndrome (see section 4.4):

There have been reports of Avastin-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephaolopathy Syndrome (PRES), a rare neurological disorder, see section 4.4.

Proteinuria (see section 4.4):

In clinical trials, proteinuria has been reported within the range of 0,7 % to 54,7 % of patients receiving Avastin. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. Grade 3 proteinuria was reported in up to 8,1 % of treated patients, Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1,4 % of treated patients.

Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical studies urine protein levels of ≥ 2 g /24 hrs led to the holding of Avastin until recovery to < 2 g/24 hrs.

Haemorrhage (see section 4.4):

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 - 5 bleeding events ranged from 0,4 % to 6,9 % in Avastin treated patients, compared with up to 4,5 % of patients in chemotherapy control group. The haemorrhagic events that have been observed in clinical studies 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 studies in patients with adenocarcinoma of the lung. Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, Avastin 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 Avastin 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 studies, while patients with unknown tumour histology were included.

In patients with adenocarcinoma of the lung, all grade events were seen with a frequency of up to 9,3 % when treated with Avastin plus chemotherapy compared with up to 5 % in the patients treated with chemotherapy alone. Grade 3 - 5 events have been observed in up to 2,3 % of patients treated with Avastin plus chemotherapy as compared with < 1 % with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

Gastro-intestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal adenocarcinoma 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 4.3) and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving Avastin has not been prospectively evaluated in randomised clinical studies. Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In a study, CNS haemorrhage was reported in 2,4 % (2/84) of patients in the Avastin alone arm (Grade 1); and in 3,8 % (3/79) of patients treated with Avastin and irinotecan (Grades 1, 2 and 4).

Mucocutaneous haemorrhage:

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50 % of Avastin-treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the Avastin 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 events of minor mucocutaneous haemorrhage in other locations, such as gingival or vaginal bleeding.

Thromboembolism (see section 4.4):

Arterial thromboembolism:

An increased incidence of arterial thromboembolic events was observed in patients treated with Avastin across indications, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence of arterial thromboembolic events ranged up to 5,9 % in the Avastin containing arms compared with up to 1,7 % in the chemotherapy control arms. Fatal outcome was reported in 0,8 % of patients receiving Avastin 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 Avastin 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 Avastin in combination with chemotherapy compared to up to 0,7 % of patients treated with chemotherapy alone. In a clinical trial, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan, arterial thromboembolic events were observed in 11 % (11/100) of patients compared to 5,8 % (6/104) in the chemotherapy control group.

In an uncontrolled clinical trial in patients with relapsed glioblastoma, arterial thromboembolic events were observed in up to 6,3 % (5/79) of patients who received Avastin in combination with irinotecan compared to up to 4,8 % (4/84) of patients who received Avastin alone.

Venous thromboembolism:

The incidence of venous thromboembolic events in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis. In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2,8 % to 17,3 % of Avastin-treated patients compared with 3,2 % to 15,6 % in the controls. In the clinical trials in NSCLC an increase of the overall incidence of venous thromboembolic events with Grade 3 - 5 severity was observed of up to 7,8 % in the Avastin containing arm compared with 4,9 % in the chemotherapy control arm. One event (0,2 %)

was fatal on the Avastin containing arm compared to none in the carboplatin-paclitaxel arm. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy versus chemotherapy alone. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, Grade 3-5 venous thromboembolic events have been reported in up to 10,6 % of patients treated with chemotherapy and Avastin compared with up to 5,4% in patients with chemotherapy alone.

In a clinical trial in patients with newly diagnosed glioblastoma, Grade 3-5 venous thromboembolic events were observed in 7,3 % of patients treated with Avastin in combination with chemotherapy and radiotherapy, compared to 8,0 % of patients treated with chemotherapy and radiotherapy alone.

Hypersensitivity, infusion reactions:

Patients may be at risk of developing infusion/hypersensitivity reactions (see section 4.8). Close observation of the patient during and following the administration of Avastin is recommended. If a reaction occurs, the infusion should be discontinued and appropriate medical therapy administered. A systemic premedication is not warranted.

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of Avastin is common (up to 5 % in Avastin-treated patients) – see section 4.8.

Congestive Heart Failure (CHF):

In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly 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 Avastin in combination with chemotherapy compared with up to 0,9 % in the control arms. For patients who received anthracyclines concomitantly with Avastin, the incidences of Grade 3 or higher CHF for the respective Avastin and control arms were similar to those in the other studies in metastatic breast cancer: 2,9 % in the anthracycline + Avastin arm and 0 % in the anthracycline + placebo arm. 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 Avastin, 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 (see section 4.5).

Osteonecrosis of the jaw (ONJ):

Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and i.v. 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 Avastin. In patients who have previously received or are receiving i.v. bisphosphonates invasive dental procedures should be avoided, if possible.

Infections:

In a clinical trial of Avastin in combination with chemotherapy plus radiotherapy for the treatment of patients with newly diagnosed glioblastoma, the incidence of all Grade and Grade 3-5 infections was 54,4 % and 12,8 % in the bevacizumab plus chemotherapy and radiotherapy arm versus 39,1 % and 7,8 % in the chemotherapy plus radiotherapy only arm, respectively.

Elderly Patients:

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events, 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; and all grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with Avastin (see sections 4.4 and 4.8, *Thromboembolism* sections).

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

Laboratory Abnormalities:

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

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

Clinical trials have shown that increases in serum creatinine (ranging between 1,5-1,9 times baseline level), both with and without proteinuria, are associated with the use of Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.

Description of selected adverse drug reactions from postmarketing experience

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis (some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness; including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for intravenous administration) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment; Retinal pigment epithelial tear; Increased intraocular pressure; Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage; Conjunctival haemorrhage.

An observational claims database study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for Avastin (adjusted HR: 1,82; 99 % CI: 1,20, 2,76) (Incidence 0,46 events per 100 patients per year; comparator 0,26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1,11; 99 % CI: 1,01, 1,23)

(Incidence 6,33 events per 100 patients per year; comparator 5,64 events per 100 patients per year).

Following variable and non-validated methods in compounding, storage, and handling of Avastin, serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

Systemic Events (reported from unapproved intravitreal use)

An observational claims database study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of haemorrhagic stroke for Avastin (adjusted HR: 1,57; 99 % CI: 1,04, 2,37) (Incidence 0,41 events per 100 patients per year; comparator 0,26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1,11; 99 % CI: 1,01, 1,23) (Incidence 6,03 events per 100 patients per year; comparator 5,51 events per 100 patients per year).

A second observational study found similar results for all-cause mortality. A randomised controlled clinical trial comparing unapproved Avastin to an approved treatment for patients with wet age-related macular degeneration has reported an increased risk of serious systemic adverse events for Avastin, most of which resulted in hospitalisation (adjusted risk ratio 1,29; 95 % CI: 1,01, 1,66) (Incidence 24,1 %; comparator 19,0 %).

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 “6.04 Adverse Drug Reaction Report Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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.

The side effects profile will be exaggerated and aggravated. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Avastin (bevacizumab) is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Avastin 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.

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.

***Absorption**:* Not applicable.

Distribution: The typical value for central volume (V_c) was 2,73 L and 3,28 L for female and male patients respectively. The typical value for peripheral volume (V_p) was 1,69 L and 2,35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger V_c (+ 20 %) than female patients.

Metabolism: 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 or hepatic impairment: No studies have been conducted to evaluate the pharmacokinetics of bevacizumab in patients with renal or hepatic impairment, since the kidneys and liver are not major organs for bevacizumab metabolism or excretion.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

α,αTrehalose dihydrate,

polysorbate 20,

sodium phosphate, and

water for injections

6.2 Incompatibilities

No incompatibilities between Avastin and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of Avastin was observed when diluted with glucose solutions (5 %). Therefore Avastin infusions should not be administered or mixed with glucose solutions

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep out of reach of children.

Store in a refrigerator at 2 °C to 8 °C. Keep the vial in outer carton to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

Avastin does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 30 days at 2 ˚C – 8 ˚C plus an additional 48 hours at 2 °C - 30 °C in 0,9 % sodium chloride solution. 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.

Disposal of unused/expired medicines:

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

6.5 Nature and contents of container

Avastin 100: packs of 1 or 4 vial/s in an outer carton.

Avastin 400: packs of 1 or 4 vial/s in an outer carton.

Not all packs may be marketed.

6.6 Special Instructions for Use, Handling and Disposal

Avastin infusions should not be administered or mixed with dextrose or glucose solutions [4 (see "Incompatibilities" section 6.2 above)].

Do not administer as an intravenous push or bolus.

Avastin should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare Avastin. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0,9 % sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1,4 - 16,5 mg/mL.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBERS

Avastin 100: A39/26/0314

Avastin 400: A39/26/0315

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 April 2006

Last revision: 19 April 2022

	Avastin 100 mg/4 mL	**Avastin 400 mg/16 mL**
Botswana	S2 BOT0901577A	S2 BOT0901577B
Namibia	NS2 07/26/0068	NS2 07/26/0069
Zimbabwe	2016/9.7/5262 PP	2016/9.7/5263 PP

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