Warning: To be sold by retail on the prescription of an Oncologist only

Bevacizumab Injection

Avastin®

अवास्तिन™

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Anti-neoplastic agent

ATC Code: L01X C07

1.2 Type of Dosage Form and Strengths

Dosage form: Concentrate for solution for infusion.
Strength: 25mg/ml

1.3 Route of Administration

Clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous (IV) infusion.

Avastin is not formulated for intravitreal use *(see section 2.4.1 Warnings and Precautions, General).*

1.4 Sterile / Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: Bevacizumab (humanised anti-VEGF monoclonal antibody).

Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 ml or 16 ml of Avastin (25 mg/ml).

Each vial contains Bevacizumab 100mg/4ml or 400mg/16ml

List of Excipients: Trehalose dihydrate, Polysorbate 20, sodium phosphate, and water for injection.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

- For the treatment of Colorectal Cancer
- Unresectable, advanced, metastatic or recurrent non-squamous non-small cell lung cancer
- First-line treatment of patients with advanced and/or metastatic Renal Cell Carcinoma
- For the treatment of Glioblastoma with progressive disease following prior therapy, as a single agent

- In combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- In combination with paclitaxel or topotecan or pegylated liposomal doxorubicin in recurrent, platinum-resistant epithelial ovarian cancer.
- In combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix.
- In combination with atezolizumab for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

2.2 Dosage and Administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

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.

Avastin should be prepared by a healthcare professional using aseptic technique *(see section 4.2 Special Instructions for Use, Handling and Disposal)*.

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.

Dose reduction of Avastin for adverse events is not recommended. If indicated, Avastin should either be permanently discontinued or temporarily suspended as described in *section 2.4.1 General (Warnings and Precautions)*.

Avastin is not formulated for intravitreal use. *(see 2.4.1 Warnings and Precautions, General).*

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:	5mg/kg or 10 mg/kg of body weight given every 2 weeks or 7.5mg/kg or 15 mg/kg of body weight given once every 3 weeks.

It is recommended that Avastin treatment be continued until progression of the underlying disease. Patients previously treated with Avastin can continue with Avastin treatment

following first progression *(see section 3.1.2, study ML18147).*

Unresectable, advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)

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.

Advanced and/or metastatic Renal Cell Carcinoma (mRCC)

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

It is recommended that Avastin treatment be continued until progression of the underlying disease.

Malignant Glioma (WHO Grade IV) - Glioblastoma

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.

It is recommended that Avastin treatment be continued until progression of the underlying disease.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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

Front-line treatment:	15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use of Avastin as single agent for 15 months or until disease progression, whichever occurs earlier.
Treatment of recurrent disease:	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 *(see section 3.1.2, study MO22224 for chemotherapy regimens)*.
	Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks *(see section 3.1.2, study*

MO22224 for chemotherapy regimen).

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 *(see section 3.1.2 study GOG-0240 for further details on the chemotherapy regimens).*

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 Avastin treatment be continued until progression of the underlying disease.

Hepatocellular Carcinoma (HCC)The recommended dosage is 15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for atezolizumab prior to initiation for recommended dosage information.

2.2.1 Special Dosage Instructions

Pediatric Use: The safety and efficacy of Avastin in children and adolescents (<18 years) have-not been established (see section *2.5.4 Pediatric Use*).

Geriatric Use: No dose adjustment 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.

2.3 Contraindications

Avastin is contraindicated in patients with known hypersensitivity to:

- Any components of the product
- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.

2.4 Warnings and Precautions

2.4.1 General

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

Gastrointestinal Perforations and Fistulae

Patients may be at increased risk for the development of gastrointestinal perforation *section 2.6.1 Undesirable Effects, Clinical Trials*) and gall bladder perforation (*see section 2.6.2 Undesirable Effects, Postmarketing Experience)* when treated with Avastin. Avastin therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae) (*see section 2.6.1 Gastrointestinal Perforations and Fistulae*).

Non-GI Fistulae (see section 2.6.1 Clinical Trial, Undesirable Effects)

Patients may be at increased risk for the development of fistulae when treated with Avastin [*see Section 2.6.1. Clinical Trials (Undesirable Effects)]*.

Permanently discontinue Avastin in patients with tracheoesophageal (TE) 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.

Hemorrhage (see section 2.6.1 Clinical Trials (Undesirable Effects)

Patients treated with Avastin have an increased risk of hemorrhage, especially tumor-associated hemorrhage *(see section 2.6.1 Hemorrhage)*. Avastin should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Avastin therapy.

An evaluation for the presence of varices is recommended within 6 months of initiation of Avastin in patients with HCC. There is lack of clinical data to support the safety of Avastin in patients with variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding because these patients were excluded from clinical trials of Avastin in HCC *(see section 3.1.2 Clinical/Efficacy Studies)*.

Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomised clinical studies *(see section 2.6.1 Haemorrhage)*. 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 increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and Avastin concomitantly.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 2.6.2 Post Marketing Experience)

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary Hemorrhage/ Hemoptysis (see section 2.6 Undesirable Effects)

Patients with non–small cell lung cancer treated with Avastin may be at risk for serious, and in some cases fatal, pulmonary hemorrhage/hemoptysis *(see section 2.6.1; Hemorrhage)*. Patients with recent pulmonary hemorrhage/hemoptysis (> 1/2 teaspoon red blood) should not be treated with Avastin.

Hypertension

An increased incidence 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 recommended during Avastin therapy *[see section 2.6.1 Clinical Trials (Undesirable Effects)]*.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. 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 *[see sections 2.6.1 Clinical Trials (Undesirable Effects and 2.6.2 Postmarketing Experience]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), a rare neurological 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 *(see sections 2.6.1 Undesirable Effects, Clinical Trials and 2.6.2 Post-Marketing).*

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischemic 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.

Patients receiving Avastin plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during Avastin therapy. Caution should be taken when treating such patients with Avastin.

Venous Thromboembolism (see section 2.6 Undesirable Effects)

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

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of venous thromboembolic events (*see section 2.6.1 Undesirable Effects, Clinical Trials, Venous thromboembolism).*

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.

Congestive Heart Failure (see section 2.6 Undesirable Effects)

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

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.

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.

In patients in AVF3694g 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. In both AVF3694g and AVF3693g, CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients

in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (*see section 2.6.1*).

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.

Wound Healing

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 (*see section 2.6.1 Undesirable Effects, Clinical Trials*).

Necrotising fasciitis including fatal cases, has rarely 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. (*see section 2.6.1 Undesirable Effects, Postmarketing Experience*)

Proteinuria (see section 2.6 Undesirable Effects)
In clinical trials, the incidence of proteinuria was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. In the event of nephrotic syndrome Avastin treatment should be permanently discontinued.

Hypersensitivity reactions, infusion reactions (see section 2.6 Clinical Trials and Postmarketing Experience (Undesirable effects))

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Ovarian failure/fertility (see section 2.5.1 Use in Special Populations, Females and Male of Reproductive Potential and 2.6.1 Undesirable Effects, Clinical Trials)

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

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machine have been performed. However, there is no evidence that Avastin treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

Avastin may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with Avastin. *(see section 2.4.1 Warnings and Precautions, General* and *section 2.6.1 Undesirable Effects, Clinical Trials).*

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility *(see section 3.3.3 Impairment of Fertility)*. A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

Contraception

In women with childbearing potential, appropriate contraceptive measures should be used during Avastin therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of Avastin.

2.5.2 Pregnancy

Angiogenesis has been shown to be critically important to fetal development. The inhibition of angiogenesis following administration of Avastin could result in an adverse outcome of pregnancy.

There are no adequate and well-controlled studies in pregnant women *(see section 3.3.4 Reproductive Toxicity)*. IgGs are known to cross the placental barrier, and Avastin may inhibit angiogenesis in the fetus. 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 2.6.2 Undesirable Effects, Postmarketing Toxicity)*.

Therefore, Avastin should not be used during pregnancy.

Labour and Delivery
Not Applicable

2.5.3 Lactation
It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and Avastin could harm infant growth and development, women should be advised to discontinue nursing during Avastin therapy and not to breast feed for at least 6 months following the last dose of Avastin.

2.5.4 Pediatric 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 pediatric patients in two phase II clinical trials: one in pediatric high grade glioma and one in pediatric 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 (*see* section *2.6.2 Postmarketing Experience and section 3.3.5 Nonclinical Safety, Other (Physeal Development)).*

2.5.5 Geriatric Use
Refer to section 2.4.1 under the sub-heading *Arterial Thromboembolism*.

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

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

2.6 Undesirable Effects
2.6.1 Clinical Trials

Summary of safety profile

Clinical trials have been conducted in patients with various malignancies treated with Avastin, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of more than 5,500 patients is presented in this section. For post marketing experience see section 2.6.2 Post marketing experience below. See section 3.1.2 Clinical/Efficacy Studies for details of major studies, including study designs and major efficacy results.

The most serious adverse drug reactions were

- Gastrointestinal Perforations [see *section 2.4.1 General (Warnings and Precautions)*]

- Hemorrhage including pulmonary hemorrhage/hemoptysis, which is more common in NSCLC patients [see *section 2.4.1 General (Warnings and Precautions)*]
- hArterial Thromboembolism [see *section 2.4.1 General (Warnings and Precautions)*]

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

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

Tabulated summary of adverse drug reactions from clinical trials

Table 1 lists adverse drug reactions 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. Adverse drug reactions 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 adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions 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, and nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1: Very Common and Common Adverse Drug Reactions

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	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anemia 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 Lacrimation increased
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
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae** Gastrointestinal 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	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive System and Breast		Pelvic pain	
Investigations			Weight decreased

* 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

Description of selected adverse drug reactions from clinical trials:

The following adverse drug reactions, reported using NCI-CTC for assessment of toxicity, have been observed in patients treated with Avastin:

Gastrointestinal Perforation and Fistulae (see section 2.4.1 Warnings and Precautions- General)

Avastin 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 breast cancer and non-squamous non-small cell lung cancer, up to 2% 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. 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 (study GOG-0240), GI perforations, (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases, underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to Avastin has not been established.

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

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

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistulae (see section 2.4.1 General (Warnings and Precautions))

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 (GOG- 240), 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 gastrointestinal tract (e.g., bronchopleural, 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.

Hemorrhage

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 to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in Avastin clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage (e.g. epistaxis).

- ***Tumor-associated hemorrhage***

Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). 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 tumor location and cavitation of tumors 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 studies, while patients with unknown tumor histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9.3% when treated with Avastin plus chemotherapy compared with 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 (see 2.4.1 General (Warnings and Precautions).

Gastrointestinal hemorrhages, including rectal bleeding and melaena have been reported in colorectal patients, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations and included a case of central nervous system (CNS) bleeding in a patient with CNS metastases and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two

subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported.

Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In study AVF3708g, 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).

Across all Avastin clinical trials, mucocutaneous hemorrhages were seen in 50% of patients treated with Avastin. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change 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 hemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Hypertension (see also section 2.4.1 General (Warnings and Precautions))

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the Avastin containing arms compared with upto to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertension 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 compared to up to 0.2% patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with bevacizumab in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

Hypertension was generally adequately controlled with oral anti-hypertensive such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of Avastin treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see also section 2.4.1 General (Warnings and Precautions)). The risk of Avastin- associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 2.4.1 Warnings and Precautions, General)

Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Thromboembolism

- Arterial thromboembolism

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

In clinical trials, the overall incidence ranged upto 5.9% in the Avastin containing arms compared upto 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.7 % of Avastin treated patients versus 0.5% of patients in the control group; myocardial infarction was reported in 1.4% of Avastin treated versus 0.7% of patients in the observed control groups.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of Avastin patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received Avastin in combination with irinotecan compared to 4.8% (4/84) of patients who received Avastin alone.

- Venous thromboembolism (see section 2.4.1 General (Warnings and Precautions))

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the Avastin containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone. 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 (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

In clinical trial BO21990, Grade 3-5 venous thromboembolic events were observed in 7.6% of patients with newly diagnosed glioblastoma treated with Avastin in combination with chemotherapy and radiotherapy, compared to 8.0 % of patients treated with chemotherapy and radiotherapy alone.

Congestive Heart Failure

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. In five phase III studies (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer CHF Grade 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 in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all grade CHF were similar between the anthracycline + Avastin (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of 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 anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF [see *section 2.4.1 General (Warnings and Precautions)*].

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R- CHOP plus bevacizumab arm.

Wound Healing (see section 2.4.1 General (Warnings and Precautions))

As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting Avastin treatment were excluded from participation in phase III trials.

Across mCRC clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting Avastin therapy. An increased incidence of post-operative bleeding or wound healing complications 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 2.4.1 Warnings and Precautions, General*).

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

In the study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent Avastin and 1.3% in patients treated with Avastin plus irinotecan.

In patients with newly diagnosed glioblastoma (study BO21990) 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.

Proteinuria (see section 2.4.1 General (Warnings and Precautions))

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. 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.

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

Hypersensitivity, infusion reactions (see section 2.4.1 Warnings and Precautions, General and section 2.6.2 Undesirable Effects Postmarketing Experience)

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 bevacizumab-treated patients).

Ovarian Failure / Fertility (see section 2.4.1 Warnings and Precautions, General and section 2.5.1 Use in Special Populations, Females and Males of Reproductive Potential)

The incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥30 mIU/mL and a negative serum β-HCG pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Infections (see section 2.4.1 Warnings and Precautions, General)

In clinical trial BO21990, a randomised, double-blind, placebo controlled, multicentre phase III study 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, transient ischemic attacks and myocardial infarction as compared to those aged ≤ 65 years when treated with Avastin (see *sections 2.4.1 General (Warnings and Precautions)* and *2.6.1 Clinical Trials (Undesirable Effects)* under Thromboembolism). 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.

From a clinical trial in patients with metastatic colorectal cancer (study AVF2107), no increase in the incidences of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure and hemorrhage, 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 count and presence of urine protein may be associated with Avastin treatment.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with Avastin compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased PT (prothrombin time), normalised ratio.

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 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.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Avastin (Table 2) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation 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).

Table 2: Adverse drug reactions from Postmarketing experience

Adverse reactions	**Frequency Category**
Infections and Infestations	
Necrotising fasciitis[1, 2]	Rare
Immune system disorders	

Hypersensitivity[3]	Unknown
Infusion reactions[3]	Unknown
Nervous system disorders	
Hypertensive encephalopathy[2,4]	Very rare
Posterior Reversible Encephalopathy Syndrome (PRES)[2]	Rare
Vascular Disorders	
Renal Thrombotic Microangiopathy, clinically manifested as proteinuria[2,4]	Unknown
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation	Unknown
Pulmonary hypertension	Unknown
Dysphonia	Common
Gastrointestinal disorders	
Gastrointestinal ulcer	Unknown
Hepatobiliary disorders	
Gallbladder perforation	Unknown
Musculoskeletal and Connective Tissue disorders	
Osteonecrosis of the Jaw (ONJ)[5]	Unknown
Osteonecrosis at sites other than the jaw[6,7]	Unknown
Congenital, familial and genetic disorders	
Foetal abnormalities[8]	Unknown

1 Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation
2 See section 2.4.1 Warnings and Precautions, General
3 The following are possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.
4 See section 2.6.1 Undesirable Effects, Clinical Trials
5 Cases of ONJ observed in Avastin-treated patients mainly in association with prior or concomitant use of bisphosphonates.
6 Cases observed in Avastin-treated pediatric patients.See section 2.5.4 Use in special populations, Pediatric use
7 Osteonecrosis observed in pediatric 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.
8 Cases have been observed in women treated with bevacizumab alone or in combinationwith known embryotoxic chemotherapeutics. See section 2.5.2~~1~~ Use in Special Populations, Pregnancy.

Description of selected adverse drug reactions from postmarketing experience

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis (frequency not known; 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 (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular hemorrhage such as vitreous hemorrhage or retinal hemorrhage (frequency not known); Conjunctival hemorrhage (frequency not known).

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 hemorrhagic 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 randomized 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 hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%).

2.7 Overdose

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

2.8 Interactions with other Medicinal Products and other forms of Interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon–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 two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated

creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate *(see Hypertension, Proteinuria, PRES in section 2.4.1 Warnings and Precautions, General)*.

Radiotherapy

The safety and efficacy of concomitant administration of chemotherapy (temozolomide), radiotherapy and Avastin was evaluated in study BO21990, a Phase III, randomised, double blind, placebo controlled 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

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

Avastin inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumors, thereby inhibiting tumor growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumor activity in human cancers, including colon, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

3.1.2 Clinical / Efficacy Studies

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of Avastin (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Avastin was combined with two chemotherapy regimens:

- **AVF2107g**: A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6-week cycle.
- **AVF0780g**: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8-week cycle (Roswell Park regimen).

- **AVF2192g**: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with Avastin haven been conducted in mCRC patients: first-line (NO16966), second-line with no previous Avastin treatment (E3200), and second-line with previous Avastin treatment following disease progression in first- line (ML18147). In these studies, Avastin was administered at the following dosing regimens, in combination with FOLFOX-4 (5FU/LV/oxaliplatin) XELOX (Capecitabine/Oxaliplatin), and fluoroprymidine / irinotecan and fluoroprymidine / oxaliplatin:

- **NO16966:** Avastin 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or Avastin 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- **E3200:** Avastin 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in Avastin naïve patients.
- **ML18147:** Avastin 5.0 mg/kg of body weight every 2 weeks or Avastin 7.5mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with Avastin. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on firstline usage of either oxaliplatin or irinotecan.

AVF2107g:

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating Avastin in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + Avastin (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV + Avastin (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of Avastin with the IFL regimen was established and considered acceptable.

The primary efficacy parameter of the trial was overall survival. The addition of Avastin to IFL resulted in a statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 3 for details). The clinical benefit of Avastin, as measured by survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumor, number of organs involved, and duration of metastatic disease.

Table 3 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL + Placebo	Arm 2 IFL + Avastin[a]
Number of Patients	411	402

Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Secondary endpoint: Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.00001)	
Overall Response Rate	34.8%	44.8%
	(p-value = 0.0036)	

[a] 5 mg/kg every 2 weeks
[b] Relative to control arm

Among the 110 patients randomised to Arm 3 (5-FU/LV + Avastin) prior to discontinuation of this arm, the median overall survival was 18.3 months, and the median progression free survival was 8.8 months.

AVF2192g:
This was a phase II randomised, double-blind, active-controlled clinical trial investigating Avastin in combination with 5-FU/leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/LV + placebo arm and 104 patients randomised to 5-FU/LV + Avastin (5 mg/kg every 2 weeks). All treatments were continued until disease progression.

The addition of Avastin 5 mg/kg every two weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as, compared with 5-FU/LV chemotherapy alone.

NO16966:
This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating Avastin 7.5 mg/kg in combination with oral capecitabine and i.v. oxaliplatin (XELOX), administered on a 3-weekly schedule; or Avastin 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with i.v. oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The study contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4- arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + Avastin, FOLFOX-4 + Avastin). In Part II, treatment assignment was double-blind with respect to Avastin.

Approximately 350 patients were randomised into each of the 4 study arms in the Part II of the trial.

Table 4 Treatment Regimens in study NO16966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	Oxaliplatin on Day 1 Leucovorin on Day 1 and 2 5-fluorouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or Avastin	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ Avastin	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	Oxaliplatin on Day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin			

The primary efficacy parameter of the trial was the duration of progression-free survival. In this study, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that Avastin in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met:

i) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4- containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per protocol population.

ii) Superiority of the Avastin-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 5).

Secondary PFS analyses, based on Independent Review Committee (IRC)- and 'on treatment'- based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (subgroup analyses shown in Table 5), consistent with the statistically significant benefit observed in the pooled analysis.

Table 5 Key efficacy results for the superiority analysis (ITT population, Study NO16966)

Endpoint (months)	**FOLFOX-4 or XELOX + Placebo (n=701)**	**FOLFOX-4 or XELOX + Bevacizumab (n=699)**	**P Value**
Primary endpoint			
Median PFS**	8.0	9.4	0.0023

Hazard ratio (97.5% CI)[a]	0.83 (0.72–0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Median PFS (Indep. review)**	8.5	11.0	<0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
Overall response rate (Invest. Assessment)**	49.2%,	46.5%	
Overall response rate (Indep. Review)**	37.5%	37.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007
**Primary analysis at clinical cut-off 31 January 2006
[a] relative to control arm

ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating Avastin 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with iv oxaliplatin (FOLFOX-4), administered on a 2- weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 4 for Study NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomization to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 Avastin + FOLFOX-4 and 244 Avastin monotherapy). The addition of Avastin to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 6).

Table 6 Efficacy Results for Study E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + Avastin[a]
Number of Patients	292	293
Overall Survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	

Progression-Free Survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective Response Rate		
Rate	8.6 %	22.2 %
	(p- value < 0.0001)	

[a] 10 mg/kg every 2 weeks
[b] Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received Avastin monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the Avastin monotherapy arm compared to the FOLFOX-4 arm.

ML18147
This was a Phase III randomized, controlled, open-label trial investigating Avastin 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine- based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with metastatic colorectal cancer who have progressed on a first line Avastin-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomized 1:1 within 3 months after discontinuation of Avastin first-line therapy to receive fluoropyrimidine/oxaliplatin or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without Avastin. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival (OS) defined as the time from randomization until death from any cause.

A total of 820 patients were randomized. The addition of Avastin to fluoropyrimidine based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen (ITT = 819) (see below table 7).

Table 7 Efficacy Results for Study ML18147

	ML18147	
	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin based chemotherapy	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin based chemotherapy+ Avastin[a]
Number of Patients	410	409
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	9-11	10-12
Hazard ratio	0.81 (p-value = 0.0062)	
Progression-Free Survival		
Median (months)	4.1	5.7
Hazard ratio	0.68 (p-value < 0.0001)	

Objective Response Rate (ORR)		
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 2.5 mg/kg/week

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and did not meet statistical significance.

Adjuvant Colon Cancer (aCC)

BO17920

This was a phase III randomized open-label, 3-arm study evaluating the efficacy and safety of Avastin administered at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with FOLFOX4, or on a 3-weekly schedule in combination with XELOX versus FOLFOX4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

More relapses and deaths due to disease progression were observed in both Avastin arms compared to the control arm. The primary objective of prolonging disease free survival (DFS) in patients with stage III colon cancer (n = 2867) by adding Avastin to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX4 + Avastin arm and 1.07 (95% CI: 0.90-1.28) for the XELOX + Avastin arm.

Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)
The safety and efficacy of Avastin in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

E4599
E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating Avastin as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with Avastin at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the Avastin + carboplatin– paclitaxel arm continued to receive Avastin as a single agent every 3 weeks until disease progression. 878 patients were randomised to the two arms.

During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of Avastin and 21.1% (89/422) of patients received 13 or more administrations of Avastin.

The primary endpoint was duration of survival. Results are presented in Table 8.

Table 8 Efficacy results for study E4599

	Arm 1 **Carboplatin/ Paclitaxel**	**Arm 2** **Carboplatin/ Paclitaxel + Avastin** **15 mg/kg q 3 weeks**
Number of Patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio		0.80 (p=0.003) 95% CI (0.69, 0.93)
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65 (p<0.0001) 95% CI (0.56, 0.76)
Overall Response Rate		
Rate (percent)	12.9	29.0 (p<0.0001)

BO17704

Study BO17704 was a randomised, double-blind phase III study of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival, secondary endpoints for the study included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 i.v. infusion on day 1 and gemcitabine 1250 mg/m^2 i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Avastin at a dose of 7.5 or15 mg/kg IV infusion day 1 of every 3-week cycle. In the Avastin-containing arms, patients could receive Avastin as a single-agent every 3 weeks until disease progression or unacceptable toxicity.

Study results show that 94% (277/ 296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 9.

Table 9 Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	**Cisplatin/Gemcitabine + Avastin** **7.5 mg/kg q 3 weeks**	**Cisplatin/Gemcitabine + Avastin** **15 mg/kg q 3 weeks**
Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)

Hazard ratio		0.75 [0.62;0.91]	0.82 [0.68;0.98]
Best Overall Response Rate [a]	20.1%	34.1% (p< 0.0001)	30.4% (p=0.0023)

[a] patients with measurable disease at baseline

Overall Survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

Advanced and/or metastatic Renal Cell Cancer (mRCC)

BO17705

Study BO17705 was a multicentre randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of Avastin in combination with interferon (IFN)-alfa-2a (Roferon®) versus IFN-alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥70%, no CNS metastases and adequate organ function. IFN-alfa-2a (x3/week at a recommended dose of 9 MIU) plus Avastin (10mg/kg q2w) or placebo was given until disease progression. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression-free survival. The addition of Avastin to IFN-alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR= 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% Avastin/IFN) received a variety of non- specified, post-protocol anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 10.

Table 10 Efficacy Results for Study BO17705

	BO17705	
	IFN + Placebo	IFN + Avastin
Number of Patients	322	327
Progression-Free Survival		
Median (months)	5.4	10.2

Hazard ratio [95% CI]	0.63 [0.52; 0.75] (p-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease		
N	289	306
Response rate	12.8 %	31.4 %
	(p-value < 0.0001)	
Overall Survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63;0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the Avastin+ IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety- seven (97) patients in the IFN alfa-2a arm and 131 patients in the Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as pre-specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a, based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months, PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical study investigating Avastin 10 mg/kg in a 2 weekly schedule with the same dose of Avastin in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this study, 53 to Avastin 10 mg/kg q2w plus placebo and 51 to Avastin 10 mg/kg q2w plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + Pl arm and the Avastin + Erl arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response.

Malignant Glioma (WHO Grade IV) - Glioblastoma

AVF3708g

The efficacy and safety of Avastin as treatment for patients with glioblastoma was studied in an open-label, multicentre, randomised, non-comparative study (study AVF3708g).

Glioblastoma patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide, were randomised (1:1) to receive Avastin (10mg/kg IV infusion every 2 weeks) or Avastin plus irinotecan (125 mg/m2 IV

or 340 mg/m2 IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility (IRF). Other outcome measures were duration of PFS, duration of response and overall survival.

Results of the study are summarized in Table 11.

Table 11 Efficacy Results from Study AVF3708g

	Avastin		**Avastin + Irinotecan**	
Number of patients	85		82	
	Inv	IRF	Inv	IRF
Primary endpoints				
6-month progression-free survival 95% CI (Inv) 97.5% CI (IRF)	43.6% (33.0, 54.3) -	42.6% - (29.6, 55.5)	57.9% (46.6, 69.2) -	50.3% - (36.8, 63.9)
Objective Response Rate 95% CI (Inv) 97.5% CI (IRF)	41.2% (30.6, 52.3) -	28.2% - (18.5, 40.3)	51.2% (39.9, 62.4) -	37.8% - (26.5, 50.8)
Secondary endpoints				
Progression-free survival (months) Median (95% CI)	4.2 (3.0, 6.9)	4.2 (2.9, 5.8)	6.8 (5.0, 8.2)	5.6 (4.4, 6.2)
Duration of objective response (months) Median (95% CI)	8.1 (5.5, *)	5.6 (3.0, 5.8)	8.3 (5.5, *)	4.3 (4.2, *)
Overall survival (months) Median (95% CI)	9.3 (8.2, *)		8.8 (7.8, *)	

ORR was determined using modified Mcdonald criteria; Inv = Investigator's assessment; IRF = Independent Review Facility
* Upper limit of the confidence interval could not be obtained

In study AVF3708g, six-month PFS based on IRF assessments was significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 42.6% in the Avastin arm and 50.3% in the Avastin plus irinotecan arm (investigator assessment: 43.6% in the Avastin arm and 57.9% in the Avastin plus irinotecan arm). Objective response rates were also significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 28.2% in the Avastin arm and 37.8% in the Avastin plus irinotecan arm (investigator assessment: 41.2% in the Avastin arm and 51.2% in the Avastin plus irinotecan arm).

The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilization over time while receiving bevacizumab treatment. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive functions while on study treatment compared to baseline. The majority of patients that remained in the study and were progression free at 24 weeks, had a

Karnofsky performance status (KPS) that remained stable.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

The safety and efficacy of Avastin in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that compared the effect of the addition of Avastin to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218

The GOG-0218 study was a Phase III multicenter, randomized, double-blind, placebo controlled, three arm study evaluating the effect of adding Avastin to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked stage III or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.

A total of 1873 patients were randomized in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by continued use of Avastin (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 12.

Table 12 Efficacy Results from Study GOG-0218

Progression-free survival						
	Investigator Assessment[1]			IRC Assessment		
	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n=1248)[2]	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n=1248)[2]
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1

Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p –value[4]		0.0204[5]	< 0.0001[5]		0.2663	< 0.0001
Objective response Rate[6]						
	Investigator Assessment			IRC Assessment		
	CPP (n= 396)	CPB15 (n= 393)	CPB15+ (n=403)	CPP (n= 474)	CPB15 (n=460)	CPB15+ (n=499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p –value[4]		0.2341	0.2041		0.0106	0.0012

Overall survival[7]			
	CPP (n= 625)	CPB15 (n= 625)[2]	CPB15+ (n= 623)[2]
Median OS (months)	40.6	38.8	43.8
Hazard Ratio (95% CI)[3]		1.065 (0.908, 1.249)	0.879 (0.745, 1.038)
p-value[4]		0.2197	0.0641

[1] Primary PFS analysis
[2] Events prior to Cycle 7 from the CPB15 and CPB15+ arms were pooled for the analyses
[3] Relative to the control arm; stratified hazard ratio
[4] One-sided log-rank p-value
[5] Subject to a p-value boundary of 0.0116
[6] Patients with measurable disease at baseline
[7] Final overall survival analysis

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone, had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received front-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding Avastin to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only), or FIGO Stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.

A total of 1528 patients were randomized in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles plus Avastin (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression Free Survival (PFS) as assessed by the investigator.

The results of this study are summarized in Table 13.

Table 13 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n= 764)	CPB7.5+ (n=764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate[1]		
	CP (n=277)	CPB7.5+ (n=272)
Response rate	41.9 %	61.8 %
	(p-value <0.0001)	
Overall Survival[2]		
	CP (n= 764)	CPB7.5+ (n=764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

[1] in patients with measurable disease at baseline
[2] Final OS analysis when 46.7% of patients died

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS.

Recurrent Ovarian Cancer

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomized, two-arm Phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (paclitaxel, topotecan, or PLD) alone or in combination with bevacizumab:

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
  - PLD 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After Cycle 1, the drug could be delivered as a 1 hour infusion.
- CT+BV Arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg

IV every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on Days 1–5 on a every 3 weeks schedule).

Eligible patients had ovarian cancer that progressed within 6 months of previous platinum therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free-survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 15:

Table 15 Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n=182)	CT+BV (n=179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (n=144)	CT+BV (N=142)
% pts with objective response	18 (12.5%)	40 (28.2%)
p –value	0.0007	
Overall Survival (final analysis)**		
	CT (n=182)	CT+BV (n=179)
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 (0.678, 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses
*Randomized Patients with Measurable Disease at Baseline
** At the time of the final OS analysis (25 January 2013), 266 patients (73.7%) had died across the two treatment arms.

Cervical Cancer

GOG-0240

The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomized, four-arm, multi-centre phase III trial.

A total of 452 patients were randomized to receive either:

- Paclitaxel 135 mg/m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 (q3w)
- Paclitaxel 135 mg/m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 and bevacizumab 15 mg/kg IV on Day 1 (q3w)
- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on days 1-3 (q3w)
- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg IV on Day 1 (q3w)

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 16.

Table 16 Overall Efficacy by Bevacizumab Treatment (ITT Population) from study GOG-0240

	Chemotherapy (n=225)	Chemotherapy + BV (n=227)
Primary Endpoint		
Overall Survival		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value[5] = 0.0132)	
Secondary Endpoints		
Progression-free survival		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54;0.81] (p-value[5] = <0.0001)	
Best Overall Response		
Response rate[2]	76 (33.8 %)	103 (45.4 %)
95% CI for Response Rates[3]	[27.6; 40.4]	[38.8; 52.1]
Difference in Response Rates	11.60	
95% CI for Difference in Response Rates[4]	[2.4; 20.8]	
p-Value (Chi-squared Test)	0.0117	

[1] Kaplan-Meier estimates
[2] Patients with best overall response of confirmed CR or PR
[3] 95% CI for one sample binomial using Pearson-Clopper method
[4] Approximate 95% CI for difference of two rates using Hauck-Anderson method
[5] log-rank test (stratified)

Hepatocellular Carcinoma (HCC)

IMbrave150 The efficacy of Avastin in combination with atezolizumab was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable and/or metastatic hepatocellular carcinoma who have not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL), and by ECOG performance status (0 vs. 1).

A total of 501 patients were randomized (2:1) to receive either atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg Avastin, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either atezolizumab or Avastin (e.g., due to adverse events) and continue on single-agent therapy until disease progression or unacceptable toxicity associated with the single-agent.

The study enrolled patients who were ECOG performance score 0 or 1 and who had not received prior systemic treatment. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22% and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per RECIST v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and mRECIST.

Efficacy results are presented in Table 17 and Figure 1.

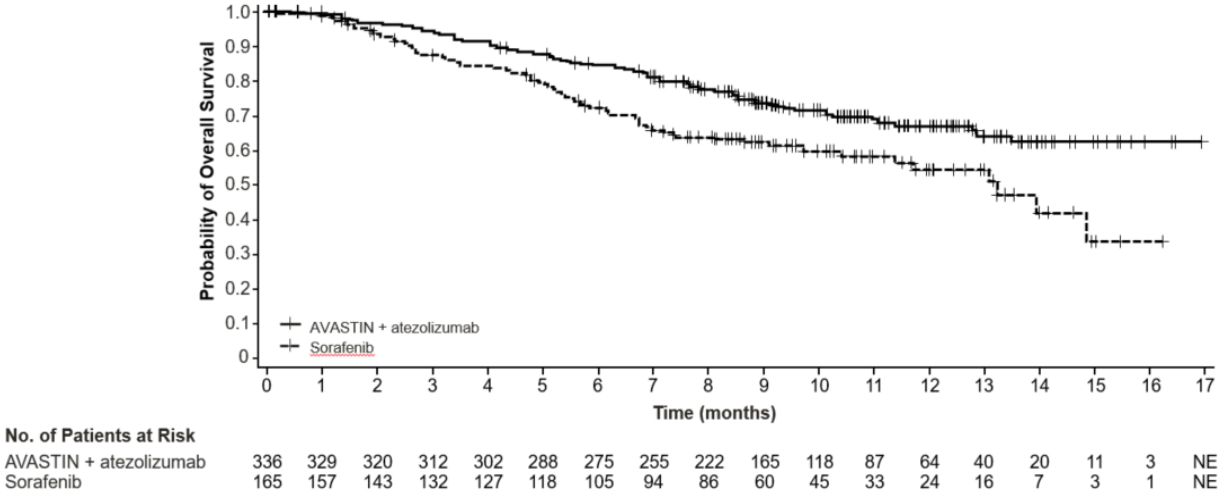
Table 17: Efficacy Results from IMbrave150

	Avastin in combination with Atezolizumab (N= 336)	**Sorafenib (N=165)**
Overall Survival		
Number of deaths (%)	96 (29)	65 (39)
Median OS in months (95% CI)	NE (NE, NE)	13.2 (10.4, NE)
Hazard ratio[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
Progression-Free Survival[3]		
Number of events(%)	197 (59)	109 (66)
Median PFS in months (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Hazard ratio[1] (95% CI)	0.59 (0.47, 0.76)	
p-value	<0.0001	
Overall Response Rate[3,5] (ORR), RECIST 1.1		
Number of responders (%)	93 (28)	19 (12)
(95% CI)	(23, 33)	(7,17)
p-value[4]	<0.0001	
Complete responses, n (%)	22 (7)	0
Partial responses, n (%)	71 (21)	19 (12)
Duration of Response[3,5] (DOR) RECIST 1.1		
	(n=93)	(n=19)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.7, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)
Overall Response Rate[3,5] (ORR), HCC mRECIST		
Number of responders (%)	112 (33)	21 (13)
(95% CI)	(28, 39)	(8, 19)
p-value[4]	<0.0001	
Complete responses, n (%)	37 (11)	3 (1.8)
Partial responses, n (%)	75 (22)	18 (11)
Duration of Response[3,5] (DOR) HCC mRECIST		
	(n=112)	(n=21)

Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)

[1] Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
[2] Based on two-sided stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on two-sided Cochran-Mantel-Haesnszel test
[5] Confirmed responses
+ Denotes a censored value
CI=confidence interval; HCC mRECIST= Modified RECIST Assessment for Hepatocellular Carcinoma; NE=not estimable; N/A=not applicable; RECIST 1.1= Response Evaluation Criteria in Solid Tumors v1.1

Figure 1: Kaplan-Meier Plot of Overall Survival in IMbrave150



3.1.3 Immunogenicity

No robust assessment of anti-drug antibodies has been done in Avastin clinical trials.

3.2 Pharmacokinetic Properties

The pharmacokinetics of bevacizumab were characterized in patients with various types of solid tumors. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterized by a low clearance, a limited volume of the central compartment (Vc), and a long elimination half-life. This enables target therapeutic bevacizumab serum levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In a population pharmacokinetic meta-analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to race when body weight is taken into account, or in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 year with 5th and 95th percentiles of 37 and 76 year]).

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.

3.2.1 Absorption
No text.

3.2.2 Distribution
The typical value for central volume (Vc) was 2.73 L and 3.28 L for female and male subjects 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 2.35L for female and male patients respectively, when bevacizumab is co-administered with anti-neoaplastic agents. After correcting for body weight, male subjects had a larger Vc (+ 20%) than females.

3.2.3 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 result in protection from cellular metabolism and the long terminal half-life.

3.2.4 Elimination
The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/ kg/wk. 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 subjects 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.

3.2.5 Pharmacokinetics in Special Populations
The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Pediatric Population: The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125kg) across 4 clinical studies using a population

pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between pediatric and adult patients when normalized by body-weight. Age was not associated with the pharmacokinetics of bevacizumab when body-weight was taken into account.

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.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity
Studies have not been performed to evaluate the carcinogenic potential of Avastin.

3.3.2 Genotoxicity
Studies have not been performed to evaluate the mutagenic potential of Avastin.

3.3.3 Impairment of Fertility
No specific studies in animals have been performed to evaluate the effect of Avastin on fertility. No adverse effect on male reproductive organ was observed in repeat dose toxicity studies in cynomolgus monkeys.

Inhibition of ovarian function was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with Avastin for 13 or 26 weeks. The doses associated with this effect were ≥ 4 times the human therapeutic dose or ≥ 2-fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of Avastin resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of Avastin is likely to result in an adverse effect on female fertility.

3.3.4 Reproductive Toxicity
Avastin has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses of 10-100 mg/kg. Information on foetal malformations observed in the post marketing setting are provided in *section 2.5.1 Use in Special Populations, Pregnancy and 2.6.2 Undesirable Effects, Postmarketing Experience*.

3.3.5 Other

Physeal Development:

In studies of up to 26 weeks duration in cynomolgus monkeys, Avastin was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Wound Healing:

In rabbits, the effects of Avastin on circular wound healing were studied. Wound re- epithelialisation was delayed in rabbits following five doses of Avastin, ranging from 2-50mg/kg, over a 2-week period. A trend toward a dose-dependent relationship was observed. The magnitude of effect on wound healing was similar to that observed with corticosteroid administration. Upon treatment cessation with either 2 or 10 mg/kg Avastin, the wounds closed completely. The lower dose of 2 mg/kg was approximately equivalent to the proposed clinical dose. A more sensitive linear wound healing model was also studied in rabbits. Three doses of Avastin ranging from 0.5-2 mg/kg dose-dependently and significantly decreased the tensile strength of the wounds, consistently with delayed wound healing. The low dose of 0.5 mg/kg was 5-fold below the proposed clinical dose.

As effects on wound healing were observed in rabbits at doses below the proposed clinical dose, the capacity for Avastin to adversely impact wound healing in human should be considered.

In cynomolgus monkeys, the effects of Avastin on the healing of a linear incision were highly variable and no dose-response relationship was evident.

Renal Function:

In normal cynomolgus monkeys, Avastin had no measurable effect on renal function treated once or twice weekly for up to 26 weeks, and did not accumulate in the kidney of rabbits following two doses up to 100 mg/kg (approximately 80-folds the proposed clinical dose).

Investigative toxicity studies in rabbits, using models of renal dysfunction, showed that Avastin did not exacerbate renal glomerular injury induced by bovine serum albumin or renal tubular damage induced by cisplatin.

Albumin:

In male cynomolgus monkeys, Avastin administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These

effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

At doses up to 50 mg/kg twice weekly in cynomolgus monkeys, Avastin showed no effects on blood pressure.

Hemostasis:

Non-clinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not find changes in haematology or coagulation parameters including platelet counts, prothrombin and activated partial thromboplastin time. A model of haemostasis in rabbits, used to investigate the effect of Avastin on thrombus formation, did not show alteration in the rate of clot formation or any other haematological parameters compared to treatment with Avastin vehicle.

4. DESCRIPTION

Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Avastin (bevacizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Avastin contains bevacizumab at a concentration of 25 mg/mL in either a 100 mg/4 mL or 400 mg/16 mL single-dose vial.

Each mL of solution contains 25 mg bevacizumab, Trehalose dihydrate, Polysorbate 20, sodium phosphate, and Water for Injection. The pH is 6.2.

5. PHARMACEUTICAL PARTICULARS

5.1 Shelf life

24 months when stored under recommended storage conditions.

Avastin should not be used after the expiry date (Expiry date) shown on the pack.

5.2 Storage

Storage
Store vials in a refrigerator at 2°C-8°C.

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

DO NOT FREEZE. DO NOT SHAKE.

Shelf-life of the solution for infusion containing the reconstituted product:

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.

5.3 Special Instructions for Use, Handling and Disposal

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

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.

Avastin is not formulated for intravitreal use.

5.4 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 dextrose solutions (5%).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. 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.

5.5 Packs

Vials 100 mg/4ml: Pack of 1 Vial (4 mL) containing Bevacizumab concentrate for solution for infusion 100mg (25mg/ml).

Vials 400 mg/16ml: Pack of 1 Vial (16 mL) containing Bevacizumab concentrate

for solution for infusion 400mg (25mg/ml).

Keep out of reach of children

6 PATIENT COUNSELLING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their healthcare provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood.

Arterial and Venous Thromboembolic Events: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure.

Posterior Reversible Encephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome.

Infusion-Related Reactions: Avastin can cause infusion-related reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

7 DETAILS OF MANUFACTURER

Manufactured by: F. Hoffmann-La Roche Ltd, CH-4070, Basel, Switzerland at –
1) Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305, Mannheim, Germany OR
2) F. Hoffmann- La Roche Ltd, Wurmisweg, CH-4303, Kaiseraugst, Switzerland
OR
3) Genentech, Inc., 4625 NE Brookwood Parkway, Hillsboro, OR 97124-9332, USA
[NOTE: Please refer outer carton and vial label for "manufactured by" details]

Imported by:
Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services Pvt. Ltd, Gala No. A1, First Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302

Distributed and Marketed by:
Cipla
Cipla Ltd.,
Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013, India

8 DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE
Permission No.: Import-1992/04 dated 17 January 2005

9 DATE OF REVISION
Current at March 2022, Version 20.0