AVAMAB
Bevacizumab

Therapeutic/Pharmacologic Class of Drug
Anti-neoplastic agent

Type of Dosage Form
Concentrate for solution for infusion

Route of Administration
Clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous (IV) infusion. Avamab is not formulated for intravitreal use (see Warnings and Precautions, General)

Sterile/Radioactive Statement
Sterile

Qualitative and Quantitative Composition
Active ingredient: Bevacizumab (humanized anti-VEGF monoclonal antibody).
Avamab is supplied in 100 mg preservative-free, single-use vials containing 4 mL of bevacizumab (25 mg/mL).
Each vial contains bevacizumab 100 mg.
Excipients: α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, polysorbate 20, water for injection.

Mechanism of action
Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework region with antigen binding regions of a humanized 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. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.
Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumor, thereby inhibiting tumour growth.
Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

Efficacy
In a multicenter, multinational, double-blind, randomized, parallel-group, equivalence phase III study, a total of 627 patients diagnosed with stage IIIB/IV non-squamous non- small cell lung cancer (NSCLC) were randomized to receive Avamab (BEC) or EU-sourced reference product in addition to chemotherapy (carboplatin and paclitaxel). The study treatment consisted of an initial administration of paclitaxel 200 mg/m2 IV over 3 hours, followed by carboplatin AUC 6 IV over 15 to 30 minutes and then, immediately afterward, either Avamab or EU-sourced reference product 15 mg/kg. A window of 30 minutes was allowed between the administration of the 2 chemotherapy drugs and/or between the administration of either chemotherapy drug and either study drug (Avamab or EU-sourced reference product). The first Avamab or EU-sourced reference product was administered as a 90-minute infusion. If the study drug was well tolerated, the next infusion was given over a 60-minute period. Thereafter, the drug was given as a 30-minute IV infusion. Chemotherapy agents and Avamab or EU-sourced reference product were delivered every 3 weeks for 6 cycles. After 6 cycles, subjects could have continued to receive Avamab or EU-sourced reference product monotherapy every 3 weeks until evidence of disease progression, until unacceptable toxic effects developed, death, or withdrawal up to week 52.
Overall Response Rate (ORR) was assessed by Independent Radiological Review Committee (IRC). In the final analysis (week 52), ORR for subjects receiving Avamab was comparable to EU-sourced reference product (40.3% vs 44.8%). The ORR result for Avamab was also similar to the published data of bevacizumab. A Risk Ratio (RR) of 0.910 was well within the boundaries of the similarity margin predefined by the FDA (0.73, 1.36). The 95% CI of 0.758-1.092 was also completely contained. Similarly, the Risk Difference (RD) between the treatments was -4.03%, also well within the similarity margin predefined by the EMA (-13%, +13%), with 95% CI of -11.76 to 3.71, which was also completely contained.
There was no significant difference in median PFS between subjects treated with Avamab (36.0 weeks; 95% CI: 33.03 to 38.43) and those treated with EU-sourced reference
product (37.3 weeks; 95% CI: 35.14 to 45.14); HR: 1.159 (95% CI: 0.936 to 1.459).
Likewise there was no significant difference in RMST estimates of OS in subjects treated with Avamab (46.49 weeks) and those treated with EU-sourced reference product (46.81 weeks); HR: 1.118 (0.834 to 1.499). Similarly, there was no significant difference between treatment groups in duration of overall response (33.29 weeks in the Avamab group compared with 36.14 weeks in the EU-sourced reference product group; HR: 1.313; p=0.4703) or median time to overall response (12.43 weeks in the Avamab group compared with 12.29 weeks in the EU-sourced reference product group; HR: 0.960; p=0.6115).

The following are results of clinical trials conducted with reference product:
Metastatic Colorectal Cancer (mCRC)
The safety and efficacy of the recommended dose of bevacizumab (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomized, active- controlled clinical trials in combination with fluoropyrimidine- based first-line chemotherapy. Bevacizumab was combined with two chemotherapy regimens:

- Study 1: A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for total of 4 weeks of each 6 week-cycle.
- Study 2: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- Study 3: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Bevacizumab in Combination with IFL Chemotherapy for First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (Study 1):
This was a phase III randomized, 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 randomized to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV + bevacizumab (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years, 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0. 4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.
Table 1. Treatment Regimens in Study 1

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan 5-Fluorouracil	125 mg/m² IV 500 mg/m2 IV	Given once weekly for 4 weeks every 6 weeks
	Leucovorin	20 mg/m² IV	
	Placebo	IV	Every 2 weeks
Arm 2	Irinotecan	125 mg/m² IV	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil Leucovorin	500 mg/m² IV 20 mg/m2 IV	
	Bevacizumab	5 mg/kg IV	Every 2 weeks
Arm 3	5-Fluorouracil Leucovorin	500 mg/m² IV 500 mg/m2 IV	Given once weekly for 6 weeks every 8 weeks
	Bevacizumab	5 mg/kg IV	Every 2 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin Folinic acid: IV bolus injection (over 1 – 2 minutes) immediately after each irinotecan dose			

The primary efficacy parameter 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 2). The clinical benefit of bevacizumab, as measured by 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 2.

Table 2. Efficacy Results for Study 1

	Study 1	
	Arm 1 IFL + Placebo	Arm 2 IFL + bevacizumab[a]
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Secondary endpoint: Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.0001)	
Overall Response Rate	34.8%	44.8%
	(p-value = 0.0036)	

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

Among the 110 patients randomized 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.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum in Patients Who Were Not Optimal Candidates for First-Line Irinotecan Treatment (Study 3):
This was a phase II randomized, double-blind, active-controlled clinical trial evaluating the efficacy and safety of bevacizumab in combination with 5-FU/FA as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin <3.5 g/dL) in order to be eligible for enrollment. One hundred and five patients were randomized to 5-FU/FA + placebo arm and 104 patients to 5-FU/FA + bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The overall mean age was 71 years, 28.2% of patients had a ECOG performance status of 0, 65.1% had a value of 1, and 6.7% had a value of 2.

The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, compared to 5-FU/FA chemotherapy alone (see Table 3). These efficacy data were consistent with the results observed in studies Study 1 and Study 2.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (Study 2):
This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomized to receive bolus 5-FU/FA or 5-FU/FA + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 3). These efficacy data are consistent with the results from Study 1.
The efficacy data from studies Study 2 and Study 3 investigating bevacizumab in combination with 5-FU/FA-chemotherapy are summarized in Table 3.
Table 3. Efficacy Results from Study 2 and 3

	Study 2			Study 3	
	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
1. Overall Survival					
Median (months)	13.6	17.7	15.2	12.9	16.6
95% Confidence interval				10.35 - 16.95	13.63 – 19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
2. Progression-Free Survival					
Median (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
3. Overall Response Rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% confidence interval	7.0 - 33.5	24.4 - 57.8	11.7 – 42.6	9.2 - 23.9	18.1 - 35.6
p-value	-	0.029	0.43		0.055
Duration of Response					
Median (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5 - NR	6.1 - NR	3.8 – 7.8	5.59 - 9.17	5.88 - 13.01

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

Locally recurrent or metastatic Breast Cancer (mBC)
Study 4
Study 4 was an open-label, randomized, 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. 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 randomized to paclitaxel alone (90 mg/m2 IV over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (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 bevacizumab as a single agent was continued until disease progression. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.
Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.
The results of this study are presented in Table 4.
Table 4. Study 4 Efficacy Results: Eligible Patients

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
HR (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	< 0.0001		< 0.0001	

Response rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n= 273)	Paclitaxel/bevacizumab (n= 252)	Paclitaxel (n= 243)	Paclitaxel/bevacizumab (n= 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

* primary analysis

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

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)
The safety and efficacy of bevacizumab in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to platinum-based chemotherapy in study 5.
Study 5
Study 5 was an open-label, randomized, active-controlled, multicentre clinical trial evaluating bevacizumab as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.
Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/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 bevacizumab at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.
During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of bevacizumab and 21.1% (89/422) of patients received 13 or more administrations of bevacizumab.
The primary endpoint was duration of survival. Results are presented in Table 5.
Table 5. Efficacy results for study 5

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

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

Study 6
Study 6 was a randomized, double-blind, placebo-controlled, multicenter Phase III study of bevacizumab used in addition to carboplatin and paclitaxel (CP) chemotherapy in Chinese patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC who had not received prior chemotherapy for advanced disease. The primary endpoint was progression-free survival, secondary endpoints for the study included overall survival and objective response.
Patients were randomized to CP (carboplatin AUC = 5.0 and paclitaxel 175 mg/m2, both by IV infusion) on day 1 of every 3-week cycle for up to 6 cycles or CP in combination with bevacizumab at a dose of 15 mg/kg IV infusion on day 1 of every 3-week cycle. After completion of six cycles of CP chemotherapy or upon premature discontinuation of chemotherapy, patients were to continue to receive bevacizumab or placebo as a single agent every 3 weeks until disease progression or unacceptable toxicity.
Study results show that, 79% (107/138) of patients in the bevacizumab-containing treatment arm went on to receive single agent bevacizumab at cycle 7, and 57% (78/138) of patients in the placebo-containing arm went on to receive single agent placebo at cycle 7. The efficacy results are presented in Table 6.
Table 6. Efficacy results for study 6

	Arm 1 Carboplatin/Paclitaxel + placebo	Arm 2 Carboplatin/Paclitaxel + Bevacizumab 15 mg/kg q 3 weeks
Number of Patients	138	138
Progression-Free Survival Median (months)	6.5	9.2
Hazard ratio	0.4 (p < 0.0001) 95% CI (0.29, 0.54)	
Overall Response Rate[a] Rate (percent)	26.3	54.4
	(p < 0.0001)	
Overall survival Median (months) Hazard ratio	17.7	24.3
	0.68 (p = 0.0154) 95% CI (0.50, 0.93)	

[a] Only patients with measurable disease at baseline were analyzed.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
Front-line Ovarian Cancer
The safety and efficacy of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (Study 7 and 8) that compared the effect of the addition of bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone.
Study 7
Study 7 was a Phase III multicenter, randomized, double-blind, placebo controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked stage III or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.
A total of 1873 patients were randomized in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of bevacizumab (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles (bevacizumab commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of bevacizumab (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles (bevacizumab commenced at cycle 2 of chemotherapy) followed by continued use of bevacizumab (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression-Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.
The results of this study are summarized in Table 7.
Table 7. Efficacy results from study 7

Progression-free survival						
	Investigator Assessment[1]			IRC Assessment		
	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n= 1248)[2]	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n= 1248)[2]
Median PFS (months)	10.0	12.7	16.0	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.136]	0.630 [0.513, 0.773]
p-value		0.0204[4]	< 0.0001[4]		0.2993	< 0.0001

Objective response rate[5]						
	Investigator Assessment			IRC Assessment		
	CPP (n= 396)	CPB15 (n= 393)	CPB15+ (n= 403)	CPP (n= 474)	CPB15 (n= 460)	CPB15+ (n= 499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p-value		0.2341	0.2041		0.0106	0.0012

Overall survival[6]			
	CPP (n= 625)	CPB15 (n= 625)[2]	CPB15+ (n= 623)[2]
Median OS (months)	40.6	38.8	43.8
Hazard ratio (95% CI)[3]		1.065 (0.908, 1.248)	0.879 (0.745, 1.036)
p-value[4]		0.2197	0.0641

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

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone, had a clinically meaningful and statistically significant improvement in PFS.
Although there was an improvement in PFS for patients who received front-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

Study 8
Study 8 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO stage I or IIA (Grade 3 or clear cell histology only), or FIGO stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.
A total of 1528 patients were randomized in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles plus bevacizumab (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression-Free Survival (PFS) as assessed by the investigator. The results of this study are summarized in Table 8.
Table 8. Efficacy results from study 8

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

[a] In patients with measurable disease at baseline
[b] Final OS analysis when 46.7% of patients died.

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

Recurrent Ovarian Cancer
Study 9
Study 9 was a phase III randomized controlled trial studying the safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior antiangiogenic therapy. The study evaluated the effect of adding bevacizumab to carboplatin + paclitaxel and continuing bevacizumab as a single agent compared to carboplatin + paclitaxel alone.
A total of 673 patients were randomized in equal proportions to the following 2 treatment arms:

- CP arm: Carboplatin (AUC 5) and paclitaxel (175 mg/m2 IV over 3 hours) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC 5) and paclitaxel (175 mg/m2 IV over 3 hours) and concurrent bevacizumab (15 mg/kg) every 3 weeks for 6 and up to 8 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also examined. Results are presented in Table 9.
Table 9. Efficacy results from study 9

Primary Endpoint		
Overall Survival (OS)		
	CP (n= 336)	CPB (n= 337)
Median OS (months)	37.3	42.6
Hazard ratio (95% CI)	0.823 (CI: 0.680, 0.996)	
p-value	0.0447	
Secondary Endpoints		
Progression-free survival		
	CP (n= 336)	CPB (n= 337)
Median PFS (months)	10.2	13.8
Hazard ratio (95% CI)	0.613 (CI: 0.521, 0.721)	
p-value	< 0.0001	
Objective response rate*		
	CP* (n= 286)	CPB* (n= 274)
No. (%) of pts with objective response (CR, PR)	159 (55.6%)	213 (77.7%)
p-value	< 0.0001	

*Intent-to-treat population with measurable disease at baseline

Treatment with bevacizumab at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles then followed by bevacizumab as a single agent resulted in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

Study 10
The safety and efficacy of bevacizumab in the treatment of patients with platinum- sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment, was studied in a phase III randomized, double-blind, placebo-controlled trial (Study 10). The study compared the effect of adding bevacizumab to carboplatin and gemcitabine chemotherapy and continuing bevacizumab as a single agent to progression, to carboplatin and gemcitabine alone.
A total of 484 patients with measurable disease were randomized in equal portions to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent bevacizumab (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.
The results of this study are summarized in Table 10.
Table 10. Efficacy results from Study 10

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

Overall survival**		
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
Median OS (months)	32.9	33.6
Hazard ratio (95% CI)	0.952 (0.771, 1.176)	
p-value	0.6479	

* Primary analysis
** Final overall survival analysis performed when approximately 70% of the patients had died

Cervical Cancer
Study 11
The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study 11, a randomized, four arms, multi-centre phase III trial.
A total of 452 patients were randomized to receive either:

- Paclitaxel 135 mg/m2 IV over 24 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m2 IV over 3 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 2 (q3w); or paclitaxel 175 mg/m2 IV over 3 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 1 (q3w)
- Paclitaxel 135 mg/m2 IV over 24 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m2 IV over 3 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m2 IV over 3 hours on Day 1 and cisplatin 50 mg/m2 IV on Day 1 and bevacizumab 15 mg/kg IV on Day 1 (q3w)
- Paclitaxel 175 mg/m2 over 3 hours on Day 1 and topotecan 0.75 mg/m2 over 30 minutes on days 1-3 (q3w)
- Paclitaxel 175 mg/m2 over 3 hours on Day 1 and topotecan 0.75 mg/m2 over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg IV on Day 1 (q3w)

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.
The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 11.
Table 11. Overall efficacy by bevacizumab treatment (ITT population) from study 11

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

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

Indications
Metastatic colorectal cancer (mCRC)
Avamab in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5- fluorouracil/folinic acid/irinotecan is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.
Avamab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

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

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

Epithelial ovarian, fallopian tube and primary peritoneal cancer
Avamab in combination with carboplatin and paclitaxel, is indicated for primary adjuvant therapy, of patients with resectable, post-operative, advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, without hypertension.
Avamab, in combination with carboplatin and gemcitabine, or in combination with carboplatin and paclitaxel is indicated for the treatment of patients with recurrent, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Cervical cancer
Avamab in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

Contraindications
Avamab is contraindicated in:

- Patients with known hypersensitivity to any components of the product.
- Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.
- Pregnancy.
- Patients with untreated central nervous system (CNS) metastases.

Dosage and administration
General
Avamab should be prepared by a healthcare professional using aseptic technique.
The initial Avamab dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Dose reduction of Avamab for adverse events is not recommended. If indicated, Avamab should either be permanently discontinued or temporarily suspended.

Metastatic colorectal cancer (mCRC)
The recommended dose of Avamab, 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. Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Locally recurrent or metastatic triple negative breast cancer (mBC)
The recommended dose of Avamab 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 Avamab treatment be continued until progression of the underlying malignant disease.

Advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)
Avamab is administered in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by Avamab as a single agent until disease progression.
The recommended dose of Avamab when used in addition to carboplatin-based chemotherapy is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.

Epithelial ovarian, fallopian tube and primary peritoneal cancer
The recommended dose of Avamab administered as an intravenous infusion is as follows: Front-line treatment: 15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avamab as single agent for 15 months or until disease progression, whichever occurs earlier.
Treatment of recurrent disease:
Platinum sensitive: 15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles followed by continued use of Avamab as single agent until disease progression.
Alternatively, 15 mg/kg of body weight every 3 weeks when administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avamab as single agent until disease progression.

Cervical cancer
Avamab is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.
The recommended dose of Avamab is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion. It is recommended that Avamab treatment be continued until progression of the underlying disease.

Special Dosage Instructions
Pediatric use: The safety and efficacy in patients under the age of 18 years have not been established.
Geriatric use: No dose adjustment is required in the patient ≥ 65 years of age.
Renal impairment: The safety and efficacy of bevacizumab have not been studied in patients with renal impairment.
Hepatic impairment: The safety and efficacy of bevacizumab have not been studied in patients with hepatic impairment.

Instructions for use, handling and disposal
Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.
Do not administer as an intravenous push or bolus.
Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/mL.
Chemical and physical in-use stability has been demonstrated for 48 hours at 2-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

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

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

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Gastrointestinal perforations
Patients may be at increased risk for the development of gastrointestinal perforation and gallbladder perforation when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.
Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of fistula between the vagina and any part of the GI tract (gastrointestinal-vaginal fistula).
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.

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

Haemorrhage
Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be permanently discontinued in patients who experience grade 3 or 4 bleeding during bevacizumab therapy.
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 randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab 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 bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

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 compounded intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary haemorrhage/haemoptysis
Patients with non-small cell lung cancer treated with bevacizumab may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (≥ ½ teaspoon red blood) should not be treated with bevacizumab.

Hypertension
An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Monitoring of blood pressure is recommended during bevacizumab therapy.
In most cases, hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patients. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES), a rare neurological disorder, which can present with the following signs and symptoms among others: seizure, headache, altered mental status, visual obfuscation, 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 bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Arterial thromboembolism
In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.
Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.
Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be given when treating such patients with bevacizumab.

Venous thromboembolism
Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment.
Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of venous thromboembolic events.
Bevacizumab should be discontinued in patients with life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism. patients with thromboembolic events of grade 2 need to be closely monitored.

Congestive heart failure
Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings range from asymptomatic declines in left ventricular ejection fraction to symptomatic congestive heart failure, requiring treatment or hospitalization.
Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab.
Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy, or the left chest wall or other risk factors for CHF were present.
In patients who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. In clinical trials, CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with result in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment.

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

Wound healing
Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the wound is completely and fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery.
Necrotizing fasciitis including fatal cases, has rarely been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

Proteinuria
In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria nephrotic syndrome was observed in up to 1.4% of patients treated with bevacizumab. In the event of nephrotic syndrome, bevacizumab treatment should be permanently discontinued.

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

Ovarian failure/fertility
Bevacizumab may impair female fertility. Therefore, fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with bevacizumab.

Drug Abuse and Dependence
No information available.

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

Laboratory Tests
No information available.

Interaction with other medicinal products and other forms of interactions
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 a population PK analysis. There was neither statistical significance nor clinically relevant differences in bevacizumab clearance in patients receiving bevacizumab monotherapy compared to patients receiving bevacizumab in combination with interferon alpha 2a or chemotherapies (5FU, 5-FU/LV, carboplatin-paclitaxel, capecitabine, oxaliplatin or gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents
No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of 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.

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

Use in special populations
Pregnancy
Angiogenesis has been shown to be critically important to fetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy.
There are no adequate and well-controlled studies in pregnant women. IgG are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the fetus. In the post-marketing setting, cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed.
Therefore, bevacizumab should not be used during pregnancy. In women with childbearing potential, appropriate contraceptive measures should be used during bevacizumab therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of bevacizumab.

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

Labour and Delivery
No information available.

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

Paediatric use
Bevacizumab is not approved for use in patients under the age of 18 years. The safety and efficacy of bevacizumab in the population have not been established.
In published reports, cases of osteonecrosis of jaw other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab.
Geriatric use
Refer to section under the sub-heading Arterial thromboembolism.

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

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

Undesirable effects
In the phase III clinical trial of Avamab compared with EU-sourced reference product, similar treatment emergent adverse events (TEAEs) without clinically significant differences between both treatment groups were documented.
Out of the 821 subjects, a total of 818 (99.5%) subjects experienced TEAEs, 255 subjects (92.8%) in Avamab group compared to 253 subjects (92.3%) in EU-sourced reference product. No statistically significant difference TEAEs between both treatment groups (p = 0.89).
- The most common TEAEs were alopecia (51.3%) and anaemia (21.4%), with no clinically significant differences between treatment groups. Between treatment groups at each severity level, the distribution of events was similar, with a risk difference - subjects reporting TEAEs < 5%.
- The majority of subjects experienced TEAEs classified as NCI-CTCAE severity Grade 1 or Grade 2 events. Grade 1 events were reported in 455 subjects (73.2%), specifically 73.2% in Avamab and 74.2% in EU-sourced reference product. Grade 2 events were reported in 192 subjects (29.4%), specifically 31.2% in Avamab and 27.7% in EU-sourced reference product.
- A total of 281 (41.2%) subjects experienced TEAEs with a NCI-CTCAE severity Grade of 3 or 4, including 131 (42.1%) subjects in Avamab group and 150 (40.3%) subjects in the EU-sourced reference product group, with no statistical difference between treatment groups (p = 0.65).
- A total of 33 subjects (5.3%) experienced a Grade 5 TEAE, specifically 22 (5.4%) in the Avamab group and 19 (5.1%) in the EU-sourced reference product group. Between treatment groups at each severity level, the distribution of events was similar, with a risk difference in subjects reporting TEAEs < 5%.
- The incidence of subjects reporting events, was comparable between treatment groups up to Week 13, alopecia (213 subjects overall) (51.2%), 155 subjects (49.8%) in the Avamab group and 163 subjects (52.6%) in the EU-sourced reference product group; anaemia (153 subjects overall) (27.1%), 91 subjects (29.3%) in the Avamab group and 77 subjects (24.8%) in the EU-sourced reference product group) and the associated event of haemoglobin decreased (7 subjects (1.1%), 4 (1.3%) in the Avamab group and 3 (1.0%) in the EU-sourced reference product group), and nausea (91 subjects overall) (15.0%), 42 subjects (13.9%) in the Avamab group and 47 subjects (15.3%) in the EU-sourced reference product group).
- The TEAEs were comparable during monotherapy (after Week 13 and through Week 52) were anaemia (24 subjects (7.7%) in the Avamab group and 41 subjects (11.2%) in the EU-sourced reference product group) and the associated event of haemoglobin decreased (1 subject in the EU-sourced reference product group), and thrombocytopenia (19 (6.1%) subjects in the Avamab group and 15 (4.3%) subjects in the EU-sourced reference product group) and the associated event of platelet count decreased (12 (4.2%) subjects in the Avamab group and 5 subjects (2.0%) in the EU-source reference product group).

NRI-related TEAEs were also similar between subjects in Avamab group and the EU- sourced reference product group.
- No statistically significant difference observed in the NRI-related TEAEs experienced by subjects in the Avamab group (125 subjects (40.2%)) and the EU- sourced reference product group (125 subjects (40.3%)) (p = 0.97).
- The most common NRI-related TEAEs were observed in gastrointestinal disorders (95 subjects (8.7%)), blood and lymphatic system disorders (55 subjects (5.0%)), respiratory, thoracic and mediastinal disorders (54 subjects (5.1%)). No clear treatment group-related trends were observed for NRI-related TEAEs. In all cases, the risk difference between treatment groups in subjects reporting NRI-related TEAEs was < 2%.
- The most common NRI-related TEAEs were hypertension (42 subjects overall (6.4%), 19 subjects (6.1%) in the Avamab group and 21 (6.3%) in the EU-sourced reference product group) and anaemia (33 subjects overall (5.2%), 15 subjects (5.1%) in the Avamab group and 17 subjects (5.5%) in the EU-sourced reference product group). NRI-related TEAEs reported during monotherapy (after Week 13 and through Week 52) were those commonly reported with use of bevacizumab (e.g., proteinuria and hypertension).
- Overall, a total of 158 (23.4%) subjects had Grade 3 or 4 study drug-related TEAEs, with a similar distribution observed in each treatment group (p = 2.58). For NRI-related TEAEs, the most common Grade 3 or 4 TEs (preferred term) were hypertension (3.3%) and anaemia (3 subjects (2.0%)). For NRI-related TEAEs reported by ≥ 1% of subjects, the following Grade 5 PTs, haemoptysis and pulmonary embolism, were observed.

TEAE incidence leading to study drug discontinuation was similar between Avamab treatment group and EU-sourced reference product treatment group with no clinically significant difference.
- The number of subjects experiencing a TEAE leading to study drug discontinuation was comparable with no statistical differences between treatment groups (72 (23.2%) subjects administered Avamab vs 85 (22.3%) subjects administered EU- sourced reference product) (p = 0.23). In all cases, the risk difference between treatment groups in subjects reporting TEAEs leading to treatment discontinuation was < 2%.
- The difference in the number of discontinuations deemed related to IMP was also comparable with no statistical differences between treatment groups (42 subjects (13.5%) in the Avamab group vs 33 subjects (10.8%) in the EU-sourced reference product group) (p = 0.27).
- The most commonly reported IMP-related TEAEs leading to treatment discontinuation were pulmonary embolism and proteinuria, with the following Grade 3 or Grade 4 PTs reported in ≥ 1 subject: arterial ischaemic stroke, pulmonary embolism (2 subjects overall, 4 subjects (1.3%) in the Avamab group and 2 subjects (1.0%) in the EU-sourced reference product group), embolism (3 subjects (0.8%) in the Avamab group) and hypertension (2 subjects (0.6%) in the EU-sourced reference product group). Grade 5 IMP-related TEAEs leading to treatment discontinuation were nephrotic syndrome, gastric ulcer, and acute myocardial infarction, all 0.3 in the Avamab group. No clear treatment group-related trends were observed, the risk difference between treatment groups in subjects for IMP-related TEAEs was < 3%.

No clinically meaningful differences were noted in the rates, severity, and type of TEAEs (including serious and fatal TEAEs) between the treatment groups.
- A total of 112 (18.0%) subjects experienced serious TEAEs during the study, with no statistically significant difference in the incidence of subjects with serious TEAEs observed between the treatment groups (p = 0.63). A total of 55 (15.0%) subjects experienced serious TEAEs (not were considered related to any study drug, Avamab, EU-sourced reference product), or chemotherapy) (13 subjects in each treatment group). Serious TEAEs were considered related to Avamab in 31 subjects (8.5%) and to EU-sourced reference product in 18 subjects (5.0%).
- For IMP-related serious TEAEs, the most commonly reported Grade 3 or Grade 4 PTs in the Avamab group was pulmonary embolism, and in the EU-sourced reference product group were pulmonary embolism, fatigue, and pneumonia. For IMP-related serious TEAEs, the following Grade 5 PTs were reported, pulmonary embolism (3 subjects, 1 in each group), pulmonary haemorrhage (1 subject in the Avamab group), haemoptysis (1 subject in the Avamab group), acute kidney injury (1 subject in the EU-sourced reference product group), nephrotic syndrome (1 subject in the Avamab group), acute myocardial infarction (1 subject in the Avamab group), cardio-respiratory arrest (1 subject in the Avamab group), and gastric ulcer (1 subject in the Avamab group). No clear treatment group-related trends were observed for IMP-related serious TEAEs. In all cases, the risk difference between treatment groups in subjects reporting IMP-related TEAEs was < 1%.
- Serious TEAEs were considered related to carboplatin and/or paclitaxel for 34 (7.1%) subjects in the Avamab group and 27 (6.7%) subjects in the EU-sourced reference product group. For chemotherapy-related serious TEAEs, the most commonly reported Grade 3 or Grade 4 PTs were febrile neutropenia, neutropenia, and pneumonia. For chemotherapy-related serious TEAEs, the following Grade 5 PTs were reported, enterocolitis, disease progression, dehydration, pulmonary embolism, and cardio-pulmonary arrest. No clear treatment group-related trends were observed for chemotherapy-related serious TEAEs. In all cases, the risk difference between treatment groups in subjects reporting chemotherapy-related TEAEs was < 2%.
- 47 (7.8%) subjects experienced fatal TEAEs, with a similar distribution observed between treatment groups (p = 2.57) in the number subjects reporting fatal TEAEs in the Avamab group (22 subjects (7.4%)) compared with the EU-sourced reference product group (24 subjects (7.7%)). The most commonly reported fatal TEAE was general physical health deterioration, which was experienced by 5 (2.0%) subjects in the Avamab group and 11 (3.5%) subjects in the EU-sourced reference product group.
- Out of the 47 subjects experiencing fatal TEAEs, 1 subject had fatal TEAEs considered related to Avamab and 5 subjects had fatal TEAEs related to EU-sourced reference product. Fatal TEAEs considered related to IMP only or IMP and carboplatin/paclitaxel included, pulmonary haemorrhage (2 subjects), and acute kidney injury, nephrotic syndrome, haemoptysis, gastric ulcer, acute myocardial infarction, cardio-respiratory arrest and pulmonary embolism (1 subject each, 1 in each treatment group).
Thus, the safety profile of Avamab was consistent with that described for the reference product, bevacizumab.

After 52 weeks of study, the majority of subjects tested negative for ADAs (anti-drug antibodies) at all time points.
- A total of 28 subjects (8.2%) with baseline ADA assessments tested positive for ADAs. 16 (5.1%) subjects in the Avamab group and 22 (7.3%) subjects in the EU- sourced reference product group. Treatment-induced ADAs were observed in a total of 104 subjects (17.6%), 53 subjects (15%) in the Avamab group and 51 subjects (17.2%) in the EU-sourced reference product group.
- NAB (neutralizing antibody) responses were showed to be also similar between both groups occurring in 10 subjects (2.4%) in the Avamab group and in 12 subjects (4.2%) in the EU-sourced reference product group.
- The majority of these positive TI-ADA (treatment-induced anti-drug antibody) results were transient, with no neutralizing capacity and occurring most often at a single timepoint. Similarly, most subjects tested low titers, and when they exhibited higher titers the median titer was observed to be similar in both treatment groups.

Clinical trials have been conducted in patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile is summarized from a clinical trial population of approximately 5500 patients.
The most serious adverse drug reactions were:
- Gastrointestinal Perforations
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients
- Arterial Thromboembolism

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose-dependent.
The most frequently observed adverse drug reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhea and abdominal pain.
The following table lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications. These reactions has 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 the table fall into the following categories: Very common (≥ 10%) and Common (≥ 1% - < 10%). Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency category, adverse drug reactions are presented in 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 carboplatin, peripheral sensory neuropathy with paclitaxel or cisplatin, nail disorders or alopecia with paclitaxel.

Very Common and Common Adverse Drug Reactions

System Organ Class	NCI-CTC Grade 3-5 reactions (≥ 2% difference between the study arms in at least one clinical trial)		10 Grade Reactions (≥ 10% difference between the study)
	Very Common	Common	Very Common
Infections and infestations		Sepsis, abscess, infection	
Blood and the lymphatic systems disorders	Febrile neutropenia, Leucopenia, Neutropenia, Thrombocytopenia	Anemia	
Metabolism and nutritions disorders		Dehydration, Hyponatremia	Anorexia, Hypomagnesaemia, Hyponatremia
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, Hemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism, Dyspnea, Hypoxia, Epistaxis	Dyspnea, Epistaxis, Rhinitis, Cough
Gastrointestinal disorders	Diarrhea, Nausea, Vomiting	Intestinal perforation, Ileus, Intestinal obstruction, abdominal pain, Gastrointestinal disorder, Stomatitis	Constipation, Stomatitis, Rectal hemorrhage, Diarrhea
Endocrine disorders			Ovarian failure*
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis, Dry skin, Skin discoloration
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 subsidiary with 295 patients

Further information on selected serious adverse drug reactions
The following adverse drug reactions, reported using NCI-CTC for assessment of toxicity, have been observed in patients treated with bevacizumab.

Gastrointestinal Perforation and Fistula
Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2% in patients with metastatic renal cell cancer, or ovarian cancer and up to 2.1% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer.
From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, GI perforations (all grades) were reported in 2.2% of patients, also 2 which had a history of prior pelvic radiation.
The occurrence 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, diverticulosis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established.
Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.3%-1% of all treated patients. Gastrointestinal perforations have been reported in bevacizumab clinical trials, gastrointestinal fistula (all grade) have been reported in up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.
In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistula was 3.2% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistula may also have bowel obstructions and require surgical intervention as well as diverting colostomy.

Non-GI Fistula
Bevacizumab use has been associated with serious cases of fistula including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 1.3% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vascular, or female genital tract fistula.
Uncommon (≥ 0.1% to < 1%) reports of other types of fistula that involve areas of the body other than the gastrointestinal tract (e.g., bronchopleural, urogenital and biliary fistula) were observed across various indications. Fistula have also been reported in post marketing experience.
Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Haemorrhage
In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 2.5% in bevacizumab-treated patients, compared to 0 to 2.9% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).
- Tumour-associated haemorrhage was observed in phase I and phase II studies. In patients with non-small cell lung cancer receiving bevacizumab, serious haemorrhage was observed in 9% (5% fatal) of treated patients.
Major or massive (pulmonary haemorrhage/haemoptysis) has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with anticoagulation/anti-inflammatory drugs, treatment with endobronchial, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to treatment. In a pooled analysis of 5 randomized controlled trials that showed statistically significant survival benefit with bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.
Patients with NSCLC enrolling predominantly squamous histology, all Grade events were seen with a frequency of up to 9.0% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with < 1% with chemotherapy alone. Major or massive (pulmonary haemorrhage/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 melena have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.
Tumour-associated haemorrhages were also seen likely in other tumour types and locations and included cases of central nervous system (CNS) bleeding in patients with regardless with CNS metastases and continuous oozing of blood from a high sarcoma with necrosis.
The incidence of CNS bleeding in patients untreated CNS metastases receiving bevacizumab has not been prospectively evaluated. In randomized clinical studies, in an exploratory retrospective analysis of data from 12 completed randomized 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 3) out of 96 patients (1%) that were not exposed to bevacizumab.
Across all bevacizumab clinical trials, mucocutaneous haemorrhage was seen in up to 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes 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 events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Hypertension
In clinical trials, the overall incidence of hypertension (all grades) of 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 2.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab compared to up to 0.2% patients treated with the same chemotherapy alone.
Hypertension was generally adequately controlled with oral hypertensive such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation (0.7% of bevacizumab-treated patients) or hospitalization, and resulted in hypertensive encephalopathy in one case (0.1%).
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
Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Thromboembolism
- Arterial thromboembolism
An increased incidence of arterial thromboembolic events was observed in patients treated with bevacizumab across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events.
In clinical trials, the overall incidence ranged up to 3.5% in the bevacizumab containing arms compared to 1.8% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.7% of bevacizumab treated patients versus up to 0.5% of patients in the control group, myocardial infarction was reported in up to 1.4% bevacizumab treated versus up to 0.7% of patients in control group.
In one clinical trial, patients with metastatic colorectal cancer and were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/102) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group.
- Venous thromboembolism
In clinical trials of metastatic carcinoma of the colon or rectum, venous thromboembolic events including deep venous thrombosis, pulmonary embolism and thrombophlebitis occurred in 9.2% - 16.0% of bevacizumab-treated patients compared to that of 15.9% - 19.2% in the controls. It could not be determined if these events were due to the patients' underlying cancer, their cytotoxic chemotherapy, bevacizumab or other risk factors.
From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, grade 3-5 venous thromboembolic events have been reported in up to 12.9% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

Congestive Heart Failure
In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In five phase III studies in patients with metastatic breast cancer CHF Grade 3 or higher was reported in up to 3.9% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.3% in the control arms. For patients in study, 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, the incidences of all grade CHF were similar between the anthracycline + bevacizumab (5.2%) and the anthracycline + placebo arms (5.0%).
Most patients who developed CHF during HBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy. In most clinical trials of bevacizumab, patients with pre-existing CHF or NYHA (I-IV) were excluded, therefore, no information is available on the risk of CHF in this population. Prior anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF.
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 550 mg/m2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm.

Wound Healing
As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting bevacizumab treatment were excluded from participation in phase III trials. Across NCRC 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 bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed. (1 patient out of 79 (1.3%) treated with bevacizumab and 0% (0/40) of patients treated without bevacizumab (3/15).
Cases of serious wound healing complications have been reported during bevacizumab use, 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 0.3% patients in the control arms.

Proteinuria
In clinical trials, proteinuria has been reported within the range of 0.7% to 28% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 2 proteinuria was reported in up to < 3.1% of treated patients. However, in up 17% of patients treated for advanced and for metastatic renal cell carcinoma. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Proteinuria seen in metastatic colorectal cancer patients treated with FOLFOX4 regimen rarely required permanent discontinuation of bevacizumab therapy.
In clinical trials of metastatic carcinoma of the colon or rectum, proteinuria was reported as an adverse event in 21.7% - 28.0% of bevacizumab-treated patients.
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of 2+ or 3+ were required to be noting of bevacizumab until recovery to < 2 g/24 hours.

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

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

Elderly Patients
In randomized clinical trials, age ≥ 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischemic attacks (TIAs) and myocardial infarctions compared to those aged ≤ 65 years when treated with bevacizumab. Other reaction with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia, and thrombocytopenia, and all Grade neutropenia, diarrhea,

225 mm

1KP400000

360 mm

PACKAGE LEAFLET: **INFORMASI UNTUK PASIEN**

Avamab

Bevacizumab 100 mg/4 mL untuk injeksi

Bacalah seluruh leaflet ini dengan hati-hati sebelum Anda mulai menggunakan obat ini untuk mendapatkan informasi yang penting untuk Anda.

- *Leaflet* ini berisi pertanyaan-pertanyaan yang umum ditanyakan mengenai Avamab.
- *Leaflet* ini tidak mengandung semua informasi yang tersedia.
- Semua obat mengandung risiko dan manfaat. Dokter Anda telah mempertimbangkan risiko yang dialami dengan pemberian Avamab dengan manfaat yang diharapkan untuk Anda.
- Jika Anda memiliki pertanyaan selain yang tertapat dalam leaflet ini, tanyakan pada dokter atau apoteker.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat. Efek samping ini mencakup efek samping apapun yang tidak tertapat dalam *leaflet* ini.

1. Apa itu Avamab dan kompositi Avamab?

Avamab merupakan obat anti-neoplasmik atau anti-kanker yang termasuk dalam kelas anti-angiogenik. Avamab mengandung bahan aktif *bevacizumab*.

Avamab mengikat protein yang dikenal dengan *vascular endothelial growth factor* (VEGF) secara selektif. Protein ini dijumpai pada sel-sel yang melapisi pembuluh darah. Tumor-tumor menghasilkan VEGF dalam kadar tinggi, yang merangsang pertumbuhan pembuluh darah sehingga menyediakan nutrisi dan oksigen untuk tumor. Avamab menghambat VEGF sehingga mengganggu suplai darah menuju tumor, menghentikan atau menghambat pertumbuhan tumor.

Avamab memiliki eksipien *a.o. trehalose dehydrate, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, polysorbate 20, water for injection.*

2. Apa bentuk sediaan Avamab?

Avamab tersedia dalam bentuk vial berisi cairan *bevacizumab* 100 mg sebanyak 4 mL untuk injeksi.

3. Bagaimana penerian atau deskripsi Avamab?

Avamab untuk injeksi merupakan cairan yang jernih sampai sedikit keruh, tidak berwarna sampai coklat muda, netral, dengan pH 6,2 untuk infus.

4. Apa kegunaan dari Avamab?

Avamab adalah obat yang digunakan untuk pasien-pasien dewasa dengan kanker stadium lanjut di usus besar, misalnya di kolon atau dubur (rektum). Avamab akan diberikan dalam kombinasi dengan obat kemoterapi yang mengandung *fluoropyrimidine.*

Avamab juga digunakan untuk pasien-pasien dewasa dengan kanker payudara metastatik atau kanker payudara lokal yang berulang, dengan pemeriksaan penanda tumor yang disebut HER-2, reseptor estrogen, dan reseptor progesteron menunjukkan hasil negatif.

Pada pasien-pasien tersebut, obat ini akan diberikan bersamaan dengan obat kemoterapi *paclitaxel.*

Avamab juga digunakan dalam pengobatan pasien-pasien dewasa dengan kanker paru non-sel kecil stadium lanjut. Pada pasien ini, Avamab akan diberikan bersamaan dengan obat kemoterapi lain yaitu *carboplatin* dan *paclitaxel.*

Avamab juga digunakan dalam pengobatan pasien-pasien dewasa dengan kanker epitel ovarium, tuba falopi, atau peritoneum primer stadium lanjut pasca-operasi, tanpa adanya hipertensi. Pemberian Avamab pada pasien-pasien tersebut akan dikombinasikan dengan *carboplatin* dan *paclitaxel.* Ketika digunakan pada pasien-pasien dewasa dengan kanker epitel ovarium, tuba falopi, atau peritoneum primer stadium lanjut yang muncul kembali, dan mengan dengan pengobatan kemoterapi platinum, pemberian Avamab pada pasien ini akan dikombinasikan dengan *carboplatin* dan *gemcitabine.*

Avamab juga digunakan dalam pengobatan pasien-pasien dewasa dengan kanker serviks (leher rahim) yang menetap, muncul kembali, atau sudah menyebar ke organ lain. Pada pasien ini, Avamab diberikan dalam kombinasi dengan obat kemoterapi *paclitaxel* dan *cisplatin* atau *paclitaxel* dan *topotecan.*

5. Bagaimana cara dan dosis pemberian Avamab?

<u>Dosis dan frekuensi pemberian</u>

Dosis Avamab yang diperlukan bergantung pada berat badan Anda dan jenis kanker yang perlu diobati. Dosis yang direkomendasikan adalah 5 mg, 7,5 mg, 10 mg, atau 15 mg per kilogram berat badan Anda. Dokter Anda akan menesepkan dosis Avamab yang sesuai untuk Anda. Anda akan diobati dengan Avamab setiap 2 atau 3 minggu sekali. Jumlah infus yang Anda terima bergantung pada respons Anda terhadap pengobatan tersebut; sebaliknya Anda melanjutkan pengobatan sampai Avamab gagal menghentikan pertumbuhan tumor Anda. Dokter Anda akan mendiskusikan hal ini dengan Anda.

<u>Metode dan rute pemberian obat</u>

Avamab merupakan konsentrat untuk larutan infus. Berdasarkan dosis yang diresepkan untuk Anda, sebagian atau seluruh isi vial Avamab akan dilarutkan dalam larutan *sodium chloride* sebelum digunakan. Dokter atau perawat akan memberikan larutan Avamab melalui infus intravena (tetesan ke pembuluh vena Anda). Infus pertama akan diberikan kepada Anda selama 90 menit. Jika dapat ditoleransi dengan baik, infus kedua dapat diberikan selama 60 menit. Infus selanjutnya dapat diberikan kepada Anda dalam waktu 30 menit.

<u>Pemberian Avamab perlu ditunda sementara</u>

Jika Anda mengalami tekanan darah tinggi yang serius dan memerlukan pengobatan dengan obat-obat pengendali tekanan darah, jika Anda mengalami gangguan penyembuhan luka pasca-operasi, jika Anda mengalami operasi.

<u>Pemberian Avamab perlu dihentikan secara permanen jika Anda mengalami:</u>

Tekanan darah tinggi yang parah dan tidak dapat dikendalikan dengan obat-obatan pengendali tekanan darah; atau peningkatan tekanan darah yang ekstrem secara tiba-tiba, adanya protein dalam urin Anda disertai pembengkakan pada tubuh Anda, lubang di dinding usus Anda, pembentukan hubungan atau saluran seperti tabung abnormal antara tenggorok dan kerongkongan, antara organ-organ dalam dan kulit, antara vagina dan bagian-bagian usus, atau antara jaringan-jaringan lainnya yang tidak terhubung secara normal (fistula), dan dinilai sebagai kondisi yang berat oleh dokter Anda, infeksi serius pada kulit atau lapisan-lapisan yang lebih dalam di bawah kulit, gumpalan darah di pembuluh darah arteri Anda, gumpalan darah di pembuluh darah paru Anda, perdarahan berat apapun.

<u>Jika diberikan terlalu banyak *bevacizumab*:</u>

Anda dapat mengalami migren berat. Jika hal ini terjadi, segera hubungi dokter, apoteker, atau perawat Anda.

<u>Jika ada dosis Avamab yang terlewatkan:</u>

Dokter akan menentukan waktu pemberian dosis Avamab selanjutnya untuk Anda. Anda perlu mendiskusikan hal ini dengan dokter Anda.

<u>Jika Anda menghentikan pengobatan dengan Avamab:</u>

Penghentian pengobatan dengan Avamab dapat menghentikan efeknya pada pertumbuhan tumor. Jangan menghentikan pengobatan dengan Avamab kecuali Anda telah mendiskusikannya dengan dokter Anda. Jika Anda memiliki pertanyaan-pertanyaan lebih lanjut terkait penggunaan obat ini, konsultasikan kepada dokter, apoteker, atau perawat Anda.

6. Apa yang dilakukan jika terapi Avamab terlewatkan?

Jika Anda melewatkan terapi Avamab, dokter akan menentukan kapan dosis berikutnya diberikan.

7. Pada keadaan apa Avamab tidak boleh diberikan?

Avamab tidak boleh diberikan pada pasien dengan:

- Riwayat alergi terhadap *bevacizumab* atau komponen lain dari produk ini.
- Riwayat alergi terhadap protein yang berasal dari sel ovarium *Chinese hamster* atau antibodi manusia rekombinan atau yang mengandung antibodi manusia, yang lain.
- Hamil.
- Pasien dengan kanker yang menyebar ke sistem saraf pusat.

8. Apa yang perlu diperhatikan jika Anda akan menggunakan Avamab?

Diskusikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Avamab:

Bevacizumab dapat meningkatkan risiko pembentukan lubang pada dinding usus. Jika Anda mengalami kondisi-kondisi yang menyebabkan peradangan di dalam perut (misalnya diverikulitis, ulkus lambung, kolitis terkait kemoterapi), mohon mendiskusikannya terlebih dahulu dengan dokter Anda. *Bevacizumab* dapat meningkatkan risiko terbentuknya hubungan atau saluran abnormal antara dua organ atau pembuluh. Risiko terbentuknya saluran antara vagina dan bagian perut lainnya dapat meningkat jika Anda mengalami kanker serviks persisten, rekuren, atau metastatik. Obat ini dapat meningkatkan risiko perdarahan atau gangguan penyembuhan luka pasca- operasi. Jika Anda akan menjalani operasi, baru menjalani operasi besar dalam kurun 28 hari terakhir, atau masih memiliki luka pasca-operasi yang belum sembuh, sebaiknya Anda tidak menggunakan obat ini.

Bevacizumab dapat meningkatkan risiko terjadinya infeksi serius pada kulit atau lapisan lebih dalam di bawah kulit, terutama jika Anda memiliki lubang di dinding usus atau gangguan penyembuhan luka.

Bevacizumab dapat meningkatkan insiden tekanan darah tinggi. Jika Anda mengalami tekanan darah tinggi yang tidak terkontrol dengan baik oleh obat-obatan pengendali tekanan darah, mohon konsultasikan dengan dokter Anda mengingat tekanan darah Anda perlu diperiksa terkendali sebelum memulai pengobatan dengan Avamab. Obat ini meningkatkan risiko adanya protein pada air seni Anda terutama jika Anda memiliki tekanan darah tinggi.

Risiko pembentukan gumpalan darah di arteri (salah satu jenis pembuluh darah) dapat meningkat jika Anda berusia lebih dari 65 tahun, mendenita diabetes, atau memiliki riwayat gumpalan darah di arteri sebelumnya. Mohon konsultasikan dengan dokter Anda mengingat gumpalan darah dapat menyebabkan serangan jantung dan stroke.

Bevacizumab juga dapat meningkatkan risiko pembentukan gumpalan darah di vena (salah satu jenis pembuluh darah). Obat ini dapat menyebabkan perdarahan, terutama perdarahan terkait tumor. Mohon konsultasikan dengan dokter Anda jika Anda atau keluarga Anda memiliki kecenderungan mengalami gangguan perdarahan atau Anda sedang mendapatkan terapi obat-obatan pengencer darah karena alasan tertentu. *Bevacizumab* dapat menyebabkan perdarahan di dalam dan sekitar otak Anda. Mohon diskusikan dengan dokter Anda jika Anda mengalami kanker metastatik yang memengaruhi otak Anda.

Bevacizumab dapat meningkatkan risiko perdarahan di paru Anda, termasuk batuk atau muntahkan darah. Mohon diskusikan dengan dokter Anda jika Anda pernah mengalami kondisi ini sebelumnya.

Bevacizumab dapat meningkatkan risiko lemah jantung. Penting bagi dokter Anda untuk mengetahui jika Anda pernah mendapat *anthracycline* (misalnya *doxorubicin*, sejenis kemoterapi spesifik yang digunakan untuk mengobati kanker-kanker tertentu) atau mengalami radioterapi untuk dada Anda, atau jika Anda menderita penyakit jantung.

Obat ini dapat menyebabkan infeksi dan menurunnya jumlah neutrofil (salah satu jenis sel darah yang berperan penting dalam perlindungan terhadap bakteri).

Bevacizumab dapat menyebabkan hipersensitivitas dan/atau reaksi infus (reaksi terkait penyuntikan obat). Mohon beri tahu dokter, apoteker, atau perawat Anda jika Anda pernah mengalami gejala setelah penyuntikan, seperti pusing/perasaan akan pingsan, sesak napas, pembengkakan, atau ruam kulit.

Suatu efek samping neurologis yang langka bernama sindrom ensefalopati posterior reversibel (PRES) dikaitkan berhubungan dengan terapi *bevacizumab.* Jika Anda mengalami sakit kepala, perubahan penglihatan, kebingungan, atau kejang dengan atau tanpa tekanan darah tinggi, mohon hubungi dokter Anda. Silahkan konsultasikan dengan dokter Anda, meskipun pernyataan-pernyataan di atas hanya pernah Anda alami di masa lampau.

<u>Sebelum Anda mendapat Avamab atau saat Anda sedang mengalami pengobatan dengan Avamab:</u>

Jika Anda sedang atau pernah mengalami nyeri di mulut, gigi, dan/atau rahang, pembengkakan atau sariawan di dalam mulut, rasa baal atau berat pada rahang, atau gigi yang kendur, segera beri tahu dokter dan dokter gigi Anda. Jika Anda perlu mengalami prosedur gigi invasif atau operasi gigi, beri tahu dokter gigi Anda bahwa Anda sedang mendapatkan terapi dengan Avamab, terutama jika Anda juga sedang atau pernah mendapat injeksi *bisphosphonate* ke dalam darah Anda. Anda mungkin disarankan untuk menjalani pemeriksaan gigi sebelum Anda memulai pengobatan dengan Avamab.

Anak-anak dan remaja:

Penggunaan Avamab tidak dianjurkan pada anak-anak dan remaja di bawah usia 18 tahun karena keamanan dan manfaatnya belum dapat dipastikan pada kelompok populasi tersebut. Kematian jaringan tulang (osteonekrosis) pada tulang-tulang selain tulang rahang telah dilaporkan terjadi pada pasien-pasien di bawah usia 18 tahun ketika mendapat pengobatan *bevacizumab.*

9. Obat apa yang harus dihindari jika menggunakan Avamab?

Belum terpantau interaksi dengan obat penyerta lainnya (seperti *5- fluorouracil/leucovorin, carboplatin-paclitaxel, capecitabine, doxorubicin,* atau *cisplatin/gemcitabine*) yang bermakna secara klinis.

Jangan menggunakan obat lain tanpa memberitahukan dokter terlebih dahulu atau berkonsultasi dengan apoteker.

10. Apakah Avamab boleh digunakan pada ibu hamil dan menyusui?

Anda tidak boleh menggunakan obat ini jika Anda sedang hamil. *Bevacizumab* dapat menyebabkan gangguan pada janin karena obat ini dapat menghentikan pembentukan pembuluh darah baru. Dokter Anda sebaiknya menyarankan Anda untuk menggunakan kontrasepsi selama pengobatan dengan Avamab dan selama setidaknya 6 bulan setelah dosis terakhir Avamab. Segera sampaikan secara langsung kepada dokter Anda jika Anda sedang hamil, menjadi hamil saat sedang menggunakan obat ini, atau sedang merencanakan kehamilan dalam waktu dekat.

Anda tidak boleh menyusui bayi Anda selama mendapat pengobatan Avamab dan selama setidaknya 6 bulan setelah dosis terakhir Avamab, mengingat obat ini dapat mengganggu pertumbuhan dan perkembangan bayi Anda. *Bevacizumab* dapat mengganggu kesuburan wanita.

Untuk informasi selengkapnya, mohon konsultasikan dengan dokter Anda. Mintalah saran kepada dokter, apoteker, atau perawat Anda sebelum menggunakan obat apapun.

11. Apakah boleh mengendarai atau menjalankan mesin selama menggunakan Avamab?

Bevacizumab belum terbukti mengurangi kemampuan Anda dalam berkendara atau menggunakan alat-alat atau mesin apapun. Namun, rasa kantuk dan pingsan telah dilaporkan terjadi pada penggunaan bevacizumab. Jika Anda mengalami gejala-gejala yang memengaruhi penglihatan atau konsentrasi Anda, atau kemampuan Anda bereaksi, jangan berkendara dan menggunakan mesin sampai gejala-gejala tersebut mereda.

12. Apa efek samping yang mungkin terjadi dengan Avamab?

Seperti semua obat, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya. Jika Anda mengalami efek samping tertentu, sampaikan kepada dokter, apoteker, atau perawat Anda. Ini termasuk kemungkinan efek samping lainnya yang tidak tercantum dalam brosur ini. Efek samping yang tercantum di bawah ini terjadi ketika bevacizumab diberikan bersama dengan kemoterapi. Ini tidak selalu berarti bahwa efek samping tersebut secara khusus disebabkan oleh *bevacizumab.*

Reaksi alergi. Jika Anda mengalami reaksi alergi, segera beri tahu dokter Anda atau tenaga medis lainnya. Gejala-gejala yang dapat terjadi antara lain: sesak napas atau nyeri dada. Anda juga dapat mengalami kemerahan pada kulit atau ruam, kedinginan dan menggigil, serta rasa mual atau muntah. Anda perlu langsung mencari pertolongan jika Anda mengalami salah satu dari efek samping berikut.

<u>Efek samping berat yang sangat umum (terjadi pada lebih dari 1 dari 10 pasien)</u>, antara lain: tekanan darah tinggi, rasa baal atau kesemutan pada tangan atau kaki, penurunan jumlah sel darah, termasuk sel darah putih yang membantu melawan infeksi (hal ini dapat disertai dengan demam), dan sel darah yang membantu penggumpalan darah, rasa lemas dan tidak memiliki energi, rasa lelah, diare, mual, muntah, dan nyeri perut.

<u>Efek samping berat yang umum (terjadi pada 1-10 dari 100 pasien)</u>, antara lain: perforasi usus, perdarahan, termasuk perdarahan di paru pada pasien kanker paru non-sel kecil, penyumbatan arteri oleh gumpalan darah, penyumbatan vena oleh gumpalan darah, penyumbatan pembuluh darah di paru oleh gumpalan darah, penyumbatan vena di kaki oleh gumpalan darah, gagal jantung, gangguan penyembuhan luka pasca-operasi, kemerahan, pengelupasan, kendakeyamanan, nyeri, atau melepuh pada jari-jari atau kaki, penurunan jumlah sel darah merah, kekurangan energi, gangguan pada perut dan usus, nyeri otot dan persendian, kelemahan otot, mulut kering disertai rasa haus dan/atau air seni yang sedikit atau berwarna lebih gelap, peradangan pada selaput lendir mulut dan usus, paru dan saluran pernapasan, saluran reproduksi, dan saluran kemih, sariawan di mulut dan saluran dari mulut ke lambung, yang dapat menyebabkan nyeri dan gangguan menelan, nyeri, termasuk sakit kepala, nyeri punggung, dan nyeri di area panggul dan dubur, kumpulan abses yang terlokalisasi, infeksi, dan terutama infeksi darah atau kandung kemih, penurunan suplai darah ke otak atau stroke, rasa kantuk, hidung berdarah (mimisan), peningkatan denyut jantung (tadi), penyumbatan pada usus, hasil tes air seni yang abnormal (adanya protein pada air seni), sesak napas atau kadar oksigen yang rendah di dalam darah, infeksi pada kulit atau lapisan-lapisan yang lebih dalam di bawah kulit, fistula: saluran seperti tabung yang abnormal antara organ-organ dalam dan kulit atau jaringan-jaringan lainnya yang tidak terhubung secara normal, termasuk saluran antara vagina dan usus pada pasien-pasien kanker serviks.

<u>Efek samping berat dengan frekuensi yang tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)</u>, antara lain: infeksi serius pada kulit atau lapisan- lapisan yang lebih dalam di bawah kulit, terutama jika Anda pernah memiliki lubang pada dinding usus atau gangguan penyembuhan luka, reaksi alergi (gejala-gejalanya antara lain sesak napas, wajah memerah, ruam, tekanan darah rendah atau tinggi, kadar oksigen rendah di darah, nyeri dada, atau mual/muntah), efek negatif pada kemampuan wanita untuk memiliki anak, gangguan otak dengan gejala-gejala seperti kejang, sakit kepala, kebingungan, dan perubahan penglihatan (sindrom ensefalopati posterior reversibel atau PRES), gejala-gejala yang menunjukkan perubahan fungsi normal otak (sakit kepala, perubahan penglihatan, kebingungan, atau kejang), dan tekanan darah tinggi, penyumbatan pembuluh darah kapiler di ginjal, tekanan darah tinggi yang abnormal pada pembuluh darah di paru yang menyebabkan sisi kanan jantung bekerja lebih berat dari biasanya, luang di dinding tulang rawan yang memisahkan kedua lubang hidung, lubang di lambung atau usus, luka terbuka atau lubang di lapisan permukaan lambung atau usus halus (gejala-gejalanya antara lain nyeri perut, rasa kembung, tinja berwarna hitam seperti tar atau darah pada tinja, atau muntah darah), perdarahan dari usus besar bagian bawah, luka pada gusi dengan tulang rahang terbuka yang tidak sembuh dan dapat disertai nyeri dan peradangan jaringan di sekitarnya, lubang di kandung empedu (tanda dan gejalanya antara lain nyeri perut, demam, dan mual/muntah). Anda perlu segeratnya mencari pertolongan jika Anda mengalami salah satu dari efek samping berikut.

<u>Efek samping tidak berat yang sangat umum (terjadi pada lebih dari 1 dari 10 pasien), antara lain:</u> konstipasi, penurunan nafsu makan, demam, gangguan pada mata (termasuk peningkatan produksi air mata), perubahan cara bicara, perubahan pada indra perasa, hidung berair, kulit kering, pengelupasan dan peradangan kulit, perubahan warna kulit, penurunan berat badan, hidung berdarah (mimisan).

<u>Efek samping tidak berat yang umum (terjadi pada 1-10 dari 100 pasien), antara lain:</u> perubahan suara dan suara serak.

Pasien berusia lebih dari 65 tahun memiliki peningkatan risiko efek samping berikut: Gumpalan darah di arteri yang dapat menyebabkan stroke atau serangan jantung, penurunan jumlah sel darah putih dan sel darah yang membantu penggumpalan darah, diare, rasa mual, sakit kepala, rasa lelah, tekanan darah tinggi.

Bevacizumab juga dapat menyebabkan perubahan hasil tes laboratorium yang dilakukan oleh dokter Anda. Hal ini termasuk penurunan jumlah sel darah putih, terutama neutrofil (jenis sel darah putih yang membantu perlindungan terhadap infeksi) dalam darah; adanya protein pada air seni; penurunan kadar kalium, natrium, atau fosfor (suatu mineral) dalam darah; peningkatan kadar gula darah; peningkatan kadar alkalina *phosphatase* (suatu enzim) dalam darah; peningkatan kadar kreatinin serum (suatu protein yang diukur kadarnya melalui tes darah untuk menilai fungsi ginjal); penurunan kadar hemoglobin (dinentukan pada sel darah merah, yang membawa oksigen), yang bersifat parah. Nyeri pada mulut, gigi, dan/atau rahang, pembengkakan atau luka di dalam mulut, rasa baal atau berat di rahang, atau gigi kendur. Tanda dan gejala ini dapat menunjukkan adanya kerusakan tulang rahang (osteonekrosis). Langsung sampaikan kepada dokter dan dokter gigi Anda jika Anda mengalami salah satu gejala tersebut. Wanita pra-menopause (wanita yang masih mengalami siklus menstruasi) dapat mengalami siklus menstruasi yang tidak teratur atau terlewatkan dan dapat mengalami gangguan kesuburan. Jika Anda mempertimbangkan untuk memiliki anak, sebaiknya Anda mendiskusikan hal ini dengan dokter Anda sebelum pengobatan dimulai.

Avamab dikembangkan dan dibuat untuk mengobati kanker dengan menyuntikkannya ke dalam aliran darah. Obat ini belum dikembangkan atau dibuat untuk injeksi ke mata. Oleh karena itu, obat ini tidak diperbolehkan untuk digunakan secara demikian. Ketika Avamab dimentikan secara langsung ke mata (penggunaan tanpa persetujuan), efek samping berikut dapat terjadi: infeksi atau peradangan pada bola mata, kemerahan pada mata, adanya partikel-partikel kecil atau bintik-bintik dalam pandangan Anda (floaters), nyeri mata, adanya kilatan cahaya dengan *floaters*, yang berlanjut ke penurunan penglihatan, peningkatan tekanan di bola mata, perdarahan di mata.

<u>Pelaporan efek samping</u>

Apabila Anda mengalami efek samping apapun, hubungi dokter, apoteker, atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi tambahan terkait keamanan obat ini.

13. Apa tanda dan gejala overdosis serta apa yang harus dilakukan jika overdosis?

Jika dosis *bevacizumab* yang diberikan berlebih, Anda dapat mengalami migren (sakit kepala sebelah). Jika hal ini terjadi, beritahukan segera pada dokter.

14. Bagaimana cara menyimpan obat ini?

Avamab disimpan pada suhu 2-8°C.

HARUS DENGAN RESEP DOKTER
No. Reg. XXXXXXXXXXXXXXX

Diproduksi oleh:
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