Product Information as approved by the CHMP on 16 December 2010, pending endorsement by the European Commission

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25 mg of bevacizumab.
Each vial contains 100 mg of bevacizumab in 4 ml and 400 mg in 16 ml respectively, corresponding to 1.4 to 16.5 mg/ml when diluted as recommended.

Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster ovary cells.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Avastin in combination with paclitaxel ~~**or docetaxel**~~ is indicated for first-line treatment of patients with metastatic breast cancer. For further information as to HER2 status, please refer to section 5.1.

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

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

4.2 Posology and method of administration

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

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

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

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Avastin, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.

Metastatic breast cancer (mBC)

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

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 is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses. For details refer to section 5.1 *Pharmacodynamic Properties, Non-small cell lung cancer (NSCLC)*.

Advanced and/or metastatic Renal Cell Cancer (mRCC)

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

Special populations

Elderly: No dose adjustment is required in the elderly.

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

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

Paediatric population

The safety and efficacy of bevacizumab in children and adolescents have not been established. There is no relevant use of bevacizumab in the paediatric population in the granted indications. Currently available data are described in section 5.2 and section 5.3 but no recommendation on a posology can be made.

Method of administration

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

Do not administer as an intravenous push or bolus.

Precautions to be taken before handling or administering the medicinal product

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Gastrointestinal perforations (see section 4.8)
Patients may be at an increased risk for the development of gastrointestinal perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

Fistulae (see section 4.8)
Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with TE (tracheoesophageal) fistula or any grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.

Wound healing complications (see section 4.8)
Avastin may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Hypertension (see section 4.8)
An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy.

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

Reversible posterior leukoencephalopathy syndrome (RPLS) (see section 4.8)
There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, 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 RPLS is not known.

Proteinuria (see section 4.8)
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 [US National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0] proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Arterial thromboembolism (see section 4.8)
In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions

(MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

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

Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.

Venous thromboembolism (see section 4.8)
Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment. Avastin should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism, patients with ≤Grade 3 need to be closely monitored.

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

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 patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases 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 therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly.

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

Congestive heart failure (CHF) (see section 4.8)
Events consistent with 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, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy.

Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with Avastin.

Neutropenia and infections (see section 4.8)
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

Hypersensitivity reactions/infusion reactions (see section 4.8)
Patients may be at risk of developing infusion/hypersensitivity reaction. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any

infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (see section 4.8)
Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and i.v. bisphosphonates are administered simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving i.v. bisphosphonates invasive dental procedures should be avoided, if possible.

Eye disorders
Adverse reactions have been reported from unapproved intravitreal use. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these appeared as serious adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents
Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from one trial in metastatic colorectal cancer patients demonstrated no significant effect of bevacizumab on the pharmacokinetics of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Results from one trial in renal cancer patients demonstrated no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a.

The potential effect of bevacizumab on the pharmacokinetics of cisplatin and gemcitabine was investigated in non-squamous NSCLC patients. Trial results demonstrated no significant effect of bevacizumab on the pharmacokinetics of cisplatin. Due to high inter-patient variability and limited sampling, the results from that trial do not allow firm conclusions to be drawn on the impact of bevacizumab on gemcitabine pharmacokinetics.

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

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

upon discontinuation of bevacizumab and sunitinib malate (see *Hypertension, Proteinuria, RPLS* in section 4.4).

Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8)
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There are no data on the use of Avastin in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. Avastin is contraindicated in pregnancy (see section 4.3).

Breastfeeding
It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development (see section 5.3), women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of Avastin.

Fertility
No specific trials in human or animals have been conducted to study the effect of bevacizumab on fertility. However, repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines 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.

4.8 Undesirable effects

The overall safety profile of Avastin is based on data from over 3,500 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

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

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

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

Table 1 lists adverse reactions associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC 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.

The adverse reactions listed in this table fall into the following categories: Very Common (≥ 1/10) and Common (≥ 1/100 - < 1/10). Adverse 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 reactions are presented in the order of decreasing seriousness.
Some of the adverse reactions are reactions commonly seen with chemotherapy, (e.g. palmar-plantar erythrodysaesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by Avastin therapy can not be excluded.

Table 1 Very common and common adverse reactions

System organ class (SOC)	***NCI-CTC grade 3-5 reactions (≥2% difference between the trial arms in at least one clinical trial)***		***All grade reactions (≥10% difference between the trial arms in at least one clinical trial)***
	Very common	***Common***	***Very common***
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Thrombocytopenia Neutropenia	Anaemia	
Metabolism and nutrition disorders		Dehydration	Anorexia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache
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

System organ class (SOC)	*NCI-CTC grade 3-5 reactions (≥2% difference between the trial arms in at least one clinical trial)*		*All grade reactions (≥10% difference between the trial arms in at least one clinical trial)*
	Very common	***Common***	***Very common***
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Intestinal Perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder Stomatitis	Constipation Stomatitis Rectal haemorrhage
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
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

** Pooled arterial thromboembolic events including cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic events.*
Data are unadjusted for the differential time on treatment.

Further information on selected serious adverse reactions

Gastrointestinal perforations (see section 4.4)
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 or non-squamous non-small cell lung cancer, and up to 2.0% in metastatic colorectal cancer patients. 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.

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

Fistulae (see section 4.4)
Avastin use has been associated with serious cases of fistulae including events resulting in death.

In clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other types of cancers. 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, urogenital and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most events occurring within the first 6 months of therapy.

Wound healing (see section 4.4)
As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials.

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

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.

Hypertension (see section 4.4)
An increased incidence of hypertension (all grades) of up to 34% has been observed in Avastin-treated patients in clinical trials compared with up to 14% in those treated with comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medicines) in patients receiving Avastin ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

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

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

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

Proteinuria (see section 4.4)
In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving Avastin.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. Grade 3 proteinuria was reported in < 3% of treated patients: however, in patients treated for advanced and/or metastatic renal cell carcinoma this was up to 7%. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of therapy. Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical trials urine protein levels of ≥ 2g/24 hrs led to the holding of Avastin until recovery to < 2g/24 hrs.

Haemorrhage (see section 4.4)
In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 5% in Avastin treated patients, compared with up to 2.9% of patients in the chemotherapy control group.

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

Tumour-associated haemorrhage (see section 4.4)

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory substances, treatment with anticoagulants, prior radiotherapy, Avastin therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Avastin therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent phase III trials, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9% 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.

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

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

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two ongoing trials in patients with treated brain metastases, one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis.

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of Avastin-treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the Avastin treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Thromboembolism (see section 4.4)

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

In clinical trials, the overall incidence of arterial thromboembolic events ranged up to 3.8% in the Avastin containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of patients treated with Avastin in combination with chemotherapy compared to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in 1.4% of patients treated with Avastin in combination with chemotherapy compared to 0.7% of patients treated with chemotherapy alone.

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 patients compared to 5.8% (6/104) in the chemotherapy control group.

Venous thromboembolism: The incidence of venous thromboembolic events in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% of Avastin-treated patients compared with 3.2% to 15.6% in the control arms.

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 treated 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.

Congestive heart failure (CHF)
In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In two phase III trials (AVF2119g and E2100) in patients with metastatic breast cancer an increase of CHF Grade 3 or more with Avastin was seen. CHF was reported in up to 3.5% of patients treated with Avastin compared with up to 0.9% in the control arms. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Avastin, patients with pre-existing CHF of NYHA (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF.

Hypersensitivity reactions/infusion reactions (see section 4.4 and *Post-marketing experience* below)
In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials of Avastin is common (up to 5% in bevacizumab-treated patients).

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

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

Paediatric population
The safety of Avastin in children and adolescents has not been established.

Laboratory abnormalities

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

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

Post-marketing experience

Table 2 Adverse reactions reported in post-marketing setting

System organ class (SOC)	***Reactions (frequency*)***
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and *Hypertension* in section 4.8) Reversible posterior leukoencephalopathy syndrome (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy, clinically manifested as proteinuria (not known). For further information on proteinuria see section 4.4 and *Proteinuria* in section 4.8.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Immune system disorders	Hypersensitivity reactions and infusion reactions (not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see also section 4.4 and *Hypersensitivity reactions/infusion reactions* above)
Osteonecrosis of the jaw	Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with Avastin, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to i.v. bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibody, ATC code: L01X C07

Mechanism of action
Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

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

Clinical efficacy

Metastatic carcinoma of the colon or rectum (mCRC)

The safety and efficacy of the recommended dose (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/folinic acid (IFL) for a total of 4 weeks of each 6 week-cycle (Saltz regimen).
- **AVF0780g**: In combination with bolus 5-fluorouracil/ folinic acid (5-FU/FA) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- **AVF2192g**: In combination with bolus 5-FU/FA 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.

Two additional trials were conducted in first (NO16966) and second line (E3200) treatment of metastatic carcinoma of the colon or rectum, with Avastin administered in the following dosing regimens, in combination with FOLFOX-4 (5FU/LV/Oxaliplatin) and XELOX (Capecitabine/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).

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/FA+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. All treatments were

continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

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

The efficacy results of Avastin in combination with IFL-chemotherapy are displayed in Table 3.

Table 3 Efficacy results for trial AVF2107g

	AVF2107g	
	Arm 1 IFL + placebo	**Arm 2 IFL + Avastin[a]**
Number of patients	411	402
Overall survival		
Median time (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)	
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	0.54 (p-value< 0.0001)	
Overall response rate		
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/FA + 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 evaluating the efficacy and safety of Avastin in combination with 5-FU/FA 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/FA + placebo arm and 104 patients to 5-FU/FA + Avastin (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as compared to 5-FU/FA chemotherapy alone.

AVF0780g
This was a phase II randomised, active-controlled, open-labelled clinical trial investigating Avastin in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomised to receive bolus 5-FU/FA or 5-FU/FA + Avastin (5 mg/kg

every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + Avastin (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 4). These efficacy data are consistent with the results from trial AVF2107g.

The efficacy data from trials AVF0780g and AVF2192g investigating Avastin in combination with 5-FU/FA-chemotherapy are summarised in Table 4.

Table 4 Efficacy results for trials AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	**5-FU/FA + Avastin[a]**	**5-FU/FA + Avastin[b]**	**5-FU/FA + placebo**	**5-FU/FA + Avastin**
Number of patients	36	35	33	105	104
Overall survival					
Median time (months)	13.6	17.7	15.2	12.9	16.6
95% Confidence interval				10.35 - 16.95	13.63 - 19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-free survival					
Median time (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall response rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% CI	7.0 – 33.5	24.4 – 57.8	11.7 – 42.6	9.2 - 23.9	18.1 - 35.6
p-value		0.029	0.43		0.055
Duration of response					
Median time (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5 – NR	6.1 – NR	3.8 – 7.8	5.59 - 9.17	5.88 - 13.01

[a] 5 mg/kg every 2 weeks.
[b] 10 mg/kg every 2 weeks.
[c] Relative to control arm.
NR = not reached.

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 IV 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 IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The trial 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 trial arms in the Part II of the trial.

Table 5 Treatment regimens in trial N016966 (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 trial, 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:

- 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.

- 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 6).

Secondary PFS analyses, based on ‘on-treatment’-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (analyses shown in Table 6), consistent with the statistically significant benefit observed in the pooled analysis.

Table 6 Key efficacy results for the superiority analysis (ITT population, trial 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)		
Overall response rate (invest. assessment)**	49.2%,	46.5%	
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

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab treated patients, HR = 0.89, 97.5% CI = [0.73 ; 1.08]; p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63 ; 0.94]; p-value = 0.0026.

The median overall survival was 20.3 months in placebo and 21.2 months in bevacizumab treated patients in the FOLFOX treatment subgroup, HR=0.94, 97.5% CI = [0.75 ; 1.16]; p-value = 0.4937, the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68 ; 1.04]; p-value = 0.0698.

ECOG E3200
This was a phase III randomised, active-controlled, open-label trial 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 5 for trial 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 7).

Table 7 Efficacy results for trial 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.

The benefit of Avastin re-treatment in metastatic colorectal cancer patients who were exposed to Avastin in previous therapies has not been addressed in randomized clinical trials.

Metastatic breast cancer (mBC)

ECOG E2100

Trial E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating Avastin in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomised to paclitaxel alone (90 mg/m^2 IV over 1 hour once weekly for three out of four weeks) or in combination with Avastin (10 mg/kg IV infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastasis, including previously treated or resected brain lesions, were excluded.

In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with Avastin as a single agent continued until disease progression. The patient characteristics were similar across the trial arms. The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 8.

Table 8 Trial E2100 efficacy results

Progression-free survival				
	Investigator assessment*		IRF assessment	
	Paclitaxel (n=354)	Paclitaxel/ Avastin (n=368)	Paclitaxel (n=354)	Paclitaxel/ Avastin (n=368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	<0.0001		<0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		IRF assessment	
	Paclitaxel (n=273)	Paclitaxel/ Avastin (n=252)	Paclitaxel (n=243)	Paclitaxel/ Avastin (n=229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	<0.0001		<0.0001	

* primary analysis

Overall survival		
	Paclitaxel (n=354)	Paclitaxel/ Avastin (n=368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722 ; 1.046)	
p-value	0.1374	

The clinical benefit of Avastin as measured by PFS was seen in all pre-specified subgroups tested (including disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and estrogen receptor (ER) status).

~~***BO17708***~~

~~**Trial BO17708 was a randomised, double-blind, placebo-controlled, multicentre (phase III) trial to evaluate the efficacy and safety of Avastin in combination with docetaxel compared with docetaxel plus placebo, as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer who have not received prior chemotherapy for their metastatic disease.**~~

~~**Patients were randomised in a 1:1:1 ratio to treatment with either**~~

- ~~**placebo + docetaxel 100 mg/m2 every 3 weeks**~~
- ~~**Avastin 7.5 mg/kg + docetaxel 100 mg/m2 every 3 weeks**~~
- ~~**Avastin 15 mg/kg + docetaxel 100 mg/m2 every 3 weeks.**~~

~~**Docetaxel, Avastin or placebo treatment was continued until disease progression/death or unacceptable toxicity. Docetaxel treatment was limited to a maximum of 9 cycles. The patient and disease characteristics were similar across the three arms.**~~

~~On documented disease progression, patients from all three treatment arms could enter into a post-trial treatment phase during which they received open-label Avastin together with a wide-range of subsequent lines of therapies. (The percentage of patients in each arm who received open-label Avastin were: placebo + doc: 42%, Avastin 7.5 + doc: 37% and Avastin 15 + doc: 26%).~~

~~The primary endpoint was progression free survival (PFS), as assessed by investigators. For the efficacy endpoints two comparisons were performed:~~

- ~~Avastin 7.5 mg/kg + docetaxel 100 mg/m2 every 3 weeks versus placebo + docetaxel 100 mg/m2 every 3 weeks~~
- ~~Avastin 15 mg/kg + docetaxel 100 mg/m2 every 3 weeks vs placebo + docetaxel 100 mg/m2 every 3 weeks.~~

~~The results of this trial are presented in Table 9. For progression free survival and response rates this includes results from the pre-specified final analysis and results from an exploratory (updated) analysis carried out at the same time as the pre-specified final OS analysis which included an additional 18 months of follow-up. Overall survival results presented are those from the pre-specified final analysis for OS. At this point approximately 45% of patients across all treatment arms had died.~~

Table 9 Efficacy results for trial BO17708

Progression-free survival			
	Docetaxel + Placebo q 3 weeks (n=241)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)**
Median PFS (months) *[updated analysis]*	**8.0** *[8.2]*	**8.7** *[9.0]*	**8.8** *[10.1]*
Hazard ratio vs placebo arm (95% CI) *[updated analysis]*		**0.79 (0.63; 0.98)** *[0.86]* *[(0.72; 1.04)]*	**0.72 (0.57; 0.90)** *[0.77]* *[(0.64; 0.93)]*
P value (log rank test) vs placebo arm *[exploratory p value from updated analysis]*		**0.0318** *[0.1163]*	**0.0099** *[0.0061]*
Progression-free survival (sensitivity analysis)*			
	Docetaxel + Placebo q 3 weeks (n=241)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)**
Median PFS (months) *[updated analysis]*	**8.0** *[8.1]*	**8.7** *[9.0]*	**8.8** *[10.0]*
Hazard ratio vs placebo arm (95% CI) *[updated analysis]*		**0.69 (0.54; 0.89)** *[0.80]* *[(0.65; 1.00)]*	**0.61 (0.48; 0.78)** *[0.67]* *[(0.54; 0.83)]*
P value (log rank test) vs placebo arm *[exploratory p value from updated analysis]*		**0.0035** *[0.0450]*	**0.0001** *[0.0002]*
Response rates (for patients with measurable disease)			
	Docetaxel + Placebo q 3 weeks (n=207)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=201)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=206)**
% pts with objective response *[updated analysis]*	**44.4** *[46.4]*	**55.2** *[55.2]*	**63.1** *[64.1]*
p-value vs placebo arm *[exploratory p value from updated analysis])*		**0.0295** *[0.0739]*	**0.0001** *[0.0003]*
Overall survival			
HR (95% CI)		**1.05 (0.81; 1.36)**	**1.03 (0.79; 1.33)**
p-value		**0.7198**	**0.8528**

*** Stratified analysis which included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression - those patients were censored at the last tumor assessment prior to the start of NPT.**

Non-small cell lung cancer (NSCLC)

The safety and efficacy of Avastin, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous non-small cell lung cancer (NSCLC), was investigated in trials E4599 and BO17704. An overall survival benefit has been demonstrated in trial E4599 with a 15 mg/kg/q3wk dose of bevacizumab. Trial BO17704 has demonstrated that both 7.5 mg/kg/q3wk and 15 mg/kg/q3wk bevacizumab doses increase progression free survival and response rate.

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

Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/m2 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 trial, 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 10.

Table 10 Efficacy results for trial 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)

In an exploratory analysis, the extent of Avastin benefit on overall survival was less pronounced in the subgroup of patients who did not have adenocarcinoma histology.

BO17704
Trial BO17704 was a randomised, double-blind phase III trial of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary

endpoint was progression free survival, secondary endpoints for the trial included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m2 i.v. infusion on day 1 and gemcitabine 1250 mg/m2 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 or 15 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. Trial 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 11.

Table 11 Efficacy results for trial 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)
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]

[a] patients with measurable disease at baseline

Advanced and/or metastatic Renal Cell Cancer (mRCC)

Avastin in Combination with Interferon alfa-2a for the First-Line Treatment of Advance and/ or Metastatic Renal Cell Cancer (BO17705)

This was a phase III randomised double-blind 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 randomized patients (641 treated) had Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Avastin 10 mg/kg was given every 2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommend starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. 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 trial including progression-free survival. The addition of Avastin to IFN-alpha-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-trial anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 12.

Table 12 Efficacy results for trial BO17705

	BO17705	
	Placebo+ IFN[a]	Bv[b] + IFN[a]
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio	0.63	
95% CI	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	0.91	
95% CI	0.76, 1.10	
	(p-value 0.3360)	

[a] Interferon alfa-2a 9 MIU 3x/week

[b] Bevacizumab 10 mg/kg q 2 wk

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 trial 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 trial, 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 trial 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 trial, 53 to Avastin 10 mg/kg every 2 weeks plus placebo and 51 to Avastin 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + Placebo arm and the Avastin + Erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result in an improvement in OS (HR = 1.764; p=0.1789), duration of objective response (6.7 vs 9.1 months) or time to symptom progression (HR = 1.172; p = 0.5076).

AVF0890
This was a randomised phase II trial conducted to compare the efficacy and safety of bevacizumab versus placebo. A total of 116 patients were randomized to receive bevacizumab 3 mg/kg every 2 weeks (n=39), 10 mg/kg every 2 weeks; (n=37), or placebo (n=40). An interim analysis showed there was a significant prolongation of the time to progression of disease in the 10 mg/kg group as compared with the placebo group (hazard ratio, 2.55; p<0.001). There was a small difference, of borderline significance, between the time to progression of disease in the 3 mg/kg group and that in the placebo group (hazard ratio, 1.26; p=0.053). Four patients had objective (partial) response, and all of these had received the 10 mg/kg dose bevacizumab; the ORR for the 10 mg/kg dose was 10%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in breast carcinoma, adenocarcinoma of the colon and rectum, lung carcinoma (small cell and non-small cell carcinoma) and kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney).

5.2 Pharmacokinetic properties

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

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

Metabolism
Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{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.

Elimination
The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

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

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

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

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

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

5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injections

6.2 Incompatibilities

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

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

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

4 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab.
16 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/ml.

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

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001 – 100 mg/4 ml vial
EU/1/04/300/002 – 400 mg/16 ml vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 January 2005
Date of latest renewal: 14 January 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA): http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
USA

Genentech, Inc.
1 Antibody Way
Oceanside, CA 92056
USA

F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
CH-4070 Basel
Switzerland

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barrell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the trials and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

Biomarker

The MAH should investigate suitable biomarkers (including VEGF-A) to allow identification and selection of a more targeted population of patients most likely to benefit from the combination of Avastin and paclitaxel in the treatment of first-line metastatic breast cancer. A report on the research programme should be submitted within 3 months of the Commission Decision. Progress reports should be submitted on a yearly basis.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab
100 mg/4 ml

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This medicinal product does not contain any preservative

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab
100 mg/4 ml

2. METHOD OF ADMINISTRATION

For intravenous use after dilution
IV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/4 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab
400 mg/16 ml

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 16 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This medicinal product does not contain any preservative

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/002

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14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab
400 mg/16 ml

2. METHOD OF ADMINISTRATION

For intravenous use after dilution
IV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/16 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT AVASTIN IS AND WHAT IT IS USED FOR

Avastin contains the active substance bevacizumab, which is a humanised monoclonal antibody. Monoclonal antibodies are proteins which specifically recognise and bind to other unique proteins in the body. Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. VEGF causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, it stops VEGF working properly. This has the effect of preventing tumour growth by blocking the growth of the blood vessels providing the nutrients and oxygen to the tumour.

Avastin is a medicine used for the treatment of advanced cancer in the large bowel, i.e., in the colon or rectum. Avastin will be administered in combination with chemotherapy treatment containing a fluoropyrimidine medicine.

Avastin is also used for the treatment of metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy drug called paclitaxel ~~**or docetaxel**~~.

Avastin is also used for the treatment of advanced non-small cell lung cancer. Avastin will be administered together with a chemotherapy regimen containing platinum.

Avastin is also used for treatment of advanced kidney cancer. When used for patients with kidney cancer, it will be administered with another type of medicine called interferon.

2. BEFORE YOU USE AVASTIN

Do not use Avastin if:
- you are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of Avastin.
- you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you are pregnant.

Take special care with Avastin:

- if you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), as it is possible that Avastin may increase the risk of developing holes in the gut wall.

- if you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine as Avastin can increase the risk of bleeding or increase the risk of problems with wound healing after surgery.

- if you have high blood pressure which is not well controlled with blood pressure medicines as Avastin can increase the incidence of high blood pressure. Your doctor should make sure that your blood pressure is under control before starting Avastin treatment.

- if you have high blood pressure, as you may have a higher risk of having protein in your urine.

- if you are over 65 years old and also have had blood clots in your arteries (a type of blood vessel) in the past, as these factors can increase the risk of further blood clots in the arteries.

- if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for the treatment of blood clots.

- if you have been coughing or spitting blood or had any bleeding in your lungs.

- if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease as Avastin can increase the risk of developing a weak heart.

- if you have headache, vision changes, confusion or seizure with or without high blood pressure, you should contact your doctor. This could be a rare neurological side effect named reversible posterior leukoencephalopathy syndrome.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Before you are given Avastin or while you are being treated with Avastin:
- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery , tell your dentist that you are being treated with Avastin, in particular when you are also receiving or have received an iv bisphosphonate.

You may be advised to have a dental check-up before you start treatment with Avastin.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Please tell your doctor if you have recently received, or are receiving, radiotherapy.

Pregnancy and breast feeding
You must not use this medicine if you are pregnant. Avastin may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with Avastin and for at least 6 months after the last dose of Avastin.

Tell your doctor straightaway if you are pregnant, become pregnant during treatment with this medicine, or plan to become pregnant in the near future.

You must not breast-feed your baby during treatment with Avastin and for at least 6 months after the last dose of Avastin, as this medicine may interfere with the growth and development of your baby.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Avastin has not been shown to impair your ability to drive or to use any tools or machines.

3. HOW TO USE AVASTIN

Dosage and frequency of administration
The dose of Avastin needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5 mg, 7.5 mg, 10 mg or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of Avastin that is right for you. You will be treated with Avastin once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until Avastin fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration
Avastin is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Avastin vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Avastin solution by intravenous infusion. The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

The administration of Avastin should be temporarily discontinued
- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,
- if you undergo surgery.

The administration of Avastin should be permanently discontinued if you develop
- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- an abnormal tube-like connection or passage between the windpipe and the gullet, or between internal organs and skin or other tissues that are not normally connected, and are judged by your doctor to be severe,
- a blood clot in your arteries,
- a blood clot in the veins of your lungs,
- any severe bleeding.

If too much Avastin is given
- you may develop a severe migraine. If this happens you should talk to your doctor or pharmacist immediately.

If a dose of Avastin is missed
- your doctor will decide when you should be given your next dose of Avastin. You should discuss this with your doctor.

If you stop treatment with Avastin
Stopping your treatment with Avastin may stop the effect on tumour growth. Do not stop treatment with Avastin unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Avastin can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The side effects listed below were seen when Avastin was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Avastin.

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Allergic reactions
If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include: difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, increased muscle tension, feeling sick (nausea) or being sick (vomiting).

You should seek help immediately if you suffer from any of the below mentioned side effects.

The **common** side effects are:
- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,
- blocking of the veins in the lungs by a blood clot.

The severe side effects, which may be **very common,** include:
- high blood pressure,
- problems with wound healing after surgery,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- lack of energy or tiredness,
- diarrhoea, nausea and vomiting.

The severe side effects, which may be **common,** include:
- allergic reactions,
- decreased number of red cells in the blood,
- bleeding associated with the tumour,
- lack of energy,
- abdominal pain,
- muscle pain,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the lining of the mouth,
- pain, including headache,
- blood clots in the veins of the legs or difficulties in getting the blood to clot,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,

- reduced blood supply to the brain or stroke,
- blood clots in the arteries, which can lead to a stroke and a heart attack,
- falling asleep or fainting,
- problems with the heart with breathing difficulties,
- nose bleed,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood.

The severe side effects, which may be **rare**, include:
- seizures (fits),
- headache,
- confusion,
- changes in vision,
- an abnormal tube-like connection between the windpipe and the passage to the stomach (gullet).

You should seek help as soon as possible if you suffer from any of the below mentioned side effects

The **very common** side effects, which were not severe, include:
- high blood pressure,
- pain, including joint pain,
- lack of energy,
- constipation, bleeding from the lower part of the large bowel, inflammation of the mouth,
- loss of appetite,
- protein in the urine,
- nose bleed,
- fever,
- headache,
- problems with the eyes (including increased production of tears).

The **common** side effects, which were not severe, include:
- shortness of breath,
- nose bleed,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- change in the sense of taste,
- voice changes, hoarseness.

Other **less common** side effects of any severity which have been reported are heart failure, bleeding from the lining of the mouth or vagina, abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected and ulcers in the digestive system (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit).

There have been **very rare** reports of patients developing a hole in the septum of the nose – the structure, which separates the nostrils.

Some side effects are more common in elderly patients. These side effects include blood clot in the arteries which can lead to a stroke or a heart attack. In addition, elderly patients have a higher risk of a reduction in the number of white cells in the blood, and cells that help the blood clot. Other side effects reported with a higher frequency in elderly patients were diarrhoea, sickness, headache and fatigue.

Avastin may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline

phosphatase (an enzyme); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.

Outside of the approved use of Avastin for cancer treatment, the following side effects may occur when Avastin is injected directly into the eye (unapproved use):

- Infection or inflammation of the eye globe,
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,
- Bleeding in the eye.

5. HOW TO STORE AVASTIN

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Infusion solutions should be used immediately after dilution. Do not use Avastin if you notice any particulate matter or discoloration prior to administration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Avastin contains

Each pack of Avastin concentrate for solution for infusion contains one vial. This vial contains either 4 ml or 16 ml of a slightly opaque, colourless to pale brown sterile liquid concentrate. The concentrate must be diluted before use to make a solution for intravenous infusion.

- Each ml contains 25 mg of bevacizumab, corresponding to 1.4 to 16.5 mg/ml when diluted as recommended.
- The other ingredients are trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections.

What Avastin looks like and contents of the pack
Avastin is a clear, colourless to pale brown liquid in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 ml of solution or 400 mg bevacizumab in 16 ml of solution.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu