Zirabev
(Bevacizumab)

1. NAME OF THE MEDICINAL PRODUCT

Zirabev Concentrate for Solution for Infusion 100 mg/4 ml and 400 mg/16 ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 25 mg of bevacizumab*.
Each 4 ml vial contains 100 mg of bevacizumab.
Each 16 ml vial contains 400 mg of bevacizumab.
For dilution and other handling recommendations, see section 6.6.

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

Excipient with known effect

Each 4 ml vial contains 3.0 mg of sodium.
Each 16 ml vial contains 12.1 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zirabev in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Zirabev in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

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

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

4.2 Posology and method of administration

Do not shake the vial.

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

Posology

Metastatic carcinoma of the colon or rectum (mCRC)

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

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

Metastatic breast cancer (mBC)

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

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

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy

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

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

Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses (see section 5.1).

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

Advanced and/or metastatic renal cell cancer (mRCC)

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

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

Special populations

Elderly patients
No dose adjustment is required in the patients ≥ 65 years of age.

Patients with renal impairment
The safety and efficacy have not been studied in patients with renal impairment (see section 5.2).

Patients with hepatic impairment
The safety and efficacy have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of bevacizumab in children aged less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

Method of administration

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

It should not be administered as an intravenous push or bolus.

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

Precautions to be taken before handling or administering the medicinal product

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch

number of the administered product should be clearly recorded.

Gastrointestinal (GI) perforations and fistulae (see section 4.8)

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal fistulae in study GOG-0240

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI fistulae (see section 4.8)

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue Zirabev in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of bevacizumab in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Zirabev should be considered.

Wound healing complications (see section 4.8)

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

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

Hypertension (see section 4.8)

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

Monitoring of blood pressure is generally recommended during therapy.

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

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Zirabev, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Posterior reversible encephalopathy syndrome (PRES) (see section 4.8)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Zirabev. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Proteinuria (see section 4.8)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all Grade (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism (see section 4.8)

In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

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

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

Venous thromboembolism (see section 4.8)

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary

embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

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

Haemorrhage

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

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Zirabev treatment discontinued in cases of intracranial bleeding.

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 therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly (NCI-CTCAE v.3).

Pulmonary haemorrhage/haemoptysis

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

Congestive heart failure (CHF) (see section 4.8)

Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Zirabev.

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. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (NCI-CTCAE v.3) (see section 4.8).

Neutropenia and infections (see section 4.8)

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions (including anaphylactic shock)/infusion reactions (see section 4.8)

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

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

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Zirabev and intravenous bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Zirabev. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Zirabev is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

Ovarian failure/fertility

Bevacizumab may impair female fertility (see sections 4.6 and 4.8). Therefore, fertility

preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Zirabev.

Excipient information

This medicinal product contains 3.0 mg sodium per 4 ml vial, equivalent to 0.15% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

This medicinal product contains 12.1 mg sodium per 16 ml vial, equivalent to 0.61% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

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

Combination of bevacizumab and sunitinib malate

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

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see Hypertension, Proteinuria, PRES in section 4.4).

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

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

Radiotherapy

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

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no clinical trial data on the use of bevacizumab in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and bevacizumab is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). Bevacizumab is contraindicated in pregnancy (see section 4.3).

Breast-feeding

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

Fertility

Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3). In a phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of bevacizumab is based on data from over 5,700 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

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

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

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

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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

Table 1 provides all adverse reactions by frequency that were determined to have a causal relationship with bevacizumab through:

- comparative incidences noted between clinical trial treatment arms (with at least a 10% difference compared to the control arm for NCI-CTCAE Grade 1-5 reactions or at least a 2% difference compared to the control arm for NCI-CTCAE Grade 3-5 reactions,
- post-authorisation safety studies,
- spontaneous reporting,
- epidemiological studies/non-interventional or observational studies,
- or through an evaluation of individual case reports.

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse reactions with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe.

Post-marketing adverse reactions are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions are provided in Table 3.

Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication.

Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal

doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1 Adverse reactions by frequency

System organ class	Very common	Common	Un-common	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis[a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, Infusion reactions[a,b,d]		Anaphylactic shock[a,d]		
Metabolism and nutrition disorders	Anorexia, Hypomagnesaemia, Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalopathy syndrome[a,b,d]	Hypertensive encephalopathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				Aneurysms and artery dissections, Renal thrombotic microangiopathy[a,b]
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal				Gastrointestinal ulcer[a]

		disorder, Proctalgia				
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b], Non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic pain				
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients
[d] For additional information refer below within section "Further information on selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in pediatric population only.

Table 2 Severe adverse reactions by frequency

System organ class	Very common	Common	Un-common	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising fasciitis[c]
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, Infusion		Anaphylactic shock[b,c]		

		reactions[a,b,c]				
Metabolism and nutrition disorders		Dehydration, Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome[a,b,c], Hypertensive encephalopathy[c]
Cardiac disorders		Congestive heart failure[a,b], Supraventricular tachycardia				
Vascular disorders	Hypertension[a,b]	Thromboembolism arterial[a,b], Haemorrhage[a,b], Thromboembolism (venous)[a,b], Deep vein thrombosis				Aneurysms and artery dissections, Renal thrombotic microangiopathy[b,c]
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b], Gastrointestinal ulcer[c], Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation[b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar erythrodysaesthesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular weakness, Back pain				Osteonecrosis of the jaw[b,c]
Renal and urinary disorders		Proteinuria[a,b]				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure[a,b]
Congenital, familial, and genetic disorder						Foetal abnormalities[a,c]

General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse reactions with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the post-marketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled "Frequency Not Known."

[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[b] For additional information refer below within section "Further information on selected serious adverse reactions"
[c] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[d] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and fistulae (see section 4.4)

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 non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation. The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

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

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

GI-vaginal fistulae in study GOG-0240

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with bevacizumab + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no

recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI fistulae (see section 4.4)

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥0.1% to <1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Wound healing (see section 4.4)

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

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting bevacizumab. 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).

Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome.

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

In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.8% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension (see section 4.4)

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab containing arms compared with up to 14% in the control arms. 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 and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received

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

Hypertension was generally adequately controlled with oral anti-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.

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

Posterior reversible encephalopathy syndrome (see section 4.4)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurological disorder. Presentation may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The clinical presentation of PRES is often nonspecific, and therefore the diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

In patients developing PRES, early recognition of symptoms with prompt treatment of specific symptoms including control of hypertension (if associated with severe uncontrolled hypertension) is recommended in addition to discontinuation of bevacizumab therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Across clinical trials, 8 cases of PRES have been reported. Two of the eight cases did not have radiological confirmation via MRI.

Proteinuria (see section 4.4)

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of Zirabev therapy. In most clinical trials urine protein levels of ≥2 g/24 hrs led to the holding of bevacizumab until recovery to <2 g/24 hrs.

Haemorrhage (see section 4.4)

In clinical trials across all indications the overall incidence of NCI-CTCAE v.3 Grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in bevacizumab treated patients, compared with up to 4.5% of patients in the chemotherapy control group.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG- 0240), grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan.

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

Tumour-associated haemorrhage (see section 4.4)

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

In patients with NSCLC excluding predominant squamous histology, all Grade reactions were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone (NCI-CTCAE v.3). Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

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

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis (NCI-CTCAE v.3).

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of bevacizumab-treated patients. These were most commonly NCI-CTCAE v.3 Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

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

Thromboembolism (see section 4.4)

Arterial thromboembolism
An increased incidence of arterial thromboembolic reactions was observed in patients treated

with bevacizumab across indications, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic reactions.

In clinical trials, the overall incidence of arterial thromboembolic reactions ranged up to 3.8% in the bevacizumab containing arms compared with up to 2.1% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.7% of patients treated with bevacizumab in combination with chemotherapy compared to up to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in up to 1.4% of patients treated with bevacizumab in combination with chemotherapy compared to up to 0.7% of patients treated with chemotherapy alone.

In one clinical trial evaluating bevacizumab in combination with 5-fluorouracil/folinic acid, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic reactions were observed in 11% (11/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

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

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

Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG- 0240), grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with bevacizumab in combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin.

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

Congestive heart failure (CHF)

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 trials (AVF2119g, E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer CHF Grade 3 (NCI-CTCAE v.3) or higher was reported in up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of Grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all Grade CHF were similar between the anthracycline + 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 (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

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

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

Hypersensitivity reactions (including anaphylactic shock)/infusion reactions (see section 4.4 and Post-marketing experience below)

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

Infections

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG- 0240), grade 3-5 infections have been reported in up to 24% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 13% of patients treated with paclitaxel and topotecan.

Ovarian failure/fertility (see sections 4.4 and 4.6)

In NSABP C-08, a phase III trial of bevacizumab in adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥30 mIU/ml and a negative serum β-HCG pregnancy test, has been evaluated in 295 premenopausal women. New cases of ovarian failure were reported in 2.6% patients in the mFOLFOX-6 group compared to 39% in the mFOLFOX-6 + bevacizumab group. After discontinuation of bevacizumab treatment, ovarian function recovered in 86.2% of these evaluable women. Long term effects of the treatment with bevacizumab on fertility are unknown.

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 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with bevacizumab with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia,

hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR).

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

Other special populations

Elderly patients

In randomised clinical trials, age >65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see sections 4.4 and 4.8 under Thromboembolism). In one clinical trial, the incidence of hypertension of grade ≥3 was two-fold higher in patients aged >65 years than in the younger age group (<65 years). In a study of platinum-resistant recurrent ovarian cancer patients, alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were also reported and occurred at a rate at least 5% higher in the CT + BV arm for bevacizumab-treated patients ≥65 years of age compared with bevacizumab-treated patients aged <65 years.

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

Paediatric population

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

In study BO25041 of bevacizumab added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with bevacizumab.

In study BO20924 of bevacizumab with current standard of care in rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, the safety profile of bevacizumab treated children was comparable with that observed in adults treated with bevacizumab.

Bevacizumab is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with bevacizumab.

Post-marketing experience

Table 3 Adverse reactions reported in post-marketing setting

System organ class (SOC)	Reactions (frequency*)
Infections and Infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see also section 4.4)
Immune system disorders	Hypersensitivity reactions and infusion reactions (common); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see also section 4.4 and Hypersensitivity reactions/infusion reactions above) Anaphylactic shock (rare) (see also section 4.4)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and Hypertension in section 4.8) Posterior Reversible Encephalopathy Syndrome (PRES), (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use. For further information on proteinuria see section 4.4 and Proteinuria in section 4.8.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been reported in patients treated with bevacizumab, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)
	Cases of non-mandibular osteonecrosis have been observed in bevacizumab treated paediatric patients (see section 4.8, Paediatric population).
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.6)

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01FG01

Zirabev is a biosimilar medicinal product. Substitution of Avastin by Zirabev should be taken place only under the supervision of the prescribing medical practitioner.

Mechanism of action

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

Pharmacodynamic effects

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

Clinical efficacy

Metastatic carcinoma of the colon or rectum (mCRC)

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

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

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

- NO16966: Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or bevacizumab 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

- E3200: Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in bevacizumab-naïve patients.

- ML18147: Bevacizumab 5.0 mg/kg of body weight every 2 weeks or bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

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/FA + 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.

The primary efficacy variable of the trial was overall survival. The addition of bevacizumab to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (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 trial AVF2107g

	AVF2107g	
	Arm 1 IFL + placebo	Arm 2 IFL + bevacizumab[a]
Number of patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% CI	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.0001)	
Overall response rate		
Rate (%)	34.8	44.8
	(p-value = 0.0036)	

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

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

AVF2192g
This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of 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. 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 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 as compared to 5-FU/FA chemotherapy alone.

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 randomised 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 trial AVF2107g.

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

Table 5 Efficacy results for trials 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 time (months)	13.6	17.7	15.2	12.9	16.6
95% CI				10.35 - 16.95	13.63 - 19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-free survival					
Median time (months)	5.2	9.0	7.2	5.5	9.2

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + bevacizumab[a]	5-FU/FA + bevacizumab[b]	5-FU/FA + placebo	5-FU/FA + bevacizumab
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall response rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% CI	7.0 - 33.5	24.4 - 57.8	11.7 - 42.6	9.2 - 23.9	18.1 - 35.6
p-value		0.029	0.43		0.055
Duration of response					
Median time (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5 – NR	6.1 - NR	3.8 - 7.8	5.59 - 9.17	5.88 - 13.01

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

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

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

Table 6 Treatment regimens in trial NO16966 (mCRC)

	Treatment	Starting dose	Schedule
FOLFOX-4 or FOLFOX-4 + bevacizumab	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 intravenous 2 h 200 mg/m^2 intravenous 2 h 400 mg/m^2 intravenous bolus, 600 mg/m^2 intravenous 22 h	Oxaliplatin on day 1 Leucovorin on day 1 and 2 5-fluorouracil intravenous bolus/infusion, each on days 1 and 2

	Placebo or bevacizumab	5 mg/kg intravenous 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + bevacizumab	Oxaliplatin Capecitabine	130 mg/m^2 intravenous 2 h 1000 mg/m^2 oral bid	Oxaliplatin on day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg intravenous 30-90 min	Day 1, prior to XELOX, q 3 weeks

5-Fluorouracil: intravenous bolus injection immediately after leucovorin

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

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

- Superiority of the bevacizumab-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 7).

Secondary PFS analyses, based on 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with bevacizumab (analyses shown in Table 7), consistent with the statistically significant benefit observed in the pooled analysis.

Table 7 Key efficacy results for the superiority analysis (ITT population, trial NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + placebo (n=701)	FOLFOX-4 or XELOX + bevacizumab (n=699)	P-value
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72–0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Overall response rate (invest. assessment)**	49.2%	46.5%	

Endpoint (months)	FOLFOX-4 or XELOX + placebo (n=701)	FOLFOX-4 or XELOX + bevacizumab (n=699)	P-value
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

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

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

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

ECOG E3200
This was a phase III randomised, active-controlled, open-label trial investigating bevacizumab 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 6 for trial NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 bevacizumab + FOLFOX-4 and 244 bevacizumab monotherapy). The addition of bevacizumab to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 8).

Table 8 Efficacy results for trial E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + bevacizumab[a]
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% CI	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective response rate		
Rate	8.6%	22.2%
	(p-value <0.0001)	

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

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

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

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

A total of 820 patients were randomised. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen (ITT = 819) (see Table 9).

Table 9 Efficacy results for study ML18147 (ITT population)

	ML18147	
	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + bevacizumab[a]
Number of patients	410	409
Overall survival		
Median (months)	9.8	11.2
Hazard ratio (95% confidence interval)	0.81 (0.69, 0.94) (p-value = 0.0062)	
Progression-free survival		
Median (months)	4.1	5.7
Hazard ratio (95% confidence interval)	0.68 (0.59, 0.78) (p-value < 0.0001)	
Objective response rate (ORR)		
Patients included in analysis	406	404
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and the difference was not significant.

Study E3200 used a 5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-naïve patients, while study ML18147 used a 2.5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-pretreated patients. A cross-trial comparison of the efficacy and safety data is limited by differences between these studies, most notably in patient populations, previous bevacizumab exposure and chemotherapy regimens. Both the 5 mg/kg/week and 2.5 mg/kg/week equivalent doses of bevacizumab provided a statistically significant benefit with regards to OS (HR 0.751 in study E3200; HR 0.81 in study ML18147) and PFS (HR 0.518 in study E3200; HR 0.68 in study ML18147). In terms of safety, there was a higher overall incidence of Grade 3-5 AEs in study E3200 relative to study ML18147.

Metastatic breast cancer (mBC)

ECOG E2100

Trial E2100 was an open-label, randomised, active controlled, multicentre 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. Patients were randomised to paclitaxel alone (90 mg/m^2 intravenous over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg intravenous infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered

unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastases, including previously treated or resected brain lesions, were excluded.

In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with bevacizumab as a single agent continued until disease progression. The patient characteristics were similar across the trial arms. The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 10.

Table 10 Trial E2100 efficacy results

Progression-free survival				
	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
Hazard ratio (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	< 0.0001		<0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		IRF assessment	
	Paclitaxel (n=273)	Paclitaxel/ 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
Hazard ratio (95% CI)	0.869 (0.722; 1.046)	
p-value	0.1374	

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

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy.

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

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

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2) and carboplatin AUC = 6.0, both by intravenous infusion (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg intravenous 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 randomised to the two arms.

During the trial, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of 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 11.

Table 11 Efficacy results for trial 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)

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

BO17704
Trial BO17704 was a randomised, double-blind phase III trial of bevacizumab in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally

advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival, secondary endpoints for the trial included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 intravenous infusion on day 1 and gemcitabine 1250 mg/m^2 intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with bevacizumab at a dose of 7.5 or 15 mg/kg intravenous infusion day 1 of every 3-week cycle. In the bevacizumab-containing arms, patients could receive bevacizumab as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Trial results show that 94% (277/296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti- cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 12.

Table 12 Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + bevacizumab 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + bevacizumab 15 mg/kg q 3 weeks
Number of patients	347	345	351
Progression-free survival			
Median (months)	6.1	6.7 (p=0.0026)	6.5 (p=0.0301)
Hazard ratio		0.75 [0.62; 0.91]	0.82 [0.68; 0.98]
Best overall response rate[a]	20.1%	34.1% (p <0.0001)	30.4% (p=0.0023)
[a] patients with measurable disease at baseline			
Overall survival			
Median (months)	13.1	13.6 (p=0.4203)	13.4 (p=0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

Advanced and/or metastatic renal cell cancer (mRCC)

Bevacizumab in combination with interferon alfa-2a for the first-line treatment of advanced and/ or metastatic renal cell cancer (BO17705)

This was a phase III randomised double-blind trial conducted to evaluate the efficacy and safety of bevacizumab in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had Karnofsky Performance Status (KPS) of ≥70%, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Bevacizumab 10 mg/kg was given every

2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommended starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

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

The efficacy results are presented in Table 13

Table 13 Efficacy results for trial BO17705

	BO17705	
	Placebo + IFN[a]	Bv[b] + IFN[a]
Number of patients	322	327
Progression-free survival Median (months) Hazard ratio 95% CI	5.4 0.63 0.52, 0.75 (p-value <0.0001)	10.2
Objective response rate (%) in Patients with measurable disease N Response rate	289 12.8% (p-value <0.0001)	306 31.4%

[a] Interferon alfa-2a 9 MIU 3x/week
[b] Bevacizumab 10 mg/kg q 2 wk

Overall survival Median (months) Hazard ratio 95% CI	21.3 0.91 0.76, 1.10 (p-value 0.3360)	23.3

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

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

AVF2938
This was a randomised, double-blind, phase II clinical trial investigating bevacizumab 10 mg/kg in a 2 weekly schedule with the same dose of bevacizumab in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this trial, 53 to bevacizumab 10 mg/kg every 2 weeks plus placebo and 51 to bevacizumab 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the bevacizumab + Placebo arm and the bevacizumab + Erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result in an improvement in OS (HR = 1.764; p=0.1789), duration of objective response (6.7 vs. 9.1 months) or time to symptom progression (HR = 1.172; p=0.5076).

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

High-grade glioma

Anti-tumour activity was not observed in two earlier studies among a total of 30 children aged >3 years old with relapsed or progressive high-grade glioma when treated with bevacizumab and irinotecan (CPT-11). There is insufficient information to determine the safety and efficacy of bevacizumab in children with newly-diagnosed high-grade glioma.

- In a single-arm study (PBTC-022), 18 children with recurrent or progressive non-pontine high-grade glioma (including 8 with glioblastoma [WHO Grade IV], 9 with anaplastic astrocytoma [Grade III] and 1 with anaplastic oligodendroglioma [Grade III]) were treated with bevacizumab (10 mg/kg) two weeks apart and then with bevacizumab in combination with CPT-11 (125-350 mg/m²) once every two weeks until progression. There were no objective (partial or complete) radiological responses (MacDonald criteria). Toxicity and adverse reactions included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.

- In a retrospective single institution series, 12 consecutive (2005 to 2008) children with relapsed or progressive high-grade glioma (3 with WHO Grade IV, 9 with Grade III) were treated with bevacizumab (10 mg/kg) and irinotecan (125 mg/m²) every 2 weeks. There were no complete responses and 2 partial responses (MacDonald criteria).

In a randomized phase II study (BO25041) a total of 121 patients aged ≥ 3 years to <18 years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade

glioma (HGG) were treated with post operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks intravenously.

The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone.

Addition of bevacizumab to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) (see section 4.2 for information on paediatric use).

Soft tissue sarcoma

In a randomized phase II study (BO20924) a total of 154 patients aged ≥ 6 months to <18 years with newly diagnosed metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma were treated with standard of care (Induction IVADO/IVA+/- local therapy followed by Maintenance Vinorelbine and cyclophosphamide) with or without bevacizumab (2.5 mg/kg/week) for a total duration of treatment of approximately 18 months. At the time of the final primary analysis, the primary endpoint of EFS by independent central review did not show a statistically significant difference between the two treatment arms, with HR of 0.93 (95% CI: 0.61, 1.41; p-value = 0.72).

The difference in ORR per independent central review was 18% (CI: 0.6%, 35.3%) between the two treatment arms in the few patients who had evaluable tumor at baseline and had a confirmed response prior to receiving any local therapy: 27/75 patients (36.0%, 95% CI: 25.2%, 47.9%) in the Chemo arm and 34/63 patients (54.0%, 95% CI: 40.9%, 66.6%) in the Bv +Chemo arm. The final overall survival (OS) analyses showed no significant clinical benefit from addition of bevacizumab to chemotherapy in this patient population.

Addition of bevacizumab to standard of care did not demonstrate clinical benefit in clinical trial BO20924, in 71 evaluable children (from age 6 months to less than 18 years old) patients with metastatic Rhabdomyosarcoma and non-Rhabdomyosarcoma Soft Tissue Sarcoma.

(See section 4.2 for information on paediatric use).

The incidence of AEs, including Grade ≥3 AEs and SAEs, was similar between the two treatment arms. No AEs leading to death occurred in either treatment arm; all deaths were attributed to disease progression. Bevacizumab addition to multimodal standard of care treatment seemed to be tolerated in this paediatric population.

Comparative Clinical Trials

Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between Zirabev and the reference biologic drug included the following:

- Study B7391001 was a comparative PK study in healthy male volunteers.

- Study B7391003 was a comparative efficacy and safety clinical trial in patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 14.

Table 14 Summary of Trial Designs and Patient Demographics

Study #	Study Design	Dosage, route of administration, duration	No. of Subjects (by Treatment Group)	Sex and Mean age (Range) (years)(by Treatment Group)
B7391001	Phase 1, randomized, double-blind (sponsor-unblinded), parallel-group, single-dose, 3-arm, comparative PK study of ZIRABEV with bevacizumab (EU) bevacizumab (US) administered to healthy male volunteers.	ZIRABEV: Single 5 mg/kg as a 90-minute IV infusion.	Randomized: 33	Sex: Male Age 37.6 (22-53)
		Bevacizumab-US: Single 5 mg/kg as a 90-minute IV infusion.	Randomized: 33	Sex: Male Age 36.0 (21-50)
		Bevacizumab-EU: Single 5 mg/kg as a 90-minute IV infusion.	Randomized: 36	Sex: Male Age 39.1 (21-55)

Study #	Study Design	Dosage, route of administration, duration	No. of Subjects (by Treatment Group)	Sex and Mean age (Range) (years) (by Treatment Group)
B7391003	Randomized, double-blind study of ZIRABEV plus paclitaxel-carboplatin and bevacizumab-EU plus paclitaxel-carboplatin for the first-line treatment of patients with advanced non-squamous NSCLC. Patients were randomized (1:1) to receive at least 4 cycles and no more than 6 cycles of either ZIRABEV plus paclitaxel-carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the previously assigned blinded bevacizumab monotherapy.	Bevacizumab: 15 mg/kg by IV infusion on Day 1 of each 21-day cycle. Paclitaxel: 200 mg/m^2 by IV infusion on Day 1 of each 21-day cycle. Carboplatin: AUC=6 by IV infusion on Day 1 of each 21 day cycle	**ZIRABEV** Randomized: 358 Treated: 356 **Bevacizumab-EU** Randomized: 361 Treated: 358	Sex: Male/Female 237/121 Age: 61.7 (25-87) Sex: Male/Female 230/131 Age: 60.9 (31-83)

Abbreviations: AUC = area under curve; EU = European Union; IV = intravenous;
No. = Number; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; US = United States.

Comparative Study Results

Comparative Bioavailability Studies

Pharmacokinetics

Study B7391001

The PK study (B7391001) demonstrated that the 90% CIs for the test-to-reference ratios of C_{MAX} and AUC_T, were within the pre-specified criteria for pharmacokinetic similarity of 80.0% to 125.0% for comparisons of ZIRABEV to bevacizumab-EU (Table 15).

Table 15 - Bevacizumab From measured data [6]Geometric Mean Arithmetic Mean (CV %)					
Parameter		**Test (ZIRABEV) [7]N=32**	**Reference (Bevacizumab-EU) N=33**	**Percent (%) Ratio (Test/Reference) Of Geometric Means**	**90% Confidence Interval for Ratio**
[2]AUC_T (mcg·hr/mL)	Geometric mean Arithmetic mean (CV%)	40330 40840 (16%)	40490 41010 (16%)	99.6	93.7 – 105.9
[1]AUC_I (mcg·hr/mL)	Geometric mean Arithmetic mean (CV%)	42490 43080 (16%)	43100 43830 (19%)	98.6	92.2 – 105.4
[3]C_{MAX} (mcg/mL)	Geometric mean Arithmetic mean (CV%)	141.5 142.9 (14%)	135.5 137.0 (15%)	104.4	N/A
[4]$T_{1/2}$ (hr)	Arithmetic mean (CV%)	396.8 (16%)	417.2 (21%)	N/A	N/A
[5]T_{max} (hr)	Median (Min-Max)	1.67 (1.65-24.00)	1.67 (1.67-4.00)	N/A	N/A

[1]AUC_I = area under the serum concentration-time profile from time 0 extrapolated to infinity, relevant when the dose is administered intravenously,
[2]AUC_T = area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration,
[3]C_{MAX} = maximum observed serum concentration,
[4]$T_{1/2}$ = Terminal half-life expressed as arithmetic mean (CV%),
[5]T_{max}= Time for C_{MAX}; Median and Range are presented,
[6]Geometric Means = exponentially transformed least squares means from the Analysis of Variance model fitted to log-transformed data, including treatment as the independent variable,
[7]N=Number of subjects in the treatment group,
All PK parameters were derived from non-compartmental analysis,
N/A: Not applicable.

Comparative Safety and Efficacy

Efficacy

Study B7391003 – Non Small Cell Lung Cancer
The primary efficacy endpoint was the objective response rate (ORR) (assessed by the investigator) based on evaluating the best overall response (BOR) achieved by Week 19 and subsequently confirmed 6 weeks later, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Comparability between ZIRABEV and bevacizumab-EU was demonstrated since the 95% confidence interval (CI) of the risk ratio in ORR was entirely contained within the pre-specified margin of (0.729, 1.371) (Table 16).

Table 16 Summary of ORR – Primary Efficacy Endpoint - ITT Population

	ZIRABEV (N=358)	**Bevacizumab-EU (N=361)**
Best overall response, n (%)		
Complete response (CR)	9 (2.5)	4 (1.1)
Partial response (PR)	153 (42.7)	157 (43.5)

	ZIRABEV (N=358)	Bevacizumab-EU (N=361)
Stable disease	154 (43.0)	166 (46.0)
Objective progression	15 (4.2)	14 (3.9)
Indeterminate[a]	27 (7.5)	20 (5.5)
[b]ORR, n (%)	162 (45.3)	161 (44.6)
95% exact CI[c]	[40.01, 50.57]	[39.40, 49.89]
Risk ratio (ZIRABEV/Bevacizumab-EU)[d]	1.0146	
95% CI of risk ratio[d]	[0.8628, 1.1933]	

Abbreviations: CI=confidence interval, CR=complete response, EU=European Union, ITT=Intent-to-Treat, n/N=number of patients with observation/total number of patients, ORR=objective response rate, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors

a. Indeterminate: Early death, unevaluable tumor assessment, and early study discontinuations.
b. ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response by Week 19 of the study in accordance with RECIST version 1.1 which was subsequently confirmed by 6 weeks thereafter.
c. Exact method based on the F-distribution was used.
d. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response.

Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Immunogenicity

Immunogenicity was evaluated in both clinical studies B7391001 and B7391003 using electrochemiluminescent (ECL) assays. Only samples confirmed positive for Anti-Drug Antibodies (ADAs) were subsequently analyzed for neutralizing antibodies (NAb).

For study B7391001, samples were evaluated for ADAs at baseline, Day 15, Day 29, Day 57, Day 71 and Day 100. For study B7391003, samples were evaluated for ADAs at baseline, cycles 1, 2, 3, 4, 6 and every other cycle through to Cycle 17 (up to Week 52) or End of Treatment.

The incidence of ADA and NAb from these 2 studies is presented in Table 17 below.

Table 17 Summary of Percentage of Patients with Anti-Drug Antibodies and Neutralizing antibodies by Study and Treatment

Number of Subjects/Patients (%)

	B7391001[a]		B7391003[a]	
	ZIRABEV N=33	Bevacizumab-EU N=35	ZIRABEV N=356	Bevacizumab-EU N=358
Anti-Drug Antibody (ADA)				
	n/N1 (%)	**n/N1 (%)**	**n/N1 (%)**	**n/N1 (%)**
Baseline[b]	0/33 (0.0)	0/33 (0.0)	1/352	3/353 (0.8)
Post dose[c]	2/33 (6.1)	2/33 (6.1)	5/339	5/350 (1.4)
Neutralizing Antibody (NAb)				
Baseline[d]	0/33 (0.0)	0/33 (0.0)	1/352	0/353 (0.0)
Post dose[e]	0/33 (0.0)	0/33 (0.0)	0/339	3/350 (0.9)

Abbreviations: ADA = Anti-drug antibodies; EU = European Union; N = Number of evaluable subjects; NAb = Neutralizing antibody; All samples were taken prior to dosing at each visit. ADA positive sample

was defined as ADA titer ≥2.29. NAb positive samples were defined as NAb titer ≥1.70.

a. ADA and NAb assay ZIRABEV as a labeling reagent. N= number of patients who received study drug.

Percentages of patients with ADA or NAb are calculated based on:

b. For calculation of the incidence of ADA at Baseline, n=number of patients with ADA positive at Baseline, N1= number of patients at Baseline.
c. For calculation of the overall incidence of ADA post dose, n= total number of patients with ADA positive sample(s) at any visit during the trial after the first dose, N1=total number of patients with at least one sample tested for ADA at any time during the trial after the first dose.
d. For calculation of the incidence of NAb at Baseline, n=number of patients with NAb positive at Baseline, N1= number of patients at Baseline.
e. For calculation of the overall incidence of NAb post dose, n= total number of patients with NAb positive sample(s) at any visit during the trial after the first dose, N1=total number patients with at least one sample tested for ADA at any time during the trial after the first dose.

Due to the low percentage of subjects with observed ADA in Study B7391001 and Study B7391003, the effects of immunogenicity on safety and efficacy could not be evaluated.

5.2 Pharmacokinetic properties

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

Distribution

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

Biotransformation

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

Elimination

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

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

Pharmacokinetics in special populations

The population pharmacokinetics were analysed in adult and pediatric patients to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Renal impairment

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

Hepatic impairment

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

Paediatric population

The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

The pharmacokinetics of bevacizumab was well characterized by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumb exposure trended lower as body weight decreased.

5.3 Preclinical safety data

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

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

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

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal

malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks. Information on foetal malformations observed in the post marketing setting are provided in section 4.6 Fertility, Pregnancy and Lactation and 4.8 Undesirable Effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Succinic acid
Disodium edetate
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

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

6.3 Shelf life

Vial (unopened)

Please refer to outer carton for the expiry date.

Diluted medicinal product

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

6.4 Special precautions for storage

Please refer to outer carton for the storage condition.
Do not freeze.

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

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

6.5 Nature and contents of container

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

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Do not shake the vial.

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

Once the vial has been opened, the dilution must be performed immediately. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of Zirabev can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 mL.

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

No incompatibilities between Zirabev and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

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

Pfizer Corporation Hong Kong Limited
FEB 2023
Version approved: 15 MAY 2023

Package leaflet: Information for the user

Zirabev 25 mg/ml concentrate for solution for infusion
bevacizumab

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zirabev is and what it is used for

Zirabev contains the active substance bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection and cancer). Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour.

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

Zirabev is also used for the treatment of adult patients with metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy medicinal product called paclitaxel.

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

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

2. What you need to know before you use Zirabev

Do not use Zirabev
- if you are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of this medicine (listed in section 6).
- if you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- if you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Zirabev:

- Your doctor should record the brand name and batch number of your medication.

- It is possible that Zirabev may increase the risk of developing holes in the gut wall. If you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), please discuss this with your doctor.

- Zirabev may increase the risk of developing an abnormal connection or passageway between two organs or vessels. The risk of developing connections between the vagina and any parts of the gut can increase if you have persistent, recurrent or metastatic cervical cancer.

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

- Zirabev may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing.

- Zirabev can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting Zirabev treatment.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- This medicine increases the risk of having protein in your urine especially if you already have high blood pressure.

- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries. Please talk to your doctor since blood clots can lead to heart attack and stroke.

- Zirabev can also increase the risk of developing blood clots in your veins (a type of blood vessel).

- This medicine may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.

- It is possible that Zirabev may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.

- It is possible that Zirabev can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.

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

- This medicine may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).

- It is possible that Zirabev can cause hypersensitivity (including anaphylactic shock) and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.

- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with bevacizumab treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

Please consult your doctor, even if these above statements were only applicable to you in the past.

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

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

Children and adolescents
Zirabev use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations.

Death of bone tissue (osteonecrosis) in bones other than the jaw have been reported in patients under 18 years old when treated with bevacizumab.

Other medicines and Zirabev
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Combinations of Zirabev with another medicine called sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects. Discuss with your doctor to make sure that you do not combine these medicines.

Tell your doctor if you are using platinum- or taxane-based therapies for lung or metastatic breast cancer. These therapies in combination with Zirabev may increase the risk of severe side effects.

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

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

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

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

Zirabev may impair female fertility. Please consult your doctor for more information.

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

Driving and using machines
Bevacizumab has not been shown to reduce your ability to drive or to use any tools or machines. However, sleepiness and fainting have been reported with bevacizumab use. If you experience symptoms that affect your vision or concentration, or your ability to react, do not drive and use machines until symptoms disappear.

Zirabev contains sodium
This medicine contains 3.0 mg sodium (main component of cooking/table salt) in each 4 ml vial. This is equivalent to 0.15% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 12.1 mg sodium (main component of cooking/table salt) in each 16 ml vial. This is equivalent to 0.61% of the recommended maximum daily dietary intake of sodium for an adult.

Depending on your body weight and your dose of Zirabev, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to use Zirabev

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

Method and route of administration
Do not shake the vial. Zirabev is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Zirabev vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Zirabev solution by

intravenous infusion (a drip into your vein). The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

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

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

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

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

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

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

4. Possible side effects

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

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

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

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

(vomiting), swelling, lightheadedness, fast heartbeat and loss of consciousness.

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

Severe side effects, which may be **very common** (may affect more than 1 in 10 people), include:
- high blood pressure,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- feeling weak and having no energy,
- tiredness,
- diarrhoea, nausea, vomiting and abdominal pain.

Severe side effects, which may be **common** (may affect up to 1 in 10 people), include:
- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,
- blocking of the veins by a blood clot,
- blocking of the blood vessels of the lungs by a blood clot,
- blocking of the veins of the legs by a blood clot,
- heart failure,
- problems with wound healing after surgery,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- decreased number of red cells in the blood,
- lack of energy,
- stomach and intestinal disorder,
- muscle and joint pain, muscular weakness,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing,
- pain, including headache, back pain and pain in the pelvis and anal regions,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- sleepiness,
- nose bleed,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood,
- infections of the skin or deeper layers under the skin,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer.
- allergic reactions (the signs may include breathing difficulty, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting).

Severe side effects, which may be rare (may affect up to 1 in 1,000 people), include:
- sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic shock).

Severe side effects of **unknown** frequency (frequency cannot be estimated from the available data), include:
- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- a negative effect on a woman's ability to have children (see the paragraphs below the list of side effects for further recommendations),
- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure,
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections),
- clogging of a very small blood vessel(s) in the kidney,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,
- a hole in the stomach or intestines,
- an open sore or hole in the lining of the stomach or small intestine (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit),
- bleeding from the lower part of the large bowel,
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue (see the paragraphs below the list of side effects for further recommendations),
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting).

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

Very common (may affect more than 1 in 10 people) side effects, which were not severe, include:
- constipation,
- loss of appetite,
- fever,
- problems with the eyes (including increased production of tears),
- changes in speech,
- change in the sense of taste,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- loss of body weight,
- nose bleeds.

Common (may affect up to 1 in 10 people) side effects, which were not severe, include:
- voice changes and hoarseness.

Patients older than 65 years have an increased risk of experiencing the following side effects:
- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,
- fatigue,
- high blood pressure.

Zirabev may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

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

Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.

Zirabev has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way. When Zirabev is injected directly into the eye (unapproved use), the following side effects may occur:

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

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zirabev

Keep this medicine out of the sight and reach of children.

Vial (unopened)

Please refer to outer carton for the expiry date.

Diluted medicinal product

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

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

Infusion solutions should be used immediately after dilution. Do not use Zirabev if you notice

any particulate matter or discolouration prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zirabev contains

- The active substance is bevacizumab. Each ml of concentrate contains 25 mg of bevacizumab.

Each 4 ml vial contains 100 mg of bevacizumab.
Each 16 ml vial contains 400 mg of bevacizumab.

- The other ingredients are sucrose, succinic acid, disodium edetate, polysorbate 80, sodium hydroxide (for pH adjustment), and water for injections (see section 2 “Zirabev contains sodium”).

What Zirabev looks like and contents of the pack
Zirabev is a concentrate for solution for infusion. The concentrate is a clear to slightly opalescent, colourless to pale brown liquid in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 ml of solution or 400 mg bevacizumab in 16 ml of solution. Each pack of Zirabev contains one vial.

Pfizer Corporation Hong Kong Limited
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