MVASI™ (Bevacizumab)

Anti-neoplastic agent

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Anti-neoplastic agent

ATC Code: L01X C07

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Clear to slightly opalescent, colourless to slightly yellow, sterile liquid for intravenous (i.v.) infusion.

1.4 Sterile / Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

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

MVASI is supplied in 100 mg preservative-free, single-use vials to deliver 4 mL of MVASI (25 mg/mL)..

MVASI is supplied in 400 mg preservative-free, single-use vials to deliver 16 mL of MVASI (25 mg/mL).

Each MVASI 100 mg vial contains 100 mg of bevacizumab.

Each MVASI 400 mg vial contains 400 mg of bevacizumab.

For excipients, see *section 4.1 List of Excipients*.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Metastatic colorectal cancer (mCRC)

MVASI (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

MVASI in combination with fluropyrimidine – based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Locally recurrent or metastatic triple negative Breast Cancer (mBC)

MVASI in combination with paclitaxel is indicated for the treatment of patients with locally recurrent or metastatic breast cancer, which is HER-2, estrogen receptor and progesterone receptor negative.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

MVASI, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

MVASI (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for primary adjuvant therapy, of patients with resectable, post-operative, advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, without hypertension.

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

2.2 Dosage and Administration

General

MVASI should be prepared by a healthcare professional using aseptic technique (see *section 4.3 Special Instructions for Use, Handling and Disposal*).

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

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

Metastatic Colorectal Cancer (mCRC)

The recommended dose of MVASI, administered as an intravenous infusion, is either 5mg/kg or 10mg/kg of body weight given once every 2 weeks or 7.5mg/kg or 15mg/kg of body weight given once every 3 weeks. Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in Special Warnings and Special Precautions for Use.

Locally recurrent or metastatic triple negative Breast Cancer (mBC)

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

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

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

MVASI is administered in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by bevacizumab as a single agent until disease progression.

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

MVASI is administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued used of MVASI as single agent for 15 months or until disease progression, whichever occurs earlier.

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

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

Treatment of recurrent disease:	Platinum sensitive:
	15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of MVASI as single agent until disease progression.

2.2.1 Special Dosage Instructions

Children and adolescents: The safety and efficacy of bevacizumab in children and adolescents has not been established.

Elderly: No dose adjustment is required in the elderly.

Renal impairment: The safety and efficacy of bevacizumab has not been studied in patients with renal impairment.

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

2.3 Contraindications

Bevacizumab is contraindicated in patients with known hypersensitivity to:

- Any components of the product
- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.
- Pregnancy (see *section 2.5 Use in Special Populations*)

Bevacizumab is contraindicated in patients with untreated Central Nervous System (CNS) metastases (see also *section 2.4 Warning and Precautions and 2.6 Undesirable Effects*).

2.4 Warnings and Precautions

2.4.1 General

Gastrointestinal Perforations

Patients may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab (see also *section 2.6.1 Clinical Trials (Undesirable Effects)*). Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

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.

Fistula (see also section 2.6.1 Clinical Trials (Undesirable Effects))

Patients may be increased risk for the development of fistula when treated with bevacizumab (see also *section 2.6.1. Clinical Trials (Undesirable Effects)*).

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

Haemorrhage (see also section 2.6.1 Clinical Trials (Undesirable Effects))

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage (see *section 2.6.1 Haemorrhage*). Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy.

The risk of CNS haemorrhage in patients with CNS metastases receiving bevacizumab could not be fully evaluated, as these patients were excluded from clinical trials. Thus, bevacizumab should not be used in these patients (see *section 2.3 Contraindications and 2.6 Undesirable Effects*).

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

Pulmonary Hemorrhage/ Hemoptysis (see section 2.6 Undesirable Effects)

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

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Monitoring of blood pressure is recommended during bevacizumab therapy (see also *section 2.6.1 Clinical Trials (Undesirable Effects)*).

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension

is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy (see also *section 2.6.1 Clinical Trials (Undesirable Effects) and 2.6.2 Post Marketing)*.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (see also *section 2.6.2 Post Marketing*).

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

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

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

Venous Thromboembolism (see section 2.6 Undesirable Effects)

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

Congestive Heart Failure (see section 2.6 Undesirable Effects)

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

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

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. In AVF3694g, CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patient receiving chemotherapy alone. This is consistent with result in patients in

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

Neutropenia

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

Wound Healing

Bevacizumab may adversely affect the wound healing process. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery (see also *section 2.6.1 Clinical Trials (Undesirable Effects)*).

Proteinuria (see section 2.6 Undesirable Effects)

In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was uncommon in patients with bevacizumab. In the event of Grade 4 proteinuria bevacizumab treatment should be permanently discontinued.

Hypersensitivity reactions, infusion reactions (see section 2.6.1 Clinical Trials and 2.6.2 Post Marketing (Undesirable Effects)

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

2.4.2 Ability to Drive and Use Machines

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

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant pharmacokinetics interaction of co-administered chemotherapy on bevacizumab pharmacokinetics has been observed based on the results of a population PK analyisis. There was neither statistical significance nor clinically relevant different in clearance of bevacizumab in patients receiving bevacizumab monotherapy compared to patients receiving bevacizumab in combination with Interferon alpha 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

Result from a drug-drug interaction study, AVF3135g, demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Result from NP18587 demonstrated no significant effect of bevacizumab on the pharmacokinetic of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Radiotherapy

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

2.5 Use in Special Populations

2.5.1 Pregnancy

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

There are no adequate and well-controlled studies in pregnant women (see *section 3.3.4 Teratogenicity*). IgGs are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the fetus. Therefore, bevacizumab should not be used during pregnancy. In women with childbearing potential, appropriate contraceptive measures are recommended during bevacizumab therapy. Based on pharmacokintetic considerations, contraceptive measures are recommended for at least 6 months following the last dose of bevacizumab.

2.5.2 Nursing mother

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

2.5.3 Pediatric Use

The safety and efficacy of bevacizumab in children and adolescents has not been established.

2.5.4 Geriatric Use

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

2.5.5 Renal Impairment

The safety and efficacy of bevacizumab has not been studied in patients with renal impairment.

2.5.6 Hepatic Impairment

The safety and efficacy of bevacizumab has not been studied in patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Clinical trials have been conducted in patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of

more than 3,500 patients is presented in this section. For post marketing experience see section *2.6.2 Post Marketing*. See *section 3.1.2 Clinical/Efficacy Studies* for details of major studies, including study design and major efficacy results.

The most serious adverse drug reactions were:

- Gastrointestinal Perforations [see *section 2.4.1 General (2.4 Warnings and Precautions)*]
- Hemorrhage including pulmonary hemorrhage/ hemoptysis, which is more common in NSCLC patients [see *section 2.4.1 General (Warnings and Precaution)*]
- Arterial Thromboembolism [see *section 2.4.1 General (2.4 Warnings and Precaution)*]

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

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

Table 1 lists adverse drug reactions associated with the use of bevacizumab 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 drug reactions listed in this table fall into the following categories: (Very common (≥ 10%) and Common (≥ 1% - < 10%)). Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. palmar-plantar erythrodysesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by bevacizumab therapy cannot be excluded.

Table 1 Very common and common Adverse Drug Reactions

System Organ Class (SOC)	*NCI-CTC Grade 3-5 reactions (≥2% difference between the study arms in at least one clinical trial)*		*All Grade Reactions (≥10% difference between the study arms in at least one clinical trial)*
	Very common	***Common***	***Very common***
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems diorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anemia	
Metabolism and nutritions disorders		Dehydration	Anorexia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnea Hypoxia Epistaxis	Dyspnea Epistaxis Rhinitis
Gastrointestinal disorders	Diarrhea Nausea Vomiting	Intestinal perforation Ileus Intestinal obstraction Abdominal pain Gastrointestinal disorder Stomatitis	Constipation Stomatitis Rectal hemorrhage Diarrhea
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia	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

Further information on selected, serious adverse drug reactions:

The following adverse drug reactions, reported using NCI-CTC (common toxicity criteria) for assessment of toxicity, have been observed in patients treated with bevacizumab, and may be potentially related to bevacizumab therapy:

Gastrointestinal perforation (see section 2.4.1 General (Warnings and Precautions))

Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, an up to 2% in patients with metastatic colorectal cancer or in patients with ovarian cancer receiving front-line treatment.

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

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 2.4.1 General (Warnings and Precautions))

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

In bevacizumab clinical trial, 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 cancer. 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 bevacizumab, with most events occurring within the first 6 months of therapy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 0.5% in bevacizumab treated patients, compared to 0 to 2.9% of patients in the chemotherapy group. The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated hemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epitaxis).

Tumour-associated haemorrhage was observed in phase I and phase II studies. In patients with non-small cell lung cancer receiving bevacizumab, serious haemorrhage was observed in 9% (6% fatal) of treated patients.

Major or massive pulmonary haemorrhage/hemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/ anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location and cavitation of tumors prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, 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 bevacizumab 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 bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary haemorrhage/ hemoptysis can occur suddenly and up to two thirds of the serious pulmonary hemorrhages resulted in a fatal outcome (see *section 2.4.1 General (Warning and Precautions)*).

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

Tumour-associated haemorrhages were also seen rarely in other tumour types and locations including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases (see *section 2.3 Contraindications*) and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all clinical trials, ***mucocutaneous haemorrhage*** were seen in up to 50% of patients treated with bevacizumab. 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 treatment the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epitaxis) may be dose-dependent.

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

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

An increased incidence of hypertension (all grades) of up to 42.1% has been observed in patients treated with bevacizumab compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab compared to up to 0.2% patients treated with the same chemotherapy alone.

Hypertension was generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation (0.7% of all bevacizumab treated patients) or hospitalisation, and resulted in hypertensive encephalopathy in one case (0.1%).

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

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

Thromboembolism (see section 2.4 Warnings and Precautions)

- Arterial thromboembolism

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

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

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan, were included. In this trail arterial thromboembolic events were observed in 11% (11/100) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group.

- Venous thromboembolism

In clinical trials of metastatic carcinoma of the colon or rectum, venous thromboembolic events, including deep venous thrombosis, pulmonary embolism and thrombophlebitis occurred in 9.0% - 16.6% of bevacizumab-treated patients compared to that of 13.5% - 15.2% in the controls. It could not be determined if these events were due to the patients' underlying cancer, their cytotoxic chemotherapy, bevacizumab or other risk factors.

- ***Congestive Heart Failure***

In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In four phase III studies (AVF2119g, E2100, BO17708, AVF3694g) in patients with metastatic breast cancer CHF Grade 3 or higher, was reported up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g in the incidences of all grade CHF were similar between the anthracycline + bevacizumab (6.2%) and the anthracycline + placebo arms (6.0%).

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

In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA II – IV were excluded, therefore, no information is available on the risk of CHF in this population.

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

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

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

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

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

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

In clinical trials, proteinuria, has been reported within the range 0.7% to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to <3.1% of treated patients: however, in up 7% of patients treated for advanced and/or metastatic renal cell carcinoma. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4 % of treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy.

In clinical trials of metastatic carcinoma of the colon or rectum, proteinuria was reported as an adverse event in 21.7% - 38.0% of bevacizumab-treated patients. No Grade 4 proteinuria was reported.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of ≥ 2g/24 hrs led to the holding of bevacizumab until recovery to < 2g/24 hrs.

Hypersensitivity, infusion reactions (see section 2.4.1 General (Warning and Precautions) and section 2.6.2 Post Marketing (Undesirable effects))

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab 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, transient ischaemic attacks (TIAs) and myocardial infarctions compared to those aged ≤ 65 years when treated with bevacizumab (see *section 2.4.1 General (Warnings and Precautions and 2.6.1 Clinical Trials, Thromboembolism*). Other reaction with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia; and all grade neutropenia, diarrhea, nausea, headache and fatigue.

No increased in the incidence other reactions, including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure and haemorrhage , was observed in

elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

In the phase III study in metastatic carcinoma of colon or rectum trial (AVF2107g), 114 out of the 392 patients who received bevacizumab were older than 65 years. Only Grade 3/4 leukopenia occurred at an incidence of ⩾ 5% in the elderly patients (> 65 years) compared to those patients aged ⩽ 65 years.

In the phase II study in metastatic carcinoma of colon or rectum trial (AVF2192g), the majority of the bevacizumab-treated patients was older than 65 years (83%). The overall safety profile of bevacizumab from this study was comparable to the overall safety profile observed in Study AVF2107g.

2.6.1.1 Laboratory Abnormalities

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

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with the increased (≥2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreases hemoglobin, hyperkalaemia, hyponatremia, decreased white blood cell count, increased PT (prothrombin time), normalised ratio.

2.6.2 Post Marketing

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 2.4 Warnings and Precautions*, and *section 2.6.1 Clinical Trials(Undesirable Effects)*) Reversible Posterior Leukoencephalopathy Syndrome (rare) (see also *section 2.4 Warnings and Precautions*)
Vascular Disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (frequency not known). For further information on proteinuria see *section 2.4 Warnings and Precautions*, and *Proteinuria* in *section 2.6.1 Clinical Trials (Undesirable Effects)*.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (frequency not known) Pulmonary hypertension (frequency not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (frequency not known)
Immune system disorders	Hypersensitivity, infusion reaction (frequency not known); with the following possible co-manifestation: dyspnoea/ difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.
Eye disorders (reported from unapproved intravitreal use)	Infectious endophthalmitis (frequency not known); Intraocular inflammation such as sterile endophthalmitis, uveitis, and vitritis (frequency not known); Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (frequency not known); Conjuctival haemorrhage (frequency not known).
Muscular/ Skeletal disorders	Cases of ONJ have been observed in bevacizumab treated patients mainly in association with prior or concomitant use of bisphosphonates.

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

2.7 Overdose

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

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic properties

3.1.1 Mechanism of Action

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at $\leq$ 0.35 ppm. Bevacizumab consist of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

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

Pharmacodynamic effects

Administration of bevacizumab or its parenteral 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.

3.1.2 Clinical/ Efficacy Studies

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of bevacizumab (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. Bevacizumab was combined with two chemotherapy regimens:

- **AVF2107g**: A weekly schedule of irinotecan/bolus 5-fluorouracil/ leucovorin (IFL regimen) for total of 4 weeks of each 6 week-cycle.
- **AVF0780g**: In combination with bolus 5-fluorouracil/ leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- **AVF2192g**: In combination with bolus 5-fluoroacil/ leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Bevacizumab in Combination with IFL Chemotherapy for First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF2107g):

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating bevacizumab 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 + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV+bevacizumab (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab 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.

Table 3 Treatment Regimens in Study AVF2107g

	Treatment	**Starting Dose**	**Schedule**
	Placebo	IV	Every 2 weeks
Arm 1	Irinotecan 5-Fluorouracil Leucovorin	125 mg/m^2 i.v 500 mg/m^2 i.v 20 mg/m^2 i.v	Given once weekly for 4 weeks every 6 weeks
	Placebo	i.v	Every 2 weeks
Arm 2	Irinotecan 5-Fluorouracil Leucovorin	125 mg/m^2 i.v 500 mg/m^2 i.v 20 mg/m^2 i.v	Given once weekly for 4 weeks every 6 weeks
	Bevacizumab	5 mg/kg i.v	Every 2 weeks
Arm 3	5-Fluorouracil Leucovorin	500 mg/m^2 i.v 500 mg/m^2 i.v	Given once weekly for 6 weeks every 8 weeks
	Bevacizumab	5 mg/kg i.v.	Every 2 weeks
5-Fluorouracil:	*i.v. bolus injection immediately after leucovorin*		
Folinic acid:	*i.v. bolus injection (over 1 – 2 minutes) immediately after each irinotecan dose*		

The primary efficacy variable of the trial was duration of survival. The addition of bevacizumab to IFL resulted in a statistically significant increase in overall survival (see Table 4). 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 bevacizumab in combination with IFL-chemotherapy are displayed in Table 4.

Table 4 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL + Placebo	**Arm 2 IFL + Bevacizumab[a]**
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]		0.660
p-value		0.00004
Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio		0.54
p-value		<0.00001
Overall Response Rate		
Rate (percent)	34.8	44.8
95% confidence interval	30.2 – 39.6	39.9 – 49.8
p-value		0.0036
Duration of Response		
Median (months)	7.1	10.4
25–75 percentile (months)	4.7 – 11.8	6.7 – 15.0

[a] 5 mg/kg every 2 weeks

[b] Relative to control arm

Among the 110 patients randomized to Arm 3 (5-FU/FA + bevacizumab), the median overall survival was 18.3 months, median progression free survival was 8.8 months, overall response rate was 39% and median duration of response was 8.5 months.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum in patients who were not optimal candidates for first-line irinotecan treatment (AVF2192g): This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of bevacizumab 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. Patients had to be either more susceptible to irinotecan toxicity (≥65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS≥1, baseline albumin < 3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomised to 5-FU/ FA + placebo arm and 104 patients to 5-FU/ FA + bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The overall mean age was 71 years; 28.2% of patients had a ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of bevacizumab 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, compared to 5-FU/ FA chemotherapy alone (see Table 5). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF0780g): This was a phase II randomised, active-controlled, open-labelled clinical trial investigating bevacizumab 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 randomized to receive bolus

5-FU/FA or 5-FU/FA. Bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA. Bevacizumab (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 bevacizumab 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 5). These efficacy data are consistent with the results from study AVF2107g.

The efficacy data from studies AVF0780g and AVF2192g investigating bevacizumab in combination with 5-FU/FA-chemotherapy are summarized in Table 5.

Table 5 Efficacy Results from Study AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	**5-FU/FA + bevacizumab[a]**	**5-FU/FA + bevacizumab[b]**	**5-FU/FA + placebo**	**5-FU/FA + bevacizumab**
Number of Patients	36	35	33	105	104
Overall Survival					
Median (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 (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% confidence interval	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 (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

Locally recurrent of metastatic Breast Cancer (mBC)

ECOG E2100

E2100 was an open-label, randomized, active controlled, multicenter clinical trial evaluating bevacizumab 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. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only of it was completed at least 12 months prior to study entry.

Patients were randomized to paclitaxel alone (90 mg/m^2 i.v. over 1 hour once weekely for three out of four weeks) on in combination with bevacizumab (10 mg/kg i.v. infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In case where patients discontinued chemotherapy prematurely, treatment with bevacizumab as a single agent was continued until disease progression. The primary endpoint was progression-free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive (2%). Patient who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 6.

Table 6 Study E2100 Efficacy Results: Eligible Patients

	Investigator Assessment*		IRF Assessment	
	Paclitaxel (n=354)	Paclitaxel/ bevacizumab (n=368)	Paclitaxel (n=354)	Paclitaxel/ bevacizumab (n=368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% Cl)	0.431 (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/ bevacizumab (n=252)	Paclitaxel (n=243)	Paclitaxel/ bevacizumab (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/bevacizumab (n=368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722; 1.046)	
p-value	0.1374	

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

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

E4599

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

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

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

The primary endpoint was duration of survival. Results are presented in Table 7.

Table 7 Efficacy Results for Study E4599

	Arm 1 Carboplatin/ Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + bevacizumab 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)

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

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

GOG-0218

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

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

CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy.

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

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

The results of this study are summarized in Table 8.

Table 8 Efficacy Results from Study GOG-0218

Progression-free survival						
	Investigator Assessment[1]			**IRC Assessment**		
	CPP (n=625)	**CPB15 (n=1248)[2]**	**CPB15+ (n=1248)[2]**	**CPP (n=625)**	**CPB15 (n=1248)[2]**	**CPB15+ (n=1248)[2]**
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p-value[3]		0.0204[4]	< 0.0001[4]		0.2663	< 0.0001
Objective response Rate[5]						
	Investigator Assessment			**IRC Assessment**		
	CPP (n=396)	**CPB15 (n=393)**	**CPB15+ (n=403)**	**CPP (n=474)**	**CPB15 (n=460)**	**CPB15+ (n=499)[2]**
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p-value3		0.2341	0.2041		0.0106	0.0012
Overall Survival[6]						
	CPP (n=625)		**CPB15 (n=1248)[2]**		**CPB15+ (n=1248)[2]**	
Median OS (months)	39.4		38.8		39.8	
Hazard ratio (95% CI)			1.088 (0.874, 1.353)		0.904 (0.721, 1.133)	
One-sided logrank p-value[4]			0.2256		0.1909	

[1] primary PFS analysis
[2] Events prior to Cycle 7 from the CPB15 and CPB15+ arms were pooled for the analysis
[3] Relative to the control arm; One-sided p-value
[4] subject to a p-value boundary of 0.0116
[5] Patients with measurable disease at baseline
[6] Final protocol-specified overall survival analysis performed when approximately 17% of the patients died

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

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

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3

or clear cell histology only), or FIGO Stage IIB – IV (all grades and all histology surgery, and in whom no further surgery was planned before progression.

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

CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles plus bevacizumab (7.5 mg/kg q3w) for up to 18 cycles.

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

The results of this study are summarized in Table 9.

Table 9 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n=764)	**CPB7.5+ (n=764)**
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate[1]		
	CP (n=277)	**CPB7.5+ (n=272)**
Response rate	41.9%	61.8%
	(p-value < 0.0001)	
Overall Survival[2]		
	CP (n=764)	**CPB7.5+ (n=764)**
Median (months)	Not reached	35.1
Hazard ratio [95% CI]	0.81 [0.63; 1.04]	

[1] in patients with measurable disease baseline

[2] Exploratory OS analysis when approximately 16% of patients died

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

Recurrent Ovarian Cancer

AVF4095g

The safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment, was studied in a phase III trial randomized, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding bevacizumab to and carboplatin and gemcitabine chemotherapy and continuing bevacizumab as a single agent to progression to carboplatin and gemcitabine alone.

A total of 484 patients with measurable disease were randomized in equal portions to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent bevacizumab (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 10.

Table 10 Efficacy Results from Study AVF4095g

Progression-free survival				
	Investigator Assessment*		IRC Assessment	
	Placebo + C/G (n = 242)	bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	bevacizumab + C/G (n = 242)
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p-value	<0.0001		<0.0001	
Objective response Rate				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	bevacizumab + C/G (n = 242)
% pts with objective response	57.4%	78.5%	53.7 %	74.8%
p-value	<0.0001		<0.0001	
Overall Survival**				
	Placebo + C/G (n = 242)		bevacizumab + C/G (n = 242)	
Median OS (months)	29.9		35.5	
Hazard ratio (95% CI)	0.751 [0.537, 1.052]			
p-value	0.094			

* Primary analysis

** Interim protocol-specified overall survival analysis performed when approximately 29% of the patients had died

3.2 Pharmacokinetic Properties

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

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

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

Low albumin and high tumor 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 tumor burden when compared with a typical patient with median values of albumin and tumor burden.

3.2.1 Distribution

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

3.2.2 Metabolism

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

3.2.3 Elimination

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

The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male 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.

3.2.4 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.

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

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

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

3.3 Preclinical Safety

3.3.1 Carcinogenicity

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

3.3.2 Mutagenicity

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

3.3.3 Impairment of Fertility

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on male reproductive organs was observed in repeat dose toxicity studies in cynomolgus monkeys.

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

3.3.4 Teratogenicity

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 fetal alterations. Adverse fetal outcomes were observed at all tested dose of 10 – 100 mg/kg.

3.3.5 Other

Physeal Development:

In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dyspepsia was characterised by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ⩾ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates. Because bevacizumab will most likely be administered to adult patients with closed growth plates, physeal dysplasia is not expected to occur in the clinical population.

Wound Healing:

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

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

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

Renal Function:

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

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

Albumin:

In male cynomolgus monkeys, bevacizumab administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

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

Hemostasis:

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

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

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

4.2 Storage

Bevacizumab should not be used after the expiry date (EXP) shown on the pack.

Store vials in a refrigerator at 2°C – 8°C.

Keep vial in the outer carton due to light sensitivity.

Shelf-life 36 months.

DO NOT FREEZE. DO NOT SHAKE.

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

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not

used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

4.3 Special Instructions for Use, Handling and Disposal

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

Do not administer as an intravenous push or bolus.

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 – 16.5 mg/ml.

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

Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of bevacizumab was observed when diluted with dextrose solutions (5%).

Disposal of unused/ expired medicines

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

4.4 Packs

Vial 100 mg/4 ml
Box, 1 vial @ 4 ml

Vial 400mg/16ml
Box, 1 vial @ 16 ml
Reg.No.: XXXXXXXXXXXXXXX

Medicine: keep out of reach and sight of children
Harus dengan resep dokter
On medical prescription only

Made by:
Patheon Manufacturing Services LLC,
5900 Martin Luther King Jr. Highway,
Greenville, NC 27834, USA

Packaged and Released by:
Amgen Manufacturing Limited, Puerto Rico, USA

Registered by:
PT. Pyridam Farma, Tbk,
Kabupaten Cianjur, Indonesia

Date: April 2021
Version: IDMVAPI01

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Informasi Produk untuk Pasien

MVASI 25 mg/ml Konsentrat untuk Larutan Infus

bevacizumab

Baca isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini mengandung informasi yang penting bagi Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat Anda.
- Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa saja yang ada pada leaflet ini

1. Apakah MVASI itu dan apa kegunaannya

MVASI mengandung zat aktif bevacizumab, yang merupakan antibodi monoklonal manusia (sejenis protein yang biasanya dibuat oleh sistem kekebalan tubuh untuk membantu pertahanan tubuh dari infeksi dan kanker). Bevacizumab mengikat protein secara selektif yang disebut *human vascular endothelial growth factor* (VEGF), yang ditemukan pada lapisan pembuluh darah dan getah bening di dalam tubuh. Protein VEGF menyebabkan pembuluh darah tumbuh di dalam tumor, pembuluh darah ini memberi nutrisi dan oksigen bagi tumor. Begitu bevacizumab terikat pada VEGF, pertumbuhan tumor dicegah dengan menghalangi pertumbuhan pembuluh darah yang memberi nutrisi dan oksigen bagi tumor.

MVASI adalah obat yang digunakan untuk pengobatan pasien dewasa dengan kanker stadium lanjut di usus besar, yaitu di kolon atau rektum. MVASI akan diberikan dalam kombinasi dengan pengobatan kemoterapi yang mengandung obat fluoropyrimidine.

MVASI juga digunakan untuk pengobatan pasien dewasa dengan kanker payudara metastatik. Bila digunakan untuk pasien dengan kanker payudara, maka akan diberikan dengan produk obat kemoterapi yang disebut paclitaxel.

MVASI juga digunakan untuk pengobatan pasien dewasa dengan *non-small cell lung*

cancer stadium lanjut, maka akan diberikan dalam kombinasi dengan carboplatin dan paclitaxel.

MVASI juga digunakan untuk pengobatan pasien dewasa dengan kanker ovarium epitel, tuba falopi, atau peritoneal primer yang belum menerima terapi sebelumnya dengan bevacizumab atau penghambat VEGF lain atau agen target reseptor VEGF . Bila digunakan untuk pasien dengan kanker ovarium epitel, tuba falopi, atau peritoneal primer, maka akan diberikan dalam kombinasi dengan carboplatin dan paclitaxel.

Bila digunakan untuk pasien dewasa dengan kanker ovarium epitel, tuba falopi, atau peritoneal primer stadium lanjut yang penyakitnya telah kembali setidaknya 6 bulan setelah terakhir diobati dengan kemoterapi yang mengandung agen platina, MVASI akan diberikan dalam kombinasi dengan carboplatin dan gemcitabine atau dengan carboplatin dan paclitaxel.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan MVASI

Untuk memperbaiki ketertelusuran obat ini, dokter atau apoteker Anda harus mencatat nama dagang dan nomor bets produk yang telah Anda gunakan di dalam file pasien Anda. Anda mungkin juga ingin membuat catatan tentang rincian ini jika Anda dimintai informasi ini di masa mendatang.

Jangan menggunakan MVASI jika:

- Anda alergi terhadap bevacizumab atau bahan lain yang terkandung dalam obat ini (tercantum pada bagian 6).
- Anda alergi terhadap produk sel *Chinese hamster ovary* (CHO) atau *recombinant human* atau antibodi manusia lainnya.
- Anda sedang hamil.

Peringatan dan perhatian

Bicaralah dengan dokter, apoteker atau perawat Anda sebelum menggunakan MVASI

- Ada kemungkinan MVASI dapat meningkatkan risiko pengembangan lubang di dinding usus. Jika Anda memiliki kondisi yang menyebabkan peradangan di dalam perut (misalnya, divertikulitis, tukak lambung, kolitis yang terkait dengan kemoterapi), diskusikan dengan dokter Anda.
- MVASI dapat meningkatkan risiko pengembangan hubungan atau jalur abnormal antara dua organ atau pembuluh darah. Risiko pengembangan hubungan antara vagina dan bagian usus manapun bisa meningkat jika Anda memiliki kanker serviks yang terus-menerus, berulang atau metastatik.
- MVASI dapat meningkatkan risiko perdarahan atau meningkatkan risiko masalah dengan penyembuhan luka setelah operasi. Jika Anda akan menjalani operasi, jika

Anda menjalani operasi besar dalam 28 hari terakhir atau jika Anda masih memiliki luka yang belum sembuh setelah operasi, Anda seharusnya tidak menerima obat ini.

- MVASI dapat meningkatkan risiko pengembangan infeksi serius pada kulit atau lapisan yang lebih dalam di bawah kulit, terutama jika Anda memiliki lubang di dinding usus atau masalah dengan penyembuhan luka.
- MVASI dapat meningkatkan kejadian tekanan darah tinggi. Jika Anda memiliki tekanan darah tinggi yang tidak terkontrol dengan baik dengan obat untuk tekanan darah, berkonsultasilah dengan dokter Anda karena penting untuk memastikan bahwa tekanan darah Anda terkendali sebelum memulai pengobatan dengan MVASI.
- MVASI meningkatkan risiko adanya kandungan protein dalam urin Anda terutama jika Anda sudah memiliki tekanan darah tinggi.
- Risiko pengembangan penggumpalan darah di pembuluh arteri Anda (sejenis pembuluh darah) dapat meningkat jika Anda berusia di atas 65 tahun, jika Anda menderita diabetes, atau jika Anda pernah mengalami penggumpalan darah sebelumnya di arteri Anda. Bicarakanlah dengan dokter Anda karena penggumpalan darah dapat menyebabkan serangan jantung dan stroke.
- MVASI juga dapat meningkatkan risiko pengembangan penggumpalan darah di pembuluh vena Anda (sejenis pembuluh darah).
- MVASI dapat menyebabkan perdarahan, terutama pendarahan terkait tumor. Berkonsultasi dengan dokter Anda jika Anda atau keluarga Anda cenderung menderita masalah pendarahan atau Anda meminum obat untuk menipiskan darah dengan alasan apapun.
- Ada kemungkinan MVASI dapat menyebabkan perdarahan di dalam dan di sekitar otak Anda. Diskusikan hal ini dengan dokter Anda jika Anda memiliki kanker metastatik yang mempengaruhi otak Anda.
- Ada kemungkinan MVASI dapat meningkatkan risiko pendarahan di paru-paru Anda, termasuk batuk atau ludah berdarah. Diskusikan dengan dokter Anda jika anda melihat hal ini sebelumnya.
- MVASI dapat meningkatkan risiko perkembangan jantung yang lemah. Penting bahwa dokter Anda mengetahui jika Anda pernah menerima anthracyclines (misalnya doksorubisin, jenis kemoterapi khusus yang digunakan untuk mengobati beberapa jenis kanker) atau pernah melakukan radioterapi di dada Anda, atau jika Anda menderita penyakit jantung.
- MVASI dapat menyebabkan infeksi dan penurunan jumlah neutrofil Anda (sejenis sel darah yang penting untuk perlindungan Anda terhadap bakteri).
- Ada kemungkinan MVASI dapat menyebabkan reaksi hipersensitivitas dan / atau infus (reaksi yang berkaitan dengan injeksi obat). Beritahu dokter, apoteker atau perawat Anda jika Anda pernah mengalami masalah setelah suntikan, seperti pusing / merasa pingsan, sesak napas, bengkak atau ruam kulit.
- Efek samping neurologis yang langka yang disebut *posterior reversible encephalopathy syndrome* (PRES) telah dikaitkan dengan pengobatan MVASI. Jika Anda mengalami sakit kepala, perubahan penglihatan, kebingungan atau *seizure* dengan atau tanpa tekanan darah tinggi, hubungi dokter Anda.

Silakan berkonsultasi dengan dokter Anda, bahkan jika pernyataan di atas hanya berlaku untuk Anda di masa lalu.

Sebelum Anda diberi MVASI atau saat Anda sedang dirawat dengan MVASI:

- Jika Anda pernah atau memiliki rasa sakit di mulut, gigi dan / atau rahang, pembengkakan dan luka di dalam mulut, mati rasa atau rahang terasa berat, atau gigi goyang segera beritahu dokter dan dokter gigi Anda.
- Jika Anda perlu menjalani perawatan gigi atau operasi gigi invasif, beritahu dokter gigi Anda bahwa Anda sedang menjalani perawatan dengan MVASI (bevacizumab), khususnya saat Anda menerima atau pernah menerima suntikan bifosfonat ke dalam darah Anda.

Anda mungkin disarankan untuk melakukan pemeriksaan gigi sebelum memulai perawatan dengan MVASI.

Anak-anak dan remaja

MVASI tidak direkomendasikan untuk anak dan remaja dibawah 18 tahun karena keamanan dan manfaat pada populasi pasien tersebut belum ditetapkan.

Kematian jaringan tulang (osteonekrosis) pada tulang selain rahang telah dilaporkan pada pasien berusia di bawah 18 tahun ketika diobati dengan bevacizumab.

Obat – obatan lain dan MVASI

Beritahu dokter, apoteker atau perawat Anda jika Anda baru saja mengkonsumsi atau mungkin mengkonsumsi obat-obatan lainnya.

Kombinasi MVASI dengan obat lain yang disebut sunitinib malate (diresepkan untuk kanker ginjal dan gastrointestinal) dapat menyebabkan efek samping yang parah. Diskusikan dengan dokter Anda untuk memastikan bahwa Anda tidak menggabungkan obat ini.

Beritahu dokter Anda jika Anda menggunakan terapi berbasis platinum atau taxane untuk kanker paru atau payudara metastatik. Terapi ini jika dikombinasikan dengan MVASI dapat meningkatkan risiko efek samping yang parah.

Beritahu dokter Anda jika Anda baru saja menerima, atau sedang menerima radioterapi.

Kehamilan, menyusui dan kesuburan

Anda tidak boleh menggunakan obat ini jika Anda hamil. MVASI dapat menyebabkan kerusakan pada janin Anda karena dapat menghentikan pembentukan pembuluh darah baru. Dokter Anda harus menyarankan Anda tentang penggunaan kontrasepsi selama pengobatan dengan MVASI dan paling tidak 6 bulan setelah dosis terakhir MVASI.

Beritahu dokter Anda langsung jika Anda sedang hamil, hamil pada saat menjalani pengobatan dengan obat ini, atau berencana untuk hamil dalam waktu dekat.

Anda tidak boleh menyusui bayi Anda selama pengobatan dengan MVASI dan paling tidak 6 bulan setelah dosis terakhir MVASI, karena obat ini dapat mengganggu pertumbuhan dan perkembangan bayi Anda.

MVASI dapat mengganggu kesuburan wanita. Silakan berkonsultasi dengan dokter Anda untuk informasi lebih lanjut.

Mintalah saran dokter, apoteker atau perawat Anda sebelum menggunakan obat apapun.

Mengemudi dan menjalankan mesin

MVASI belum terbukti mengurangi kemampuan Anda menyetir atau menggunakan alat atau mesin apa pun. Namun, rasa kantuk dan pingsan telah dilaporkan pada penggunaan MVASI. Jika Anda mengalami gejala yang mempengaruhi penglihatan atau konsentrasi, atau kemampuan Anda untuk bereaksi, jangan mengemudi dan menggunakan mesin sampai gejala hilang.

3. Bagaimana cara penggunaan MVASI

Dosis dan frekuensi pemberian

Dosis MVASI yang dibutuhkan tergantung pada berat badan dan jenis kanker yang akan diobati. Dosis yang dianjurkan adalah 5 mg, 7,5 mg, 10 mg atau 15 mg per kilogram berat badan. Dokter Anda akan meresepkan dosis MVASI yang tepat untuk Anda. Anda akan diobati dengan MVASI setiap 2 atau 3 minggu sekali. Jumlah infus yang Anda terima akan tergantung pada bagaimana Anda merespons pengobatan; Anda harus terus menerima obat ini sampai MVASI gagal menghentikan pertumbuhan tumor Anda. Dokter Anda akan membicarakan hal ini dengan Anda.

Metode dan rute administrasi

MVASI adalah konsentrat untuk larutan infus. Bergantung pada dosis yang ditentukan untuk Anda, sebagian atau semua isi vial MVASI akan diencerkan dengan larutan natrium klorida sebelum digunakan. Dokter atau perawat akan memberi Anda larutan MVASI yang telah dilarutkan ini melalui infus intravena (menetes ke pembuluh vena Anda). Infus pertama akan diberikan kepada Anda selama lebih dari 90 menit. Jika ditoleransi dengan baik, infus kedua bisa diberikan selama lebih dari 60 menit. Infus selanjutnya mungkin diberikan kepada Anda selama lebih dari 30 menit.

Pemberian MVASI harus dihentikan sementara

- jika Anda mengalami tekanan darah tinggi yang parah yang memerlukan perawatan dengan obat untuk tekanan darah,
- jika Anda memiliki masalah dengan penyembuhan luka setelah operasi,
- jika Anda menjalani operasi.

Pemberian MVASI harus dihentikan secara permanen jika Anda mengalami

- tekanan darah tinggi yang parah yang tidak dapat dikendalikan oleh obat untuk tekanan darah; atau peningkatan secara mendadak tekanan darah yang parah,
- adanya kandungan protein dalam urin anda disertai pembengkakan tubuh Anda,
- lubang di dinding usus Anda,
- sambungan mirip tabung atau saluran yang tidak normal antara tenggorokan dan kerongkongan, antara organ dalam dan kulit, antara vagina dan bagian usus atau antara jaringan lain yang tidak terhubung secara normal (*fistula*), dan dinilai oleh dokter menjadi parah,
- infeksi serius pada kulit atau lapisan yang lebih dalam di bawah kulit,
- penggumpalan darah di pembuluh arteri Anda,
- penggumpalan darah di pembuluh darah pada paru-paru Anda,
- perdarahan hebat.

Jika MVASI yang diberikan terlalu banyak

- Anda mungkin mengalami migrain yang parah. Jika ini terjadi, Anda harus segera berbicara dengan dokter, apoteker atau perawat Anda.

Jika dosis MVASI terlewat

- dokter Anda akan memutuskan kapan Anda harus diberi MVASI dosis berikutnya. Anda harus membicarakan hal ini dengan dokter Anda.

Jika Anda menghentikan pengobatan dengan MVASI

Menghentikan pengobatan dengan MVASI dapat menghentikan efek pada pertumbuhan tumor. Jangan menghentikan pengobatan dengan MVASI kecuali jika Anda telah membicarakan hal ini dengan dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

4. Kemungkinan efek samping

Seperti semua obat-obatan, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini.

Efek samping yang tercantum di bawah ini terlihat saat MVASI diberikan bersamaan dengan kemoterapi. Namun belum tentu efek samping ini disebabkan oleh MVASI.

Reaksi alergi

Jika Anda memiliki reaksi alergi, segera beritahu dokter atau anggota staf medis. Tanda-tandanya bisa meliputi: kesulitan bernafas atau sakit dada. Anda juga bisa mengalami kemerahan atau kemerahan yang tidak segera hilang pada kulit atau ruam, kedinginan dan menggigil, mual atau muntah.

Anda harus segera mencari bantuan jika mengalami salah satu dari efek samping yang disebutkan di bawah ini.

Efek samping yang parah, yang mungkin **sangat umum** (dapat mempengaruhi lebih dari 1 dari 10 orang), meliputi:
- tekanan darah tinggi,
- mati rasa atau kesemutan di tangan atau kaki,
- penurunan jumlah sel dalam darah, termasuk sel darah putih yang membantu melawan infeksi (mungkin disertai demam), dan sel yang membantu pembekuan darah,
- merasa lemah dan tidak memiliki energi,
- kelelahan,
- diare, mual, muntah dan sakit perut.

Efek samping yang parah, yang mungkin **umum** (dapat mempengaruhi hingga 1 dari 10 orang), meliputi:
- perforasi usus,
- perdarahan, termasuk pendarahan di paru-paru pada pasien *non-small cell lung cancer*,
- pemblokiran pembuluh arteri oleh gumpalan darah,
- pemblokiran pembuluh vena oleh gumpalan darah,
- pemblokiran pembuluh darah pada paru-paru oleh gumpalan darah,
- pemblokiran pembuluh vena pada kaki oleh gumpalan darah,
- gagal jantung,
- masalah dengan penyembuhan luka setelah operasi,
- kemerahan, pengelupasan, nyeri tekan, nyeri, atau pelepuhan pada jari atau kaki,
- penurunan jumlah sel darah merah dalam darah,
- kekurangan energi,
- gangguan perut dan usus,
- nyeri otot dan sendi, kelemahan otot,
- mulut kering disertai dengan haus dan / atau berkurangnya urin atau urin menjadi gelap,
- pembengkakan lapisan lembab pada mulut dan usus, paru-paru dan saluran udara, saluran reproduksi, dan saluran kemih,

- luka di mulut dan saluran dari mulut ke perut, yang mungkin terasa sakit dan menyebabkan kesulitan menelan,
- nyeri, termasuk sakit kepala, nyeri punggung dan nyeri di daerah panggul dan daerah dubur,
- kumpulan nanah yang terlokalisasi,
- infeksi, dan khususnya infeksi pada darah atau kandung kemih,
- penurunan suplai darah ke otak atau stroke,
- mengantuk,
- hidung berdarah,
- peningkatan detak jantung (denyut nadi),
- penyumbatan pada usus,
- tes urine abnormal (adanya kandungan protein dalam urin),
- sesak nafas atau kadar oksigen rendah dalam darah,
- infeksi kulit atau lapisan yang lebih dalam di bawah kulit,
- fistula: hubungan atau jalur abnormal antara organ dalam atau kulit atau jaringan lain yang biasanya tidak terhubung, termasuk hubungan antara vagina dan bagian usus pada pasien kanker serviks.

Efek samping yang parah yang **tidak diketahui** frekuensi kejadiannya (frekuensi tidak dapat diperkirakan dari data yang ada), meliputi:
- infeksi serius pada kulit atau lapisan yang lebih dalam di bawah kulit, terutama jika Anda memiliki lubang di dinding usus atau masalah dengan penyembuhan luka,
- reaksi alergi (tanda-tandanya meliputi kesulitan bernapas, wajah kemerahan, ruam, tekanan darah rendah atau tekanan darah tinggi, kadar oksigen rendah di dalam darah, nyeri dada, atau mual / muntah),
- efek negatif pada kemampuan wanita untuk memiliki anak (lihat paragraf di bawah daftar efek samping untuk rekomendasi lebih lanjut),
- kondisi otak dengan gejala termasuk *seizures* (*fits*), sakit kepala, bingung, dan perubahan penglihatan (*Posterior Reversible Encephalopathy Syndrome* atau PRES)
- gejala yang menunjukkan perubahan fungsi normal otak (sakit kepala, perubahan penglihatan, kebingungan, atau *seizures*), dan tekanan darah tinggi,
- penenyumbatan pembuluh darah yang sangat kecil di ginjal,
- tekanan darah tinggi yang tidak normal di pembuluh darah paru-paru yang membuat sisi kanan jantung bekerja lebih keras dari biasanya,
- lubang di dinding tulang rawan yang memisahkan lubang hidung,
- lubang di perut atau usus,
- luka terbuka atau lubang di lapisan perut atau usus kecil (tanda-tandanya bisa termasuk sakit perut, terasa kembung, tinja berlendir hitam atau darah di tinja atau darah di dalam muntahan),
- perdarahan dari bagian bawah usus besar,
- lesi pada gusi dengan tulang rahang yang terbuka yang tidak sembuh dan mungkin terkait dengan rasa sakit dan pembengkakan jaringan sekitarnya (lihat paragraf di bawah daftar efek samping untuk rekomendasi lebih lanjut),
- lubang di kantong empedu (gejala dan tanda bisa termasuk sakit perut, demam, dan mual / muntah).

Anda harus mencari bantuan sesegera mungkin jika Anda menderita salah satu dari efek samping yang disebutkan di bawah ini.

Efek samping yang **sangat umum** (dapat mempengaruhi lebih dari 1 dari 10 orang), yang tidak parah, meliputi:

- sembelit,
- kehilangan selera makan,
- demam,
- masalah dengan mata (termasuk peningkatan produksi air mata),
- perubahan dalam kemampuan bicara,
- perubahan dalam kemampuan mengecap,
- hidung meler,
- kulit kering, pengelupasan dan radang pada kulit, perubahan warna kulit,
- kehilangan berat badan,
- pendarahan hidung.

Efek samping yang **umum** (dapat mempengaruhi hingga 1 dari 10 orang), yang tidak parah, meliputi:

- perubahan suara dan suara serak.

Pasien yang berusia lebih dari 65 tahun memiliki risiko lebih besar mengalami efek samping berikut ini:

- penggumpalan darah di arteri yang bisa menyebabkan stroke atau serangan jantung,
- penurunan jumlah sel darah putih dalam darah, dan sel yang membantu pembekuan darah,
- diare,
- rasa sakit,
- sakit kepala,
- kelelahan,
- tekanan darah tinggi.

MVASI juga dapat menyebabkan perubahan dalam tes laboratorium yang dilakukan oleh dokter Anda. Hal ini termasuk penurunan jumlah sel darah putih dalam darah, terutama neutrofil (satu jenis sel darah putih yang membantu melindungi terhadap infeksi) dalam darah; adanya kandungan protein dalam urin; penurunan kadar kalium darah, natrium atau fosfor (mineral); peningkatan gula darah; peningkatan fosfatase alkalin darah (enzim); peningkatan kreatinin serum (protein yang diukur dengan tes darah untuk melihat seberapa baik ginjal Anda bekerja); penurunan hemoglobin (ditemukan pada sel darah merah, yang membawa oksigen), yang mungkin parah.

Nyeri di mulut, gigi dan / atau rahang, pembengkakan atau luka di dalam mulut, mati rasa atau rahang terasa berat, atau gigi goyang. Ini bisa jadi tanda dan gejala kerusakan tulang pada rahang (osteonekrosis). Beritahu dokter dan dokter gigi Anda segera jika Anda mengalami salah satunya.

Wanita pra-menopause (wanita yang memiliki siklus haid) mungkin memperhatikan bahwa menstruasi mereka menjadi tidak teratur dan mungkin mengalami gangguan kesuburan. Jika Anda mempertimbangkan untuk memiliki anak Anda harus membicarakannya dengan dokter Anda sebelum pengobatan dimulai.

MVASI telah dikembangkan dan dibuat untuk mengobati kanker dengan cara menyuntikkannya ke dalam aliran darah. Injeksi ke mata belum dikembangkan atau dibuat. Oleh karena itu tidak diizinkan untuk digunakan dengan cara ini. Bila bevacizumab disuntikkan langsung ke mata (penggunaan yang tidak disetujui), efek samping berikut mungkin terjadi:

- Infeksi atau pembengkakan bola mata,
- Kemerahan pada mata, partikel kecil atau bintik-bintik dalam penglihatan anda (*floaters)*, sakit mata,
- Melihat kilatan cahaya dengan *floaters*, berlanjut ke kehilangan sebagian penglihatan anda,
- Meningkatnya tekanan mata,
- Perdarahan di mata.

Pelaporan efek samping

Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat Anda. Ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi keamanan obat ini.

5. Bagaimana cara penyimpanan MVASI

Jauhkan obat ini dari jangkauan dan penglihatan anak-anak.

Jangan menggunkan obat ini setelah tanggal kadaluarsa yang tertera pada dus dan label vial setelah EXP. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan pada lemari pendingin (2°C - 8°C).
Jangan dibekukan.
Simpan vial di dalam dus agar terlindung dari cahaya.

Larutan infus harus segera digunakan setelah diencerkan. Jangan menggunakan MVASI jika Anda menyadari adanya partikel atau perubahan warna.

Jangan menbuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana cara membuang obat-obatan yang sudah tidak digunakan. Langkah ini dapat membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apakah kandungan MVASI

- Zat aktifnya adalah bevacizumab. Setiap ml konsentrat mengandung 25 mg bevacizumab, sesuai dengan 1,4 sampai 16,5 mg/ml bila diencerkan sesuai anjuran
- Setiap vial 4 ml mengandung 100 mg bevacizumab, sesuai dengan 1,4 mg/ml bila diencerkan sesuai anjuran
- Setiap vial 16 ml mengandung 400 mg bevacizumab, sesuai dengan 16,5 mg/ml bila diencerkan sesuai anjuran
- Bahan-bahan lainnya adalah trehalosa dihidrat, natrium fosfat, polisorbat 20 dan air untuk injeksi.

Seperti apa MVASI dan isi kemasannya

MVASI adalah konsentrat untuk larutan infus. Konsentrat berupa cairan yang agak jernih, tidak berwarna hingga sedikit kuning dalam vial kaca dengan stopper karet. Setiap vial mengandung bevacizumab 100 mg dalam 4 ml larutan atau bevacizumab 400 mg dalam 16 ml larutan. Setiap dus MVASI berisi satu vial.

Diregister oleh:
PT. Pyridam Farma, Tbk
Kabupaten Cianjur, Indonesia

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Patheon Manufacturing Services LLC,
5900 Martin Luther King Jr. Highway,
Greenville, NC, NC 27834, USA

Dikemas dan Dirilis oleh:
Amgen Manufacturing Limited, Puerto Rico, USA

Nomor Izin Edar:
xxxxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Leaflet ini direvisi terakhir kali pada April 2021

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