

Data Sheet

Avastin[®]

bevacizumab (rch)

CAS 216974-75-3

Bevacizumab is an immunoglobulin G (IgG) composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

Description

AVASTIN is a clear to slightly opalescent, colourless to pale brown, sterile solution for intravenous (IV) infusion. AVASTIN is not formulated for intravitreal use (*see Precautions, Severe Eye Infections Following Compounding for Unapproved Intravitreal Use*).

AVASTIN is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively, of bevacizumab (25 mg/mL). AVASTIN also contains α,α -trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

Pharmacology

Mechanism of Action

AVASTIN is an anti-neoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at ≤ 0.35 ppm.

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

Pharmacokinetics

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

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

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

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 the typical patient with median values of albumin and tumour burden.

Absorption and Bioavailability

Not applicable.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients respectively, 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.

Metabolism

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

Elimination

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

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

Pharmacokinetics in Special Populations

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

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

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

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

Clinical Trials

Metastatic Colorectal Cancer

The safety and efficacy of AVASTIN in metastatic colorectal cancer were studied in two randomised, active-controlled clinical trials. AVASTIN was combined with two chemotherapy regimens:

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

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

- **NO16966:** AVASTIN 7.5 mg/kg every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or AVASTIN 5 mg/kg every 2 weeks in combination with leucovorin[†] plus fluorouracil bolus, followed by fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- **E3200:** AVASTIN 10 mg/kg every 2 weeks in combination with leucovorin[†] and fluorouracil bolus, followed by fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

[†] The New Zealand Approved Name for leucovorin is calcium folinate

Study AVF2107g

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating AVASTIN in combination with IFL as first-line treatment for metastatic colorectal cancer. Eight hundred and thirteen patients were randomised to receive IFL plus placebo (Arm 1) or IFL plus AVASTIN (Arm 2) (see Table 1). A third group of 110 patients received FU/LV plus AVASTIN (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of AVASTIN with the IFL regimen was established and considered acceptable. The median age of patients was 60 years (range 21-88) and 60% were male.

Table 1: Treatment regimens in study AVF2107g

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan Fluorouracil Leucovorin	125 mg/m ² IV 500 mg/m ² IV 20 mg/m ² IV	Given once weekly for 4 weeks every 6 weeks
	Placebo	IV	Every 2 weeks
Arm 2	Irinotecan Fluorouracil Leucovorin	125 mg/m ² IV 500 mg/m ² IV 20 mg/m ² IV	Given once weekly for 4 weeks every 6 weeks
	AVASTIN	5 mg/kg IV	Every 2 weeks
Arm 3	Fluorouracil Leucovorin	500 mg/m ² IV 500 mg/m ² IV	Given once weekly for 6 weeks every 8 weeks
	AVASTIN	5 mg/kg IV	Every 2 weeks

Fluorouracil: IV bolus injection immediately after Leucovorin

Leucovorin: IV bolus injection (over 1-2 minutes) immediately after each irinotecan dose

The primary efficacy endpoint of the trial was overall survival. At the time of data cut-off, 399 deaths had occurred in patients randomised to Arm 1 ($n = 225$) and Arm 2 ($n = 174$). The addition of AVASTIN to IFL resulted in a statistically significant increase in overall survival. Results are presented in Table 2 and Figure 1. The clinical benefit of AVASTIN, as measured by survival, progression-free survival and objective response, was seen in all pre-specified patient subgroups (see Figure 2).

Table 2: Efficacy results for study AVF2107g

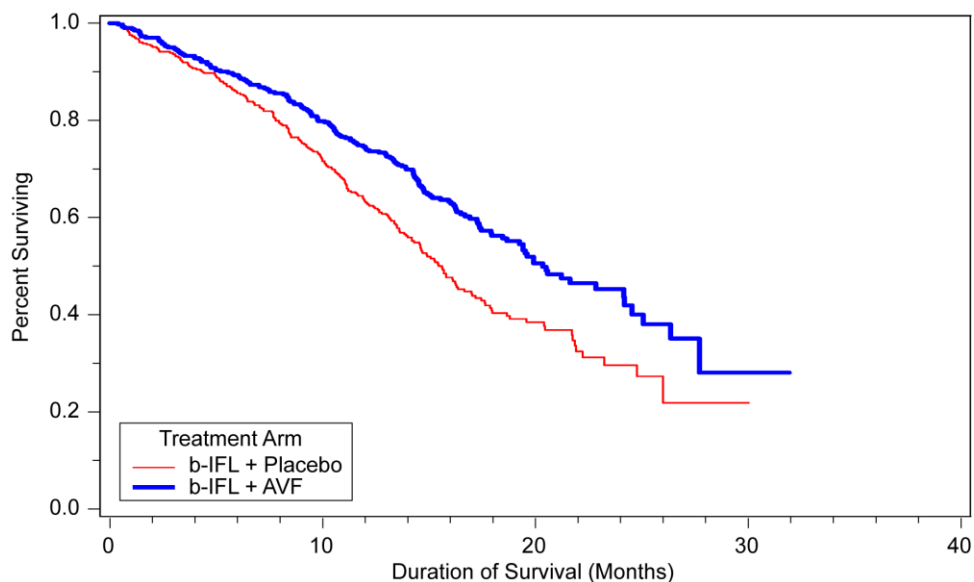
	Arm 1 IFL + placebo ($n = 411$)	Arm 2 IFL + AVASTIN ^a ($n = 402$)	Arm 3 FU/LV + AVASTIN ^a ($n = 110^b$)
Overall Survival			
Median (months)	15.6	20.3	18.3
Hazard ratio ^c (95% CI)		0.660 (0.54, 0.81)	–
<i>p</i> -value (log rank)		0.00004	–
Progression-Free Survival			
Median (months)	6.2	10.6	8.8
Hazard ratio (95% CI)		0.54 (0.45, 0.66)	–
<i>p</i> -value (log rank)		< 0.0001	–
Overall Response Rate			
Rate (percent)	34.8	44.8	40.0
Between-arm difference (%) (95% CI)		10 (3.3, 16.7)	–
<i>p</i> -value (log rank)		0.0036	–
Duration of Response			
Median (months)	7.1	10.4	8.5
25–75 percentile (months)	4.7-11.8	6.7-15.0	5.5-11.9

^a 5 mg/kg every 2 weeks; ^b Recruitment stopped as per protocol; ^c Relative to control arm.

CI = confidence interval; IFL = irinotecan/fluorouracil/leucovorin (calcium folinate);

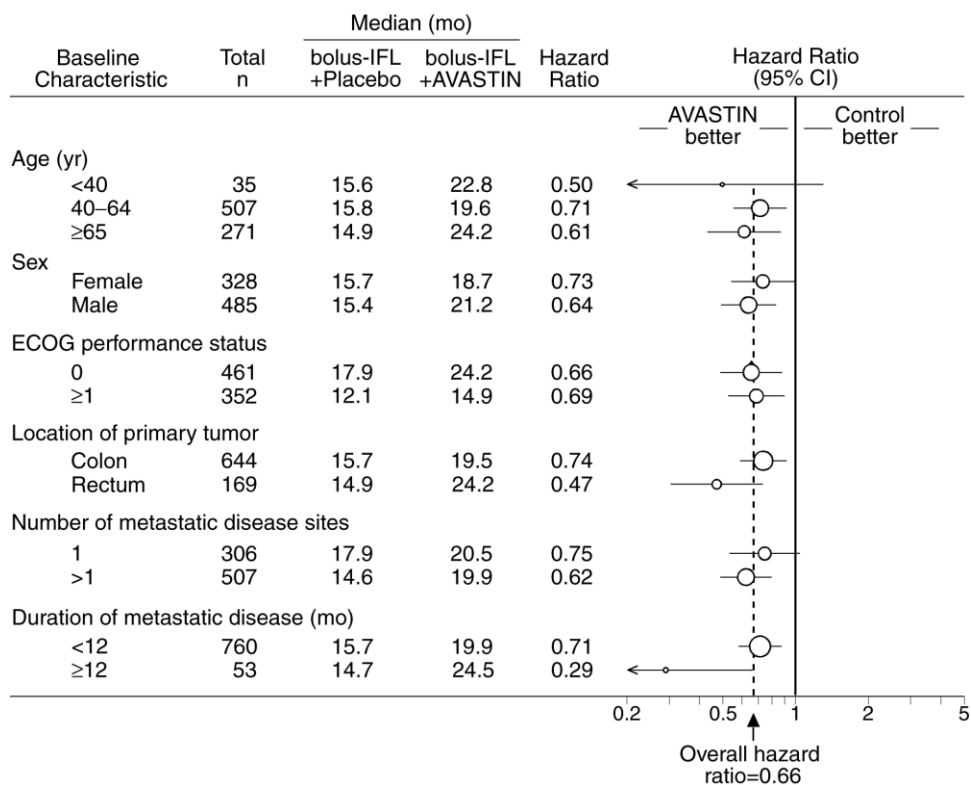
FU/LV = fluorouracil/leucovorin (calcium folinate)

Figure 1: Plot of Kaplan Meier Estimates for Survival in Study AVF2107g



IFL = irinotecan/fluorouracil/leucovorin (calcium folinate); AVF = AVASTIN

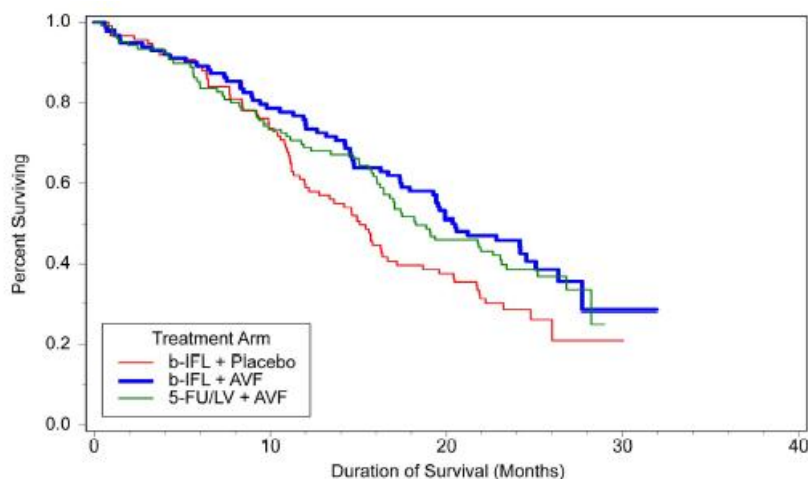
Figure 2: Duration of Survival by Baseline Risk Factor in Study AVF2107g



CI = confidence interval; IFL = irinotecan/fluorouracil/leucovorin (calcium folinate); mo = months. Hazard ratio <1 indicates a lower hazard of death in the IFL plus AVASTIN arm compared with the IFL plus placebo arm. Size of circle is proportional to the number of patients in the subgroup. Confidence interval is indicated by the horizontal line.

Results for the 110 patients in Arm 3 were compared to the first 100 patients enrolled in Arm 1 and Arm 2. There was a trend towards prolonged survival in the AVASTIN plus FU/LV arm as compared to the IFL plus placebo arm in this subset of patients (see Figure 3). Although the results did not show a statistical difference, the results were consistently better for the AVASTIN plus FU/LV arm than for IFL plus placebo arm for all efficacy parameters measured.

Figure 3: Plot of Kaplan Meier Estimates for Survival in Study AVF2107g: Patients Enrolled in Arm 3 and Concurrently Enrolled Patients in Arms 1 and 2



*AVF = AVASTIN; IFL = irinotecan/fluorouracil/leucovorin (calcium folinate);
5-FU/LV = fluorouracil/leucovorin (calcium folinate)*

Study AVF0780g

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating AVASTIN in combination with FU/LV as first-line treatment of metastatic colorectal cancer. Seventy one patients were randomised to receive bolus FU/LV or FU/LV plus AVASTIN (5 mg/kg every 2 weeks). A third group of 33 patients received bolus FU/LV plus AVASTIN (10 mg/kg every 2 weeks). Patients were treated until disease progression. The median age was 64 years (range 23-85) and 57% were male. The primary efficacy endpoints of the trial were objective response rate and progression-free survival. The addition of AVASTIN (5 mg/kg every 2 weeks) to FU/LV resulted in higher objective response rates, longer progression-free survival and a trend in longer survival, compared with FU/LV chemotherapy alone (see Table 3). This efficacy data is consistent with the results from study AVF2107g.

Table 3: Efficacy Results for Study AVF0780g

	FU/LV (n = 36)	FU/LV plus AVASTIN ^a (n = 35)	FU/LV plus AVASTIN ^b (n = 33)
Overall Survival			
Median (months)	13.6	17.7	15.2
Hazard ratio ^c	-	0.52	1.01
p-value (log-rank)	-	0.073	0.978
Progression-Free Survival			
Median (months)	5.2	9.0	7.2
Hazard ratio ^c	-	0.44	0.69
p-value (log-rank)	-	0.005	0.217
Overall Response Rate			
Rate ^d (%) (95% CI)	16.7 (7.0-33.5)	40.0 (24.4-57.8)	24.2 (11.7-42.6)
p-value (log-rank)	-	0.03	0.43
Duration of Response			
Median (months)	NR	9.3	5.0
25 – 75 percentile (months)	5.5-NR	6.1-NR	3.8-7.8

^a 5 mg/kg every 2 weeks; ^b 10 mg/kg every 2 weeks; ^c Relative to control arm; ^d independent review; NR = not reached; FU/LV = fluorouracil/leucovorin (calcium folinate)

Study NO16966

This was a phase III randomised, double-blind (for bevacizumab) clinical trial investigating AVASTIN 7.5 mg/kg in combination with oral capecitabine and IV oxaliplatin (XELOX), administered on a 3 weekly schedule; or AVASTIN 5 mg/kg in combination with leucovorin with fluorouracil bolus, followed by fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2 weekly schedule. The study contained two parts (see Table 4): an initial un-blinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + AVASTIN, FOLFOX-4 + AVASTIN). In Part II, treatment assignment was double-blind with respect to AVASTIN. Approximately 350 patients were randomised into each of the four study arms in Part II of the trial.

Table 4: Treatment Regimens in Study N016966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + AVASTIN	Oxaliplatin Leucovorin Fluorouracil	85 mg/m ² IV 2 h 200 mg/m ² IV 2 h 400 mg/m ² IV bolus, 600 mg/ m ² IV 22 h	Oxaliplatin on Day 1 Leucovorin on Day 1 and 2 Fluorouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or AVASTIN	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ AVASTIN	Oxaliplatin Capecitabine	130 mg/m ² IV 2 h 1000 mg/m ² oral bd	Oxaliplatin on Day 1 Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)
	Placebo or AVASTIN	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q3 weeks
Fluorouracil: IV bolus injection immediately after leucovorin			

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

- i) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of PFS and overall survival in the eligible per-protocol population.
- ii) Superiority of the AVASTIN containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of PFS in the ITT population (see Table 5).

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

Table 5: Key Efficacy Results for the Superiority Analysis (ITT population, Study NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + Placebo (n = 701)	FOLFOX-4 or XELOX + AVASTIN (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)**, ^b	7.9	10.4	< 0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Median PFS (Independent review)**	8.5	11.0	< 0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
Overall response rate (Investigator Assessment)**	49.2%	46.5%	
Overall response rate (Independent Review)**	37.5%	37.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007

** Primary analysis at clinical cut-off 31 January 2006

CI = confidence interval; PFS = progression-free survival; ^a Relative to control arm; ^b On-treatment analysis includes only tumour assessments and death events occurring no later than 28 days after the last confirmed intake of any study medication in the primary study treatment phase.

Study ECOG E3200

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

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

Table 6: Efficacy Results for Study E3200

	FOLFOX-4	FOLFOX-4 + AVASTIN^a
	(n = 292)	(n = 293)
Overall Survival		
Median (months)	10.8	13.0
95% CI	10.12 – 11.86	12.09 – 14.03
Hazard ratio ^b	0.751	
95% CI	(0.632 - 0.893)	
	(p-value = 0.0012)	
Progression-Free Survival		
Median (months)	4.5	7.5
Hazard ratio	0.518	
95% CI	(0.416 - 0.646)	
	(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; CI = confidence interval

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

Adjuvant Colon Cancer

BO17920

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

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

Advanced and/or metastatic Renal Cell Cancer

Study BO17705

BO17705 was a multicentre randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of AVASTIN in combination with interferon (IFN)-alfa-2a (ROFERON[®] A) versus IFN-alfa-2a alone as first-line treatment in metastatic renal cell cancer (mRCC). The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases

and adequate organ function. IFN-alfa-2a (9 MIU three times a week) plus AVASTIN (10mg/kg q2w) or placebo was given until disease progression. For patients who were unable to tolerate IFN alfa-2a treatment, treatment with AVASTIN was permitted to continue in the absence of progressive disease. A lower starting IFN alfa-2a dose (3 or 6 MIU) was permitted as long as the recommended 9MIU dose was reached within the first 2 weeks of treatment. If 9 MIU was not tolerated, IFN alfa-2a dosage reduction to a minimum of 3 MIU three times a week was also permitted. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression-free survival (PFS). The addition of AVASTIN to IFN-alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% AVASTIN/IFN) received a variety of non-specified post-protocol anti-cancer therapies, including anti-neoplastic agents, which may have impacted the analysis of overall survival. The efficacy results are presented in Table 7.

Table 7: Efficacy Results for Study BO17705

	IFN + Placebo (n = 322)	IFN + AVASTIN (n = 327)
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio	0.63 [0.52; 0.75] (p-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease		
Number of Patients	289	306
Response rate (%)	12.8	31.4
	(p-value < 0.0001)	
Overall Survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (p-value < 0.3360)	

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

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

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

The safety and efficacy of AVASTIN in the first-line treatment of patients with NSCLC other than predominantly squamous cell histology, were studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

Study E4599

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

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3 week cycle for up to 6 cycles or PC in combination with AVASTIN at a dose of 15 mg/kg IV infusion day 1 of every 3 week cycle. After completion of six cycles of PC chemotherapy or upon premature discontinuation of chemotherapy, patients in the AVASTIN + PC arm continued to receive AVASTIN as a single agent every 3 weeks until disease progression. 878 patients were randomised to the two arms.

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

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

Table 8: Efficacy results for study E4599

	Arm 1 Carboplatin/Paclitaxel	Arm 2 Carboplatin/Paclitaxel +AVASTIN 15 mg/kg q3w
Number of Patients	444	434
Overall Survival^a		
Median (months)	10.3	12.3
Hazard ratio		0.80
		95% CI (0.69, 0.93)
Progression-Free Survival^b		
Median (months)	4.8	6.4
Hazard ratio		0.65
		95% CI (0.56, 0.76)
Overall Response Rate^c		
Rate (%)	12.9	29.0

^a $p = 0.003$ by stratified log rank test

^b $p < 0.0001$ by stratified log rank test

^c $p < 0.0001$ by stratified χ^2 test includes patients with measurable disease at baseline.

q3w: every 3 weeks

Study BO17704

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

Patients were randomised to platinum-based chemotherapy (cisplatin 80 mg/m² IV infusion on day 1 and gemcitabine 1250 mg/m² IV infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles) (CG) with placebo or CG with AVASTIN at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the AVASTIN-containing arms, patients could receive AVASTIN as a single agent every 3 weeks until disease progression or unacceptable toxicity.

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

The efficacy results are presented in Table 9.

Table 9: Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + AVASTIN 7.5 mg/kg q3w	Cisplatin/Gemcitabine + AVASTIN 15 mg/kg q3w
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; q3w: every 3 weeks			
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]

Metastatic Breast Cancer Study E2100

(Note that the efficacy and safety of the combination of bevacizumab and paclitaxel have not been compared with anthracycline-based therapies for first-line therapy in metastatic breast cancer. The efficacy of the combination of bevacizumab and paclitaxel in second and third line treatment of metastatic breast cancer has not been demonstrated.)

E2100 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating AVASTIN in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. 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 study entry.

Patients were randomised to paclitaxel alone (90 mg/m² IV over 1 hour once weekly for three out of four weeks) or in combination with AVASTIN (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued

chemotherapy prematurely, treatment with AVASTIN as a single agent was continued until disease progression. The primary endpoint was progression-free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (98%) had metastatic disease, with 13 patients enrolled with locally recurrent breast cancer. The majority of patients (90%) were HER2-negative, with a small number of patients with a HER2 receptor status either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority of patients (65%) had received adjuvant chemotherapy, including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 10 and Figure 4. The addition of AVASTIN to paclitaxel chemotherapy resulted in a significant reduction of risk of disease progression or death, as measured by PFS (HR = 0.42; $p < 0.0001$). The resulting median PFS in the AVASTIN-containing arm was 11.4 months compared with 5.8 months in the control arm. The small improvement in overall survival was not statistically significant.

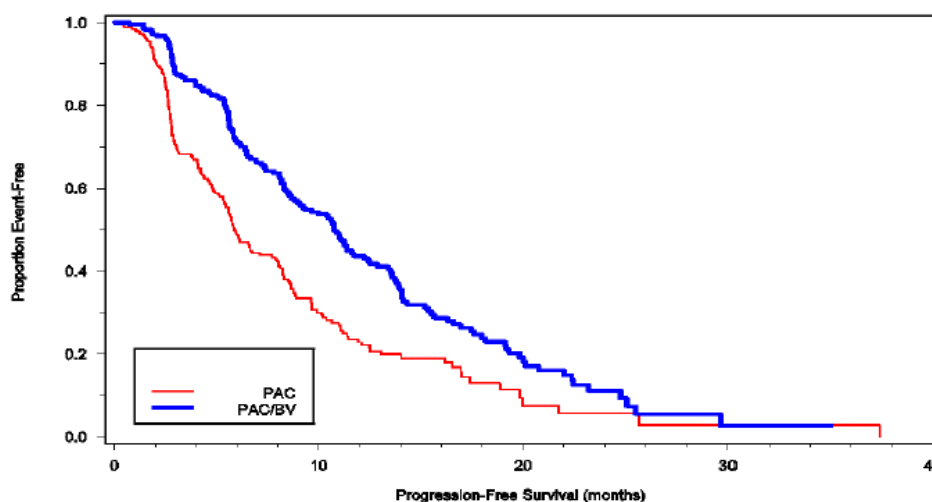
Table 10: Study E2100 Efficacy Results: Eligible Patients

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

* Primary analysis; IRF = Independent review facility

Overall Survival (Investigator Assessment)		
	Paclitaxel (n=354)	Paclitaxel/AVASTIN (n=368)
Median OS (months)	24.8	26.5
Hazard ratio (95% CI)	0.869 (0.722; 1.046)	
<i>p</i> -value	0.1374	

Figure 4: Kaplan-Meier curves for progression free survival in study E2100



Relapsed malignant glioma (WHO Grade IV) – Glioblastoma (GBM)

Study AVF3708g

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

Patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving AVASTIN) and temozolomide, were randomised (1:1) to receive AVASTIN (10mg/kg IV infusion every 2 weeks) or AVASTIN plus irinotecan (125 mg/m² IV or 340 mg/m² IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month PFS and objective response rate (ORR) as assessed by an independent review facility. Other outcome measures were duration of PFS, duration of response and overall survival.

Results of the study are summarised in Table 11.

Table 11: Efficacy Results from Study AVF3708g

	AVASTIN		AVASTIN + Irinotecan	
	<u>Inv</u>	<u>IRF</u>	<u>Inv</u>	<u>IRF</u>
Number of patients	85		82	
Primary endpoints				
6-month progression-free survival	43.6%	42.6%	57.9%	50.3%
95% CI (Inv)	(33.0, 54.3)	-	(46.6, 69.2)	-
97.5% CI (IRF)	-	(29.6, 55.5)	-	(36.8, 63.9)
Objective Response Rate (ORR)	41.2%	28.2%	51.2%	37.8%
95% CI (Inv)	(30.6, 52.3)	-	(39.9, 62.4)	-
97.5% CI (IRF)	-	(18.5, 40.3)	-	(26.5, 50.8)
Secondary endpoints				
Progression-free survival (months)				
Median	4.2	4.2	6.8	5.6
(95% CI)	(3.0, 6.9)	(2.9, 5.8)	(5.0, 8.2)	(4.4, 6.2)

Duration of objective response (months)				
Median	8.1	5.6	8.3	4.3
(95% CI)	(5.5, *)	(3.0, 5.8)	(5.5, *)	(4.2, *)
Overall survival (months)				
Median	9.3		8.8	
(95% CI)	(8.2, *)		(7.8, *)	

ORR was determined using modified MacDonald criteria; CI = confidence interval;

* Upper limit of the CI could not be obtained

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

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

Indications

Metastatic Colorectal Cancer

AVASTIN (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Advanced and/or metastatic Renal Cell Cancer

AVASTIN (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

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

AVASTIN (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable advanced, recurrent or metastatic NSCLC.

Metastatic Breast Cancer

AVASTIN (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated.

Relapsed high grade malignant glioma

AVASTIN (bevacizumab) as a single agent is indicated for the treatment of patients with high grade relapsed malignant glioma.

Contraindications

AVASTIN is contraindicated in:

- patients with known hypersensitivity to any components of the product; Chinese hamster ovary cell products or other recombinant human or humanised antibodies,
- NSCLC patients with recent pulmonary haemoptysis (see Precautions, *Pulmonary haemorrhage*)

Precautions

Gastrointestinal perforation

Patients may be at increased risk for the development of gastrointestinal (GI) perforation and gallbladder perforation when treated with AVASTIN. AVASTIN should be permanently discontinued in patients who develop GI perforation.

AVASTIN has been associated with serious cases of GI perforation. GI perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or NSCLC, and up to 2% in metastatic colorectal cancer patients. Cases of GI perforations have also been observed in patients with relapsed glioblastoma.

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

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

Hypertension

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

In most cases, hypertension was controlled adequately using standard anti-hypertensive treatment appropriate for the individual situation of the affected patient. AVASTIN should be permanently discontinued if medically significant hypertension cannot be adequately controlled with anti-hypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy (see also Adverse Effects, *Post-Marketing Experience*).

An increased incidence of hypertension (all grades) of up to 34% has been observed in patients treated with AVASTIN compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of Grade 3-4 hypertension in patients receiving AVASTIN ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with AVASTIN compared to up to 0.2% patients treated with the same chemotherapy alone.

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

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see also Adverse Effects, *Post-Marketing Experience*). The risk of AVASTIN associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Wound healing

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

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

In locally recurrent and metastatic breast cancer trials, National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving AVASTIN compared with up to 0.9% of patients in the control arms.

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

Thromboembolism

Arterial thromboembolic events

An increased incidence of arterial thromboembolic events has been observed in patients treated with AVASTIN, across all indications; including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic events.

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

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

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

Venous thromboembolic events

In clinical trials across all indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the AVASTIN-containing arms compared to 3.2% to 15.6% in the

chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

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

Grade 3–5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus AVASTIN compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive AVASTIN in combination with chemotherapy versus chemotherapy alone.

Haemorrhage

Patients treated with AVASTIN have an increased risk of haemorrhage, especially tumour-associated haemorrhage. AVASTIN should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during AVASTIN therapy.

The risk of Central Nervous System (CNS) haemorrhage has not been evaluated in randomised clinical studies with AVASTIN. Patients with untreated CNS metastases have been routinely excluded based on imaging procedures or signs and symptoms. Patients should be monitored for signs and symptoms of CNS bleeding, and AVASTIN treatment discontinued in case of intracranial bleeding.

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

In clinical trials across all indications, the overall incidence of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade 3-5 bleeding events ranged from 0.4% to 5% in AVASTIN-treated patients, compared to 0% to 2.9% of patients in the chemotherapy control group. Haemorrhagic events observed in AVASTIN clinical trials were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage

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

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9% when treated with AVASTIN plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with AVASTIN plus chemotherapy as compared with < 1% with chemotherapy alone.

Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

Tumour-associated haemorrhages have also been seen rarely in other tumour types and locations, and include cases of CNS bleeding in patients with CNS metastases and glioblastoma (GBM).

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

Intracranial haemorrhage can occur in patients with relapsed GBM. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the single-agent AVASTIN arm (Grade 1) and in 3.8% (3/79) of patients treated with AVASTIN and irinotecan (Grades 1, 2 and 4).

Mucocutaneous haemorrhage

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

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

Pulmonary haemorrhage

Patients with NSCLC treated with AVASTIN may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> 1/2 teaspoon red blood) should not be treated with AVASTIN.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

Proteinuria

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

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

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

Congestive Heart Failure (CHF)

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

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

Events consistent with CHF were reported in clinical trials in all cancer indications studied to date. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In phase III studies (AVF2119g and E2100) in patients with metastatic breast cancer, CHF Grade 3 or higher was reported in up to 3.5% of patients treated with AVASTIN in combination with chemotherapy compared with up to 0.9% in the control arms. Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

An increased incidence of CHF has been observed in a phase III clinical trial of patients with diffuse large B-cell lymphoma when receiving AVASTIN with a cumulative doxorubicin dose greater than 300 mg/m². This clinical trial compared rituximab / cyclophosphamide / doxorubicin / vincristine / prednisone (R-CHOP) plus AVASTIN to R-CHOP without AVASTIN. 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 AVASTIN arm.

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

Neutropenia

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

Fistulae

Patients may be at increased risk for the development of fistulae when treated with AVASTIN. AVASTIN use has been associated with serious cases of fistulae including events resulting in death.

In AVASTIN clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other

types of cancer. Uncommon ($\geq 0.1\%$ to $< 1\%$) reports of other types of fistulae that involve areas of the body other than the GI tract (e.g. bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

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

Hypersensitivity Reactions, Infusion Reactions

In some clinical trials, anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving AVASTIN in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of AVASTIN is common (up to 5% in AVASTIN-treated patients) (see also Adverse Effects, *Post-marketing experience*).

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of AVASTIN 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.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use

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

Ovarian Failure

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

Effects on Fertility

AVASTIN may impair female fertility, therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with AVASTIN. Long term effects of the treatment with AVASTIN on fertility are unknown. A sub-study with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the AVASTIN group compared to the control group (39% compared to 2.6%).

No specific studies in animals have been performed to evaluate the effect of AVASTIN on fertility, however, repeat dose safety studies in animals have shown that AVASTIN may have an adverse effect on female fertility. No adverse effect on the male reproductive organ was observed in repeat dose toxicity studies in cynomolgus monkeys, but inhibition of ovarian function was observed in females. This was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in

cynomolgus monkeys treated with AVASTIN. The lowest dose tested in the 26 week study (2 mg/kg weekly, which corresponds to 0.6-fold the human therapeutic dose based on AUC) caused a reduction in uterine weight, however the reduction was not statistically significant. In rabbits, administration of 50 mg/kg of AVASTIN IV for 3 or 4 doses every 4 days resulted in decreases in ovarian and/or uterine weight and number of corpora lutea. The changes in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of AVASTIN is likely to result in an adverse effect on female fertility.

Use in pregnancy – Category D

There are no adequate and well-controlled studies in pregnant women. IgGs are known to cross the placental barrier, and AVASTIN may inhibit angiogenesis in the foetus. Angiogenesis is critically important to foetal development. The inhibition of angiogenesis following administration of AVASTIN could result in an adverse outcome of pregnancy. Therefore, AVASTIN should not be used during pregnancy.

In women with childbearing potential, appropriate contraceptive measures are recommended during AVASTIN therapy. Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 6 months following the last dose of AVASTIN.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses. At the lowest dose tested, maternal serum AUC values were about 0.7-fold those observed in humans at the recommended clinical dose.

Use in lactation

Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should be advised to discontinue breastfeeding during AVASTIN therapy and not to breast feed for at least 6 months following the last dose of AVASTIN.

Paediatric use

The safety and effectiveness of AVASTIN in children and adolescent patients have not been established.

Use in the elderly

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction, as compared to those aged ≤ 65 years when treated with AVASTIN (see Precautions). Other reactions with a higher frequency seen in patients > 65 years were Grade 3 - 4 leucopenia and thrombocytopenia; and all grade neutropenia, diarrhoea, nausea, headache and fatigue.

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

Carcinogenesis and mutagenesis

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

Effects on the ability to drive or operate machines

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

Interactions with other medicines

Effect of anti-neoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other anti-neoplastic agents

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

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

Results from study B017705 demonstrated no significant effect of bevacizumab on the pharmacokinetics of IFN alfa-2a.

Results from B017704 demonstrated no significant effect of bevacizumab on the pharmacokinetics of cisplatin. Due to high inter-patient variability and limited sampling, the results from B017704 do not allow firm conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics to be drawn.

Combination of bevacizumab and sunitinib malate

In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7/19 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 AVASTIN and sunitinib malate (see Precautions, *Hypertension*, *Proteinuria* and *RPLS*).

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and AVASTIN have not been established.

Adverse Effects

Experience from clinical trials

Clinical trials have been conducted in patients with various malignancies treated with AVASTIN, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of more than 3,500 patients is presented in this section.

The most serious adverse drug reactions were:

- gastrointestinal perforations (see Precautions)
- haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see Precautions)
- arterial thromboembolism (see Precautions)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with AVASTIN therapy are likely to be dose-dependent (see Precautions).

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

Table 12 lists adverse drug reactions associated with the use of AVASTIN in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3 - 5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1 - 5 reactions), in at least one of the major clinical trials. The adverse drug reactions listed in Table 12 fall into the following categories: Very Common ($\geq 10\%$) and Common ($\geq 1\% - < 10\%$). Adverse drug reactions have been included in the appropriate category in Table 12 according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. palmar-plantar erythrodysesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by AVASTIN therapy cannot be excluded.

Table 12: Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions ($\geq 2\%$ difference between the study arms in at least one clinical trial)		All Grade Reactions ($\geq 10\%$ difference between the study arms in at least one clinical trial)
	<i>Very Common</i>	<i>Common</i>	<i>Very Common</i>
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia	
Metabolism and nutrition disorders		Dehydration	Anorexia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension

Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Intestinal perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder Stomatitis	Constipation Stomatitis Rectal haemorrhage Diarrhoea
Endocrine disorders			Ovarian failure [#]
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia	Arthralgia
Renal and urinary disorders		Proteinuria Urinary tract infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal Inflammation	Pyrexia Asthenia Pain Mucosal Inflammation

[#]Based on a substudy from AVF3077s (NSABP C-08) with 295 patients

Laboratory abnormalities

Decreased neutrophil count, decreased white blood count and presence of urine protein maybe associated with AVASTIN treatment.

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

Post-marketing experience

Table 13: Adverse Reactions Reported in Post-marketing Setting

System Organ Class (SOC)	Reactions (frequency)[#]
Nervous system disorders	Hypertensive encephalopathy (very rare) (see Precautions) Reversible Posterior Leukoencephalopathy Syndrome (rare) (see Precautions)
Vascular disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (frequency not known) (see Precautions).
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gallbladder perforation (not known)
Immune system disorders	Hypersensitivity, infusion reactions (not known) possibly associated with the following co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting

Eye disorders (reported from unapproved intravitreal use)	Infectious endophthalmitis ^{1,5} (some cases leading to permanent blindness) (not known); Intraocular inflammation ^{1,2} (some cases leading to permanent blindness) such as sterile endophthalmitis, uveitis and vitritis (see Precautions); Retinal detachment (not known); Retinal pigment epithelial tear (not known); Intraocular pressure increased (not known); Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (not known); Conjunctival haemorrhage (not known) Increased risk for cataract surgery ^{1,2} .
Systemic Events (reported from unapproved intravitreal use)	Increased risk of haemorrhagic stroke ^{1,2} (see Precautions) Increased risk for overall mortality ^{1,2,3} . Increased risk of serious systemic adverse events, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%) ^{1,4} .
Muscular/Skeletal disorders	Cases of ONJ have been observed in Avastin treated patients mainly in association with prior or concomitant use of bisphosphonates.

[#] if specified, the frequency has been derived from clinical trial data

¹ As compared to an approved treatment in patients treated for wet age-related macular degeneration

² Gower et al. Adverse Event Rates Following Intravitreal Injection of Avastin or Lucentis for Treating Age-Related Macular Degeneration ARVO 2011, Poster 6644, Data on file

³ Curtis LH, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128(10):1273-1279

⁴ CATT Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoal102673

⁵ One case reported extraocular extension of infection resulting in meningoencephalitis

Dosage and Administration

Recommended dose

Metastatic Colorectal Cancer

The recommended dose of AVASTIN, administered as an IV 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 AVASTIN treatment be continued until progression of the underlying disease.

Advanced and/or metastatic Renal Cell Cancer

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

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

AVASTIN should be given in combination with IFN alfa-2a (ROFERON A). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, the dosage may be reduced to 6 MIU and further to 3 MIU three times a week (see Clinical Trials). Please also refer to the ROFERON A Data sheet.

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

The recommended dose of AVASTIN in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

AVASTIN is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by AVASTIN as a single agent until disease progression.

Metastatic Breast Cancer

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

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

Relapsed high grade malignant glioma

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

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

Dose reduction

Dose reduction of AVASTIN for adverse reactions is not recommended. If indicated, AVASTIN should either be discontinued or temporarily suspended (see Precautions).

Special dosage instructions

Children and adolescents: The safety and efficacy of AVASTIN in children and adolescents have not been established.

Elderly: No dose adjustment is required in the elderly.

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

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

Preparing the infusion

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

No incompatibilities between AVASTIN and polyvinyl chloride or polyolefin bags have been observed.

AVASTIN infusions should not be administered or mixed with dextrose or glucose solutions.

Method of administration

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

Do not administer as an intravenous push or bolus.

AVASTIN is not formulated for intravitreal use (see Precautions, *Severe Eye Infections Following Compounding for Unapproved Intravitreal Use*).

Overdosage

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

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdose.

Presentation and Storage Conditions

AVASTIN is available as a:

- 100 mg pack containing one 4 mL single-dose vial
- 400 mg pack containing one 16 mL single-dose vial.

Store vials at 2 – 8°C. (Refrigerate. Do not freeze.) Do not shake.

Protect from light. Keep vial in outer carton due to light sensitivity until use.

AVASTIN does not contain any anti-microbial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single-use in one patient only. Discard any residue. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2 – 30°C in 0.9% sodium chloride solution. To reduce microbiological hazard, the product should be used as soon as practicable after preparation. If storage is necessary, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2 – 8°C.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Medicine Classification

Prescription Medicine.



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