SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OFTHE MEDICINALPRODUCT

Bevacizumab100mg/4Ml concentratefor solution in single use vial for intravenous (IV) infusion

2 QUALITATIVEAND QUANTITATIVE COMPOSITION

Active Ingredient: Bevacizumab (humanized anti-VEGF monoclonal antibody)

100 mg/ 4mL:

Each single use vial contains 100 mg of Bevacizumab in 4 mL (25mg/mL)

3 PHARMACEUTICAL FORM

Concentrate for solution in single use vial for intravenous (IV) infusion. Clear to slightly opalescent, colourless to pale brown solution.

Sterile/radioactive statement

Sterile

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bevacizumab is indicated for the treatment of:

1. In addition to platinum-based chemotherapy, indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
2. Metastatic carcinoma of the colon or rectumin adult patients in combination with fluoropyrimidine-based chemotherapy.
3. Advanced and/or metastatic renal cell cancer in adult patients as first line treatment in combination with Interferon alfa-2a.
4. Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients as the front-line treatment in combination with carboplatin and paclitaxel. For treatment of adult patients with first recurrence of platinum-sensitive epithelia lovarian, fallopian tube or primary peritoneal cancer and naïve to VEGF receptor-targeted agents including Bevacizumab
5. Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients in combination with paclitaxel, topotecan orpegylated doxorubicin who received only up to two prior chemotherapy regimens and naïve to

VEGF receptor-targeted agents including bevacizumab.

6. Persistent, recurrent, or metastatic carcinoma of the cervixin adult patients in combination with paclitaxel and cisplatin/topotecan who cannot receive platinum therapy.
7. Glioblastoma with progressive disease in adult patients following prior therapy as a single agent.
8. Metastatic breast cancer as first line treatment in combination with capecitabine in adult patients in whom treatment with other chemotherapy options including taxanesor anthracyclines is not considered appropriate. Metastatic breast cancer as first line treatment in adult patients in combination with paclitaxel.

4.2 Posology and Method of Administration

Posology

Bevacizumab was administered at the dose level of 7.5mg/kg of body weight every 3 weeks as an IV infusion in addition to platinum-based chemotherapy during clinical trial in patients with unresectable or metastatic NSCLC.

Information provided below is based on the innovator

data. Non-small celllung cancer (NSCLC)

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

Bevacizumab is administered in addition to platinum-based chemotherapy for upto6cyclesof treatment followed by Bevacizumab as a single agent until disease progression.

The recommended dose of Bevacizumab is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an IV infusion. Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic carcinoma of the colon or rectum(mCRC)

The recommended dose of Bevacizumab, administered as an IV infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of Bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an IV infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment: Bevacizumab is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

Treatment of platinum-sensitive recurrent disease: Bevacizumab is administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of bevacizumab as single agent until disease progression. The recommended dose of bevacizumab is 15 mg/kgof body weight given once every 3 weeks as an IV infusion.

Treatment of platinum-resistant recurrent disease: Bevacizumab is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an IV infusion. When bevacizumab is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.

Cervical Cancer

Bevacizumab is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. The recommended dose of bevacizumab is15 mg/kg of body weight given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Glioblastoma

The recommended dose of Bevacizumab is 10 mg/kg every 2 weeks as an IV infusion.

Metastatic breast cancer(mBC)

The recommended dose of Bevacizumab is 10 mg/kg of body weight given once every 2 weeks or 15mg/kg of body weight given once every 3 weeks as an IV infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Special populations

Elderly patients

No dose adjustment is required in the

elderly. Patients with renal impairment

The safety and efficacy have not been studied in patients with renal

impairment. Patients with hepatic impairment

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

Paediatric population

The safety and efficacy of Bevacizumab in children less than 18 years old have not been established. There is no relevant use of Bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with Bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Bevacizumab in children with glioblastoma.

Method of administration

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

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

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

Precautions to be taken before handling or administering the medicinal product:

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies.
- Pregnancy

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4.4 Special warnings and precautions for use

Information provided in this section is based on the innovator data.

Gastrointestinal (GI) perforations and Fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation and

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

GI-vaginal Fistulae

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

Non-GIFistulae

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

Wound healing complications

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

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

Hypertension

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

Inmostcases hypertension was controlled adequately using standard antihypertensive

treatment appropriate for the individual situation of the affected patient.The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of Proteinuria when treated with Bevacizumab. There is evidence suggesting that all Grade Proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 Proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome.

Arterial thromboembolism

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

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

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

Venous thromboembolism

Patients may be at risk of developing venous thrombo embolic reactions, including pulmonary embolism under Bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with Bevacizumab in combination with paclitaxel and cisplatin may be at increasedr isk of venous thromboembolic events. Bevacizumab should be discontinued in patients with life-

threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade3 need to be closely monitored.

Haemorrhage

Patients treated with Bevacizumab have an increased risk of haemorrhage, especially tumour- associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade3 or 4bleedingduring 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 randomised clinical trials. 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 therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade3or above bleeding when treated with a full dose of warfarin and Bevacizumab concomitantly.

Pulmonary haemorrhage/haemoptysis

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

Congestive Heart Failure (CHF)

Reactions consistentwithCHF werereportedin clinical trials.The findingsrangedfrom asymptomaticdeclinesinleftventricular ejectionfractionto symptomaticCHF,requiring treatmentorhospitalization.Cautionshouldbe exercisedwhentreating patientswith clinically significant cardiovasculardiseasesuch aspre-existing coronary arterydisease, or congestive heart failurewithbevacizumab.

Mostofthepatients who experiencedCHF hadmetastaticbreast cancer andhad received previoustreatmentwith anthracyclines,priorradiotherapy totheleft chestwallorotherrisk factors for CHF werepresent.

Inpatientswho receivedtreatmentwith anthracyclines andwho hadnotreceived anthracyclines before,noincreasedincidenceof allGradeCHF wasobservedinthe anthracycline+ bevacizumabgroup comparedtothetreatmentwith anthracyclinesonly. CHF Grade3 orhigher reactions were somewhatmore frequent amongpatientsreceiving bevacizumabin combination with chemotherapy thaninpatientsreceiving chemotherapy alone.This is consistentwithresults inpatientsinother studiesof metastaticbreast cancer who did notreceive concurrent anthracyclinetreatment.

Neutropenia and

infections

Increasedratesofsevere neutropenia,febrileneutropenia,or infectionwithorwithoutsevere neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Bevacizumab in comparison to chemotherapy alone. This has mainly been seen in combination with platinum-ortaxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions/infusion reactions

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

Osteonecrosis of the jaw (ONJ)

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

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

Intravitreal use

Bevacizumab is not formulated forintravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Bevacizumab compounded from vials approved for IV administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis andvitritis, retinal detachment, retinal pigment epithelialtear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted invarious degrees of visualloss, including permanent blindness.

Systemic effects following intravitreal use

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

Ovarian failure/fertility

Bevacizumab may impair female fertility. Therefore, fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with bevacizumab.

4.5 Interactions with other medicinal products and other forms of interaction

Information provided in this section is based on the innovator data.

Effect of antineoplastic agents on bevacizumab pharmacokinetics

Noclinically relevant interaction of co-administered chemotherapy on bevacizumab pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There were neither statistically significant nor clinically relevant differences in bevacizumab clearance in patients receiving Bevacizumab monotherapy compared to patients receiving Bevacizumab in combination with interferon alfa-2a, erlotinibor chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicinor cisplatin/gemcitabine).

Effect of Bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevantinteractionofbevacizumabwasobservedonthepharmacokineticsof co-administered interferon alpha 2a, erlotinib(andits activemetaboliteOSI-420), or the chemotherapies irinotecan(and its active metabolite SN38), capecitabine, oxaliplatin(as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of Bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate

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

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

Combination with platinum-or taxane-based therapies

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

Radiotherapy

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

EGFR monoclonalantibodies in combination with bevacizumabchemotherapyregimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be

administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the two randomised phase III studies in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with Bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with Bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Information provided in this section is based on the innovator data.

Women of childbearing potential/ Contraception in males and females

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

Pregnancy

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

Bevacizumab is contraindicated in pregnancy.

Breast-feeding

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

Fertility

Repeat dose toxicitystudies in animals haveshown that bevacizumab mayhave an adverse effect onfemalefertility. In aphaseIII trialinthe adjuvanttreatmentofpatientswith colon cancer,a substudy withpremenopausalwomenhasshownahigherincidenceofnew casesofovarianfailureinthebevacizumab group comparedtothe control group. Afterdiscontinuationof bevacizumabtreatment,ovarianfunctionrecoveredinthemajority of patients. Longterm effects ofthe treatmentwith bevacizumab on fertility are unknown.

4.7 Effects on Ability to Drive and Use Machines

Information provided in this section is based onthe innovatordata.

Bevacizumabhasnoornegligibleinfluenceon the ability to drive andusemachines.However, somnolence and syncopehave beenreportedwithbevacizumabuse. If patients are experiencing symptomsthat affecttheirvisionor concentration,ortheir abilityto react, theyshould be advised not to drive anduse machines until symptoms abate.

4.8 Undesirable Effects

Information provided belowis based on the studyconducted withBevacizumab.

In a prospective, randomized, open label, multicentre, comparative, parallel-group, active controlledphaseIIIstudy,129IndianpatientswithunresectableormetastaticNSCLCwere administered with 7.5 mg/kg Intas Bevacizumab drug productor Avastin™(F. Hoffman-La Roche Limited,Switzerland)every3weeks,incombinationwithcisplatin(80 mg/m2 onday1ofeachcycle)andgemcitabine(1250mg/m2 onday1and8ofeachcycle),for fourcycles.Of129patients,87receivedIntasBevacizumabdrugproductand42received Avastin™.Atotalof419adverseevents(AEs)werereportedby99patientsduringtheconductof study: 312 in patients treated with Intas Bevacizumaband 107 inpatients treated with Avastin™. Of theseadverseevents,258AEsweregrade1(mild),118AEswere grade2 (moderate), 38AEsweregrade3(severe)and4AEsweregrade5(death)innature.MajorityofAEswere judgedunlikelytoberelatedtotheadministereddrugandwererecovered completely. Total10deaths were reported in the study: 4 in patients receivingIntasBevacizumabdrug product and 6 in patients receiving Avastin™.

The most frequently reported AEs with incidence of more than 4% during the study were nausea, vomiting, hypertension, asthenia, anaemia, leukopenia, neutropenia, thrombocytopenia, tachycardia, constipation, diarrhoea, abdominal pain, hypochlorhydria, pyrexia, mucosalulceration,lossof appetite,pain,fatigue,respiratory distress,dizziness, alopecia, dyspnoea and cough,hypokalaemia, hyponatremia,headache andbackpain.These were the expectedAEs reported with the use of Bevacizumab and other chemotherapy agents used during the conduct of the study. Overall, Intas Bevacizumab drug product and Avastin™ were well tolerated in patients with NSCLC.

Information provided belowis based on the innovator

data. ***a. Summaryof thesafetyprofile***

The overall safety profile of bevacizumab is based on data from over 5,400 patients with various malignancies, predominantly treated with bevacizumabincombinationwith chemotherapy in clinical trials.

Themostseriousadverse reactionswere:

- Gastrointestinalperforations.
- Haemorrhage,includingpulmonaryhaemorrhage/haemoptysis,whichismorecommoni n NSCLCpatients.
- Arterial thromboembolism.

Themostfrequently observed adversereactions across clinicaltrialsinpatientsreceiving bevacizumab were hypertension, fatigueor asthenia, diarrhoea and abdominal pain.

Analysesofthe clinicalsafety datasuggestthat theoccurrenceof hypertension andproteinuria with bevacizumab therapy arelikelyto be dose-dependent.

b. Tabulated list of adverse reactions

The adversereactionslistedinthissectionfallintothefollowingfrequency categories:Very common(≥1/10); common(≥1/100to<1/10);uncommon(≥1/1,000to<1/100);rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table1 and2list adverse reactions associated withtheuse ofbevacizumabin combinationwith different chemotherapy regimens in multiple indications.

Table1provides all adverse reactions by frequency thatweredeterminedtohavea causal relationshipwith bevacizumab through:

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

Table2providesthe frequency ofsevere adverse reactions. Severe reactions aredefined as adverse eventswith atleasta2%difference comparedtothe control armin clinicalstudiesforNCI-CTCAEGrade 3-5reactions. Table2 also includes adversereactionswhich are considered to be clinicallysignificant or severe.

Post-marketing adversereactions (innovatordata) areincludedinbothTables1 and2,whereapplicable. Detailed information about thesepost-marketing reactions are provided in Table 3.

Adverse reactions are addedtothe appropriatefrequency category inthetablesbelow according to thehighest incidence seen in anyindication.

Within eachfrequency category, adversereactions are presentedintheorderofdecreasing seriousness.

Someofthe adverse reactions arereactions commonly seenwith chemotherapy;however, bevacizumabmay exacerbatethese reactions when combinedwith chemotherapeutic agents. Examplesincludepalmar-plantar erythrodysaesthesia syndromewithpegylatedliposomal doxorubicinor capecitabine,peripheralsensoryneuropathy withpaclitaxeloroxaliplatin,nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

For those eventspresentedinthe Table1below, for which grade wasnoted asboth all grade and grade3-5 adversedrug reactions in clinicaltrials,thehighestfrequency observedinpatientshas been reported. Data wasunadjusted forthe differential timeon treatment.

Table 1: Adverse Reactions by Frequency

System organ class	Very common	Common	Uncommon	Rare
Infectionsand infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis[a]
Blood and lymphatic systemdisorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombocytopenia	Anaemia, Lymphopenia		
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]		
Metabolism and nutrition disorders	Anorexia	Dehydration		
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalopathy
Eye disorders	Eye disorder, Lacrimation increased			
Cardiac disorders		Congestiveheartfailure[b,d], Supraventricular tachycardia		
Vascular disorders	Hypertension[b,d], Thromboembolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep veinthrombosis		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Epistaxis, Hypoxia, Dysphonia[a]		
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis,	Gastrointestinal perforation[b,d], Intestinal		

System organ class	Very common	Common	Uncommon	Rare
	Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal Disorder, Proctalgia		
Hepatobiliary disorders				
Skin and subcutaneous tissuedisorders	Wound healing complications[b,d], Exfoliativedermatitis, Dryskin, Skindiscoloration	Palmar-plantar erythro-dysaesthesia syndrome		
Musculoskeletal andconnective tissuedisorders	Arthralgia	Fistula[b,d], Myalgia, Muscular weakness, Back pain		
Renal andurinarydisorders	Proteinuria[b,d]			
Reproductive system and breastdisorders	Ovarian failure[b,c,d]	Pelvic Pain		
Congenital, familial, and geneticdisorder				
Generaldisorders and administration siteconditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy		
Investigations	Weightdecreased decreased			

[a]For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

[b]Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA(Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardialinfarction, transient ischaemic attack and other arterial thromboembolic reactions).

[c]Based on a substudy from NSABP C-08 with 295 patients

[d]For additional information refer below within section "Further information on selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in paediatric population only.

Table 2: Severe Adverse Reactions by Frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections andinfestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising Fasciitis[c]
Blood and lymphatic systemdisorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombocytopenia	Anaemia, Lymphopenia				
Immune systemdisorders						Hypersensitivity, Infusionreactions[a,b,c]
Metabolism and nutrition disorders		Dehydration				
Nervous systemdisorders	Peripheral sensoryNeuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome [a,b,c], Hypertensive encephalopathy[c]
Cardiac disorders		Congestiveheartfailure[a,b],				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Supraventricular tachycardia				
Vascular disorders	Hypertension[a,b]	Thromboembolism arterial[a,b], Haemorrhage[a,b] Thromboembolism (venous)[a,b], Deep veinthrombosis				Renal thrombotic microangiopathy[b,c]
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea,Hypoxia				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b], Gastrointestinal ulcerc, Rectalhaemorrhage
Hepatobiliary disorders						Gallbladder perforation[b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar erythrodysaesthesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular				Osteonecrosis of the jaw[b,c]

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		weakness, BackPain				
Renal and urinarydisorders		Proteinuria[a,b]				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure[a,b]
Congenital, familial, and genetic disorder						Foetal abnormalities [a,c]
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal Inflammation				

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

[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

[b]For additional information refer below within section "Further information on selected serious adversereactions"

[c]For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

[d]Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Safety profileof bevacizumabintreatmentofglioblastoma was assessedin163patientswho

received bevacizumab alone orbevacizumab plusirinotecan. All patientsreceived prior radiotherapy and temozolomide. Bevacizumabwas administered at10mg/kg every2weeks aloneorin combinationwithirinotecan. Bevacizumabwasdiscontinueddueto adverse eventsin 4.8%of patients treatedwith bevacizumab alone.

In patients receiving bevacizumab alone (N = 84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to bevacizumab: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving bevacizumab alone or bevacizumab plus irinotecan (N = 163), the incidence of bevacizumab-related adverse events (Grade 1−4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and PRES (1%). The incidence of Grade 3−5 events in these163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

d) Description of selected serious adverse reactions

Gastrointestinal (GI)perforations and Fistulae

Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinalperforations have been reported in clinical trials with an incidence of less than 1% in patients with non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

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

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

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

GI-vaginalFistulae in studyGOG-0240

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI- vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whomhad a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with bevacizumab + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with recurrence outside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GIFistulae

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

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

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

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

Wound healing

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

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

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

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

In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.2% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab containing arms

compared with up to 14% in thecontrol arms. The overall incidence of NCI-CTCGrade 3 and 4 hypertension in patients receiving Bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLCwith EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with bevacizumab in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

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

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' baselinecharacteristics, underlying disease or concomitant therapy.

Posterior Reversible EncephalopathySyndrome

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

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

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

Proteinuria

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

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria

(nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical trials urine protein levels of ≥2g/24 hrs led to the holding of bevacizumab until recovery to < 2g/24 hrs.

Haemorrhage

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

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

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

Tumour-associated haemorrhage

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

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

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

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

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain

metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis (NCI-CTCAE v.3).

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

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

Thromboembolism

*Arterialthromboembolism:*An increased incidence of arterial thromboembolic reactions was observed in patients treated with bevacizumab across indications, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic reactions.

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

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

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

In clinical trials across indications, the overall incidence of venous thromboembolic reactions ranged from 2.8% to 17.3% of bevacizumab-treated patients compared with 3.2% to 15.6% in the control arms. Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus

bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

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

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

Congestiveheart failure (CHF)

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

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

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

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

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse largeB-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than300mg/m2.This phase III clinical trialcomparedrituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to RCHOP 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. Theseresults suggest that close clinical observation with appropriate cardiac assessments should beconsidered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m2 when combined with bevacizumab.

Hypersensitivity reactions/infusion reactions

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapy than with

chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab-treated patients).

Infections

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

Ovarian failure/fertility

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

Laboratory abnormalities

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

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

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immune response to bevacizumab. The detection of antibody formation is highly dependent on the sensitivity and specificity of assay. Additionally, observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to bevacizumab in studies described below with incidence of antibodies in other studies or other products may be misleading.

In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL)based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab (innovator product) using an

enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Information provided below is based on the study conducted with Intas Bevacizumab.

Immunogenicity of Intas Bevacizumab was evaluated during a prospective, randomized, open-label, multicenter, parallel-group, active-controlled study in 129 Indian patients with unresectable or metastatic NSCLC. Patients were administered with Intas Bevacizumab drug product (N=87) or Avastin™ (N=42) at the dose level of 7.5 mg/kg every 3 weeks, in combination with cisplatin and gemcitabine, for four cycles. Pre-dose (baseline) and post- dose (end of 4 cycles) samples were analyzed from 20 patients from Intas Bevacizumab arm. No incidence of anti-drug antibodies against bevacizumab was observed in any patient.

Other special populations

Elderlypatients

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

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

e) Paediatric population

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

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

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

Bevacizumab is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of18 years treated with bevacizumab.

Post-marketingexperience
(innovatordata)

Table 3:Adverse Reactions ReportedinPost-marketing Setting

System organ class (SOC)	**Reactions (frequency*)**
Infectionsand Infestations	Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinalperforation or fistula formation (rare)
Immune systemdisorders	Hypersensitivityreactionsandinfusionreactions(notknown); with thefollowingpossible co-manifestations:dyspnoea/difficultybreathing,flushing/redness/rash, hypotensionor hypertension,oxygendesaturation,chestpain,rigorsandnausea/vomiting.
Nervous system disorders	Hypertensive encephalopathy (very rare) Posterior Reversible Encephalopathy Syndrome (PRES), (rare)
Vasculardisorders	Renal thrombotic microangiopathy, which may be clinically manifested asproteinuria(not known) with or without concomitant sunitinib use.
Respiratory,thoracic andmediastinal disorders	Nasalseptumperforation(notknown) Pulmonaryhypertension(not known) Dysphonia(common)
Gastrointestinal disorders	Gastrointestinalulcer(not known)
Hepatobiliarydisorders	Gallbladderperforation(notknown)
Musculoskeletaland connectivetissuedisorders	CasesofOsteonecrosisoftheJaw(ONJ)havebeen reportedinpatientstreatedwith Bevacizumab,mostofwhichoccurredinpatientswhohadidentifiedrisk factorsfor
	ONJ,inparticularexposuretoIVbisphosphonatesand/ora historyofdentaldisease requiringinvasivedentalprocedures
	Casesofnon-mandibulararosteonecrosishavebeenobservedin Bevacizumabtreated paediatricpatients.
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or incombination with known embryotoxic chemotherapeutics have been observed.

*Ifspecified,frequencyhasbeenderivedfromclinical trialdata.

4.9 Overdose

Information provided in this section is based onthe innovatordata.

Thehighestdosetested inhumans(20 mg/kg ofbodyweight, IV every 2weeks)was

associated with severemigrainein several patients.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents,other antineoplastic agents, monoclonal antibodies, ATC code: L01X C07

Mechanismof action

Bevacizumabbindstovascular endothelial growthfactor (VEGF),the keydriverof vasculogenesis and angiogenesis, andtherebyinhibitsthebinding ofVEGFtoitsreceptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological activity of VEGF regressesthe vascularizationoftumours,normalizesremaining tumourvasculature, andinhibitstheformationofnewtumourvasculature,thereby inhibiting tumour growth.

Pharmacodynamiceffects

Administrationofbevacizumabor itsparentalmurine antibody to xenotransplantmodelsof cancer in nudemice resulted in extensive anti-tumour activityin human cancers, including colon, breast,pancreas and prostate.Metastatic diseaseprogressionwas inhibited and microvascular permeabilitywas reduced.

Clinical efficacy

Information provided in this section is based onthe studyconductedwithIntasBevacizumab.

Efficacy and safety profile of Intas Bevacizumab drug product and Avastin™(F. Hoffman-La Roche Limited, Switzerland) was evaluated during a prospective, randomized, open label, multicenter,comparative, parallel-group, active controlled, phase III study in 129 Indian patients with unresectable or metastatic NSCLC. Chemotherapy- naïve male or female patients withhistologicallyor cytologically confirmedNSCLCwererandomized (2:1) toreceive IV cisplatin80 mg/m² on day 1 and IV gemcitabine 1250 mg/m² on day 1 and 8 of each cycle in combination witheitherIntasBevacizumab (n=87)orAvastin™(n=35)atadoseof7.5mg/kgeverythree weekly for total of four cycles. Patients with predominant squamous histology, brain metastasis, gross haemoptysis (≥1/2 tsp of bright red blood), unstable angina, or receiving anticoagulant therapywereexcluded.Theprimary efficacy parameter wasbestoverall response(bestresponse recorded across all time points from start of treatment until end of treatment; complete response [CR] + partial response [PR])at the end of 4th chemotherapy cycle. Other efficacy parameters includeddiseasecontrolrate(CR+PR+stabledisease)andoverallresponserate(CR+PR)at theendof4th chemotherapycycle.Outof129patientsenrolledanddosed,110patients(n=75for Intas Bevacizumab and n=35 for Avastin™) were included in per protocol population.

Efficacyresults atthe endofstudy(4thcycle) asmeasured by bestoverallresponse rate,disease

controlrateandoverallresponseratearesummarizedinbelowTable4.Overall,efficacyprofile of Intas Bevacizumab and Avastin™ was found to be similar.

Table 4: EfficacyResults ofIntasBevacizumabinNSCLC(PerProtocolPopulation)

Response	Per-		DifferenceofTreatments [95%CI]
	IntasBevacizumab (N=75)	Avastin™ (N=35)	
Bestoverallresponserate(	31(41.33%)	14(40.00	1.33%[-18.35,21.02%]
Diseasecontrolrate(CR+	71(94.67%)	33(94.29	0.38%[-8.84,9.60%]
Overallresponserate(CR+	27(36.00%)	12(34.29	1.71%[-17.40,20.83%]

5.2 Pharmacokinetic properties

Information provided in this section is based onthe studyconducted withIntas Bevacizumab.

Pharmacokinetic (PK) profile of Intas Bevacizumab was evaluated in subset of patients duringcomparative,open-label,randomized,multicenterphaseIIIstudyinpatients with unresectable or metastaticNSCLC.Ineach21-daycycle,patientswereadministeredIntas BevacizumaborAvastin™as IVinfusionat7.5mg/kgdoseincombinationwithcisplatinand gemcitabine, fortotalfourcycles.Serumsampleswerecollectedfrom10patientseachfrom IntasBevacizumabandAvastin™armduringcycle1.Descriptivestatisticswereusedtoreport thePKparametersofIntas Bevacizumaband Avastin™ (Table 5).

Table 5: PharmacokineticParameters ofIntas BevacizumabinNSCLCpatients(Cycle1)

Parameters(Units)	Mean± SD(Untransformeddata)	
	IntasBevacizumab(N=09)	Avastin™(N=10)
AUC_{0-480}(µg*h/mL)	1805.912± 293.6909	2155.212± 577.5223
C_{max}(µg/mL)	29.038±4.3307	35.790±4.2238
T_{max}(h)*	1.750(1.500–2.000)	1.750 (1.500 – 2.000)

*MedianvaluereportedforT_{max}

Information provided in this section is based onthe innovatordata.

The PKdatafor bevacizumab are availablefromten clinicaltrialsinpatientswithsolidtumours. In all clinicaltrials,bevacizumab was administered as an IV infusion.The rate of infusionwas basedontolerability,with aninitialinfusiondurationof90minutes.The PKofbevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

The typical valuefor centralvolume(Vc) was2.73L and3.28Lfor female andmalepatients respectively,whichis inthe range thathasbeendescribedfor IgGs andother monoclonal

antibodies.The typical valuefor peripheralvolume(Vp) was1.69L and2.35L forfemale and male patientsrespectively,whenbevacizumab is co-administeredwith anti-neoplastic agents. After correcting for bodyweight, malepatients had alarger Vc (+20%) than femalepatients.

Metabolism

Assessmentofbevacizumabmetabolismin rabbitsfollowing asingle IVdoseof 125I-bevacizumabindicated thatitsmetabolic profilewassimilartothat expectedfora native IgG moleculewhichdoesnotbindVEGF.The metabolism and eliminationof bevacizumabissimilar to endogenous IgGi.e.primarily via proteolytic catabolismthroughoutthebody,including endothelial cells, and doesnotrely primarilyon eliminationthroughthekidneys andliver. Bindingof the IgGtothe FcRn receptor resultsinprotectionfrom cellular metabolism andthe longterminal half-life.

Elimination

Thevaluefor clearanceis,on average, equalto0.188 and0.220 L/day forfemale and male patients,respectively.After correctingforbody weight,male patientshadahigherbevacizumab clearance (+17%)thanfemales. Accordingto thetwo-compartmentalmodel,the elimination half-lifeis 18 daysfor a typical female patient and20 daysfora typical male patient.

Low albumin andhightumourburden aregenerally indicative ofdiseaseseverity. Bevacizumab clearance was approximately30%fasterinpatientswithlowlevelsofserum albumin and7% faster insubjectswithhigher tumour burdenwhen comparedwitha typicalpatientwithmedian values of albumin and tumour burden.

<u>Pharmacokinetics in special populations</u>

The population PKwere analyzedin adult andpediatric patientsto evaluate the effectsof demographic characteristics. In adults, theresultsshowed no significantdifferenceinthe PK of bevacizumab in relation to age.

Paediatric population

The PKofbevacizumabwere evaluatedin152 children, adolescents and young adults(7months to21 years, 5.9to125 kg) across 4 clinicalstudiesusinga population PKmodel.The PKresults showthatthe clearance andvolumeofdistributionofbevacizumabwere comparablebetween paediatric and young adultpatientswhennormalized bybodyweight, with exposuretrending lower as bodyweight decreased. Agewas not associated with the PK of bevacizumab whenbody weight was taken into account.

The PKof bevacizumabwas well characterized bythepaediatricpopulation PKmodelfor70 patients in Study BO20924((1.4to17.6 years; 11.6to77.5 kg) and59patientsin Study BO25041(1to17 years;11.2to82.3 kg). In Study BO20924, bevacizumab exposurewas generallylower comparedtoa typical adult patient atthesamedose. In Study BO25041, bevacizumab exposure wassimilar comparedtoa typical adult atthe samedose.

Inbothstudies, bevacizumab exposuretrended lower as bodyweight decreased.

Renal impairment

Notrialshavebeen conductedtoinvestigatethe PKofbevacizumabin renally impairedpatients sincethe kidneys arenotamajororganforbevacizumab metabolism or excretion.

Hepaticimpairment

No trialshave been conducted toinvestigate the PKof bevacizumab inpatientswithhepatic impairment sincethe liver is not a major organ forbevacizumab metabolism or excretion.

5.3 Preclinical safety data

Information provided belowis based on the studies conducted with Intas Bevacizumab.

In acute toxicity studies, maximum tolerated dose of IntasBevacizumab was found to be 1845mg/kgand915mg/kginmiceandrats,respectivelywhenadministeredbyIVroute.In 28-dayrepeat-dosetoxicitystudies,noobservedadverseeffectlevelofIntas Bevacizumabwas foundtobe91.5and192 mg/kg/week in rats and rabbits, respectively when administered by IV route. In localtolerance studies, IntasBevacizumab was found to be non-irritant andnon-sensitizerinrabbitsand guinea pigs, respectively.

Information provided belowis based on the innovator data.

Instudiesofupto26 weeksdurationin cynomolgusmonkeys,physealdysplasia wasobserved in young animalswith open growthplates, atbevacizumab averageserum concentrationsbelow the expectedhumantherapeutic averageserum concentrations. In rabbits,bevacizumabwas showntoinhibitwoundhealing atdoses belowtheproposed clinical dose.Effectsonwound healing wereshown to be fully reversible.

Studiesto evaluatethemutagenic and carcinogenicpotentialofbevacizumab havenotbeen performed.Nospecific studiesin animals have been conducted to evaluatethe effectonfertility. An adverse effecton femalefertility canhoweverbe expected asrepeatdosetoxicity studiesin animalshaveshowninhibitionofthematurationofovarianfollicles andadecrease/absence ofcorporalutea and associateddecreaseinovarian anduterusweight as well asadecreaseinthe numberof menstrual cycles.

Bevacizumabhasbeen showntobe embryotoxic andteratogenicwhen administeredtorabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetalresorptions and anincreasedincidence of specific gross andskeletalfoetalmalformations. Adversefoetaloutcomeswere observed at alltesteddoses,ofwhichthelowestdoseresultedin averageserum concentrations approximately3timeslargerthaninhumansreceiving5 mg/kg every 2 weeks. Informationonfoetalmalformationsobservedinthepostmarketingsetting are provided in section on Fertility, Pregnancy and Lactation and UndesirableEffects.

6 Pharmaceutical Particulars

6.1 List of excipients

Trehalose dihydrate

Mono-Sodiumdihydrogenphosphate

monohydrate di-Sodiumhydrogenphosphate

anhydrous Polysorbate 20

Ortho phosphoricacid

Sodiumhydroxide

Water forinjection

6.2 Incompatibilities

Noincompatibilitiesbetween bevacizumab andpolyvinyl chloride andpolyolefin bagshave been observed.

6.3 Shelf life

Vial (unopened)

24 months when stored under recommended storage conditions

Diluted medicinal product

Chemical andphysical in-usestability hasbeendemonstratedfor24hours at25°Cinsodium chloride9 mg/mL (0.9%)solutionforinjection. Fromamicrobiologicalpointofview,the productshould be used immediately. If not used immediately, in-use storage times and conditions aretheresponsibilityoftheuser andwouldnormallynotbe longerthan24hours at25 ± 2°C, unless dilutionhas taken placein controlled and validated aseptic conditions.

6.4 Special precautions for storage

Bevacizumab should not beused afterthe expirydate shown on

pack. Storevials in a refrigerator at 2°Cto 8°C.

Do not freeze. Do not shake.

Keep the vial in the outercarton in order to protectfrom

light. Keep out of reach and sight of children.

Theproductdoesn’tcontainanyanti-microbialpreservative;therefore,caremustbetakento ensuresterilityof theprepared solution.

6.5 Nature and contents of container

Intas Bevacizumab 100mg/4mL: 4 mL solution in a vial (Type-I glass) with a stopper (flurotec coated)containing100 mgof bevacizumab.

Pack of 1 vial.

6.6 Special precautions for administration, disposal and other handling

Bevacizumab infusions should not be administered or mixed with dextroseor glucosesolutions.Do not administer asIVpush or bolus.

Itshouldbeprepared by ahealthcareprofessionalusing aseptictechnique. Withdrawthe necessary amountof bevacizumab anddilutetotherequired administrationvolumewith0.9% sodium chloride solution.The concentrationof the final bevacizumabsolutionshouldbe kept within the rangeof 1.4 to16.5 mg/mL.

Discard anyunusedportionleftina vial, astheproduct containsnopreservatives. Parenteral drugproductsshouldbeinspectedvisually forparticulatematter anddiscolorationpriorto administration.

7 Marketing Authorization Holder

Intas Pharmaceuticals Limited

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Gujarat,India

8. Marketing Authorization number

TAN 22 HM 0107

9. Date of first Authorization

10/01/2022

10. Date of review of the text

April, 2022