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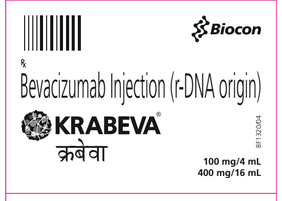

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For the use only of a Registered Medical Practitioner, Oncologist, Specialist, Hospital or Laboratory

In vitro, preclinical and clinical studies have demonstrated similarity between KRABEVA® and the reference bevacizumab product. Hence, this document includes publicly available information on the reference bevacizumab product. In this document, when information on the reference (originator) bevacizumab product is being referred to, the term "bevacizumab (Reference Product)" is used. The term "bevacizumab" is used to describe properties generally applicable to the bevacizumab molecule that are described based on observations with the reference product. Where information or instructions specific to KRABEVA® is presented, the term "KRABEVA®" is used.

NAME OF THE MEDICINAL PRODUCT
Rx
KRABEVA®

GENERIC NAME
Bevacizumab Injection (r-DNA origin) concentrate for solution for intravenous infusion.

COMPOSITION
Each **KRABEVA®** 100 mg in 4 mL vial contains 100 mg of bevacizumab (25mg/ml) concentrate for solution for intravenous infusion supplied in a single use vial.
Each **KRABEVA®** 400 mg in 16 mL vial contains 400 mg of bevacizumab (25mg/ml) concentrate for solution for intravenous infusion supplied in a single use vial.

LIST OF EXCIPIENTS
Trehalose dihydrate, Sodium phosphate, Polysorbate, Water for injections

DOSAGE FORM
Concentrate for solution for intravenous infusion.
Clear to slightly opalescent, colourless to pale brown liquid.

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, AND HAEMORRHAGE

Gastrointestinal Perforations
Gastrointestinal perforation, some fatal, is reported in bevacizumab-treated patients. Bevacizumab must be discontinued in patients with gastrointestinal perforation *[see Sections Dose and Method of Administration, Warnings and Precautions].*

Surgery and Wound Healing Complications
Bevacizumab-treated patients have increased incidence of wound healing and surgical complications, including serious and fatal complications. Bevacizumab must be discontinued in patients with wound dehiscence. The appropriate interval between termination of bevacizumab and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence is not known. Bevacizumab must be discontinued at least 28 days before elective surgery. Bevacizumab must not be initiated for at least 28 days after surgery and until the surgical wound is fully healed *[see Sections Dose and Method of Administration, Warnings and Precautions, Undesirable Effects].*

Haemorrhage
In patients receiving bevacizumab, severe or fatal haemorrhage, including haemoptysis, gastrointestinal bleeding, central nervous system (CNS) haemorrhage, epistaxis, and vaginal bleeding occur more frequently. Bevacizumab must not be administered to patients with serious haemorrhage or recent haemoptysis *[see Sections Dose and Method of Administration, Warnings and Precautions, Undesirable Effects].*

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacodynamic Properties
Therapeutic/pharmacologic class: Antineoplastic and immunomodulating agents/antineoplastic agents/other antineoplastic agents/monoclonal antibodies
ATC code: L01X C07

Mechanism of Action [1,2]
Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to human vascular endothelial growth factor (VEGF) and neutralises its biologic activity. **KRABEVA®** 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. By binding to VEGF, bevacizumab blocks the interaction of VEGF and its receptors (Flt-1 and KDR), present on the surface of endothelial cells. Bevacizumab inhibits the formation of tumour vasculature, thereby inhibiting tumour growth. In xenograft cancer models in nude (athymic) mice, bevacizumab or the parent murine antibody had notable anti-tumour activity, and inhibited metastatic disease progression as well as reduced microvascular permeability.

Pharmacokinetic Properties
A double-blind, randomized, active-controlled, parallel-arm, comparative PK, efficacy, safety and immunogenicity study of **KRABEVA®** and bevacizumab (Reference Product), both in combination with capecitabine and oxaliplatin in patients with metastatic colorectal cancer (mCRC) showed that the pharmacokinetic profile of **KRABEVA®** was similar to that of bevacizumab.

Pharmacokinetics in Special Populations [1,2]
Population pharmacokinetic analysis showed no significant effect of race (adjusted for body weight) or age on the pharmacokinetics of bevacizumab (Reference Product). The pharmacokinetics of bevacizumab have not been studied specifically in patients with renal impairment or patients with hepatic impairment, since neither the kidneys nor the liver are major organs of bevacizumab metabolism or excretion. In the limited number of paediatric patients studied, volume of distribution and clearance were comparable to that in adult patients.

CLINICAL EFFICACY
The clinical efficacy of **KRABEVA®** was assessed in a double-blind, randomized, active-controlled, parallel-arm, comparative PK, efficacy, safety and immunogenicity study of **KRABEVA®** and bevacizumab (Reference Product), both in combination with capecitabine and oxaliplatin in patients with first-line mCRC. There were no significant differences between **KRABEVA®** and bevacizumab with regard to efficacy in terms of progression-free survival (PFS) rate, clinical benefit (disease control rate [DCR]), or overall response rate (ORR).

PRECLINICAL SAFETY DATA
During conventional single- and repeat-dose toxicity studies of **KRABEVA®** in mice, rabbits, and cynomolgus monkeys, no clinically relevant adverse events were observed at the highest dose levels tested. Local tolerance was also evaluated in these toxicity studies, and no clinically relevant effects were observed. No meaningful differences were observed between the toxicity profiles of **KRABEVA®** and bevacizumab (Reference Product).

The inhibition of angiogenesis following administration of bevacizumab may result in an adverse effect on female fertility. [1,2]

THERAPEUTIC INDICATIONS [1,2]
- Treatment of adult patients with metastatic carcinoma of the colon or rectum (in combination with fluoropyrimidine-based chemotherapy)
- First-line treatment of non-squamous non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy
- First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib
- Treatment of glioblastoma, as a single agent for adult patients with progressive disease following prior therapy
- First-line treatment (in combination with interferon alpha-2a) of adult patients with advanced and/or metastatic renal cell cancer
- Front-line treatment (in combination with carboplatin and paclitaxel) of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Treatment (in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by use as a single agent) of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab, other VEGF inhibitors, or VEGF receptor–targeted agents
- Treatment (in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin) of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab, other VEGF inhibitors, or VEGF receptor–targeted agents
- Treatment of persistent, recurrent, or metastatic carcinoma of the cervix in adult patients, in combination with paclitaxel and cisplatin; or, alternatively, paclitaxel and topotecan (for those who cannot receive platinum therapy)

DOSE AND METHOD OF ADMINISTRATION [1,2]
General
A healthcare professional should prepare bevacizumab infusion solution using aseptic technique *(see Section Storage and Handling).* Prepare bevacizumab infusion solution using normal saline only. Do not administer or prepare in dextrose solution. Bevacizumab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Deliver the initial bevacizumab dose as an intravenous infusion, over 90 minutes. The second infusion can be administered over 60 minutes, if the first is well tolerated; and subsequent infusions can be administered over 30 minutes, if infusion over 60 minutes is tolerated.

Bevacizumab must not be administered as an intravenous push or bolus; but only as an intravenous (IV) infusion. Bevacizumab must not be initiated until at least 28 days after major surgery; and must be administered after the surgical incision has fully healed.

Dose reduction for adverse reactions is not recommended for bevacizumab.
Bevacizumab should either be permanently discontinued or temporarily suspended, if indicated, as described below.

Bevacizumab should be permanently discontinued for **gastrointestinal perforations** *[see Boxed Warning, Section Warnings and Precautions];* **wound dehiscence and wound healing complications** requiring medical intervention [see Section Warnings and Precautions]; **serious haemorrhage** (i.e., requiring medical intervention) [see Boxed Warning, Section Warnings and Precautions]; **severe arterial thromboembolic events** [see Section Warnings and Precautions]; **life-threatening (Grade 4) venous thromboembolic events,** including pulmonary embolism *[see Section Warnings and Precautions];* hypertensive crisis or hypertensive encephalopathy *[see Section Warnings and Precautions];* **Posterior Reversible Encephalopathy Syndrome (PRES)** *[see Section Warnings and Precautions];* **nephrotic syndrome** *[see Section Warnings and Precautions].*

Bevacizumab should be temporarily suspended for (1) at least 4 weeks before elective surgery *[see Section Warnings and Precautions];* (2) severe hypertension not controlled with medical management *[see Section Warnings and Precautions];* (3) moderate to severe proteinuria *[see Section Warnings and Precautions];* (4) severe infusion reactions *[see Section Warnings and Precautions].*

Bevacizumab is not for intravitreal use *(see Section Warnings and Precautions).*

Metastatic Colorectal Cancer (mCRC)
Following are the dose recommendations for bevacizumab, administered as an intravenous infusion:
The recommended dose of bevacizumab, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.
It is recommended to continue bevacizumab treatment until progression of the underlying disease or unacceptable toxicity. If a patient has been previously treated with bevacizumab, bevacizumab treatment can be continued after the first progression.

Non-small cell lung cancer (NSCLC)
First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy
The recommended dose of bevacizumab is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion, in addition to platinum-based chemotherapy for up to 6 cycles of treatment, followed by bevacizumab as a single agent until disease progression of the underlying disease, or until unacceptable toxicity.

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib
EGFR mutation testing should be performed prior to initiation of treatment with the combination of bevacizumab and erlotinib. In patients with EGFR activating mutations, a bevacizumab dose of 15 mg/kg of body weight, given as an intravenous infusion once every three weeks, is recommended when used in addition to erlotinib. The interaction of anti-EGFR antibodies and bevacizumab has not been studied. Bevacizumab should not be administered in combination with EGFR monoclonal antibodies *(see Drug Interactions).*

Continue bevacizumab treatment with erlotinib until progression of the underlying disease or unacceptable toxicity.

Advanced and/or Metastatic Renal Cell Carcinoma (mRCC)
A dose of 10 mg/kg of body weight is recommended, given as an intravenous infusion once every 2 weeks, in combination with interferon alpha.

Continue bevacizumab treatment until progression of the underlying disease or unacceptable toxicity.

Malignant Glioma (WHO Grade IV) - Glioblastoma
A dose of 10 mg/kg of body weight given once every 2 weeks is recommended, given as an intravenous infusion; or a dose of 15mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Continue bevacizumab treatment until progression of the underlying disease or unacceptable toxicity.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Following are the dose recommendations for bevacizumab, to be given as an intravenous infusion:
For front-line treatment, 15 mg/kg of body weight once every 3 weeks is recommended, when given in addition to carboplatin and paclitaxel for up to six cycles of treatment; thereafter continue bevacizumab as a single agent for 15 months or until disease progression, whichever occurs earlier.

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

Platinum-resistant: 10 mg/kg body weight once every 2 weeks is recommended when given in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin.

Alternatively, 15 mg/kg every 3 weeks when given in combination with topotecan given on days 1-5, every 3 weeks.

Continue bevacizumab treatment until progression of the underlying disease or unacceptable toxicity.

Cervical Cancer
Administer bevacizumab in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. 15 mg/kg of body weight of bevacizumab is recommended, given as an intravenous infusion once every 3 weeks.
Continue bevacizumab treatment until progression of the underlying disease or unacceptable toxicity.

Special Dosage Instructions [1,2]
Bevacizumab is not approved for use in patients under the age of 18 years. No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment, since the liver is not a major organ for bevacizumab metabolism or excretion.
Children and adolescents: The safety and efficacy of bevacizumab has not been studied in children and adolescents.
Elderly: Elderly patients do not require any dose adjustment.
Renal impairment: The safety and efficacy of bevacizumab in patients with renal impairment has not been studied.
Hepatic impairment: The safety and efficacy of bevacizumab have not been studied in patients with hepatic impairment.

USE IN SPECIAL POPULATIONS [1,2]
Pregnancy
Female patients of reproductive potential should be advised to use effective contraception during treatment with bevacizumab and for 6 months following the last dose of bevacizumab.

Summary of Risks
Based on findings in animals and the drug's mechanism of action, bevacizumab may cause harm to the foetus *[see Section Mechanism of Action].* A limited number of cases of foetal malformations have been observed in women treated with bevacizumab (Reference Product) alone or in combination with known embryotoxic chemotherapeutics. These reports are however insufficient to determine bevacizumab-associated risks. In pregnant rabbits, intravenous administration of bevacizumab (Reference Product) every 3 days during organogenesis (doses were approximately 1 to 10 times the clinical dose of 10 mg/kg) caused foetal resorptions, decreased maternal and foetal weight gain and multiple congenital malformations; which included corneal opacities and abnormal ossification of the skull and skeleton (including limb and phalangeal defects). Animal models also link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofoetal development, and postnatal development. Pregnant women should be advised of the potential risk to a foetus.

Summary of Animal Data
Decreases in maternal and foetal body weights and increased foetal resorptions were observed in pregnant rabbits given 10 to 100 mg/kg bevacizumab (Reference Product) [approximately 1 to 10 times the clinical dose, 10 mg/kg] every three days during organogenesis (gestation days 6–18). The number of litters containing foetuses with any type of malformation increased in relation to dose (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose); as did the number of litters containing foetuses with foetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and 61.2% for the 100 mg/kg dose). All dose levels showed skeletal deformities. Some abnormalities including meningocele were seen only at the 100 mg/kg dose level. Reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges, were some of the teratogenic effects observed.

Lactation
There is no data to indicate whether bevacizumab is present in human milk; has effects on the breast fed infant; or effects on milk production. The literature suggests that antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts; though human IgG is present in human milk. Nursing women should be advised that breastfeeding is not recommended during treatment with bevacizumab, because of the potential for serious adverse reactions in breastfed infants. Nursing women should not breast-feed for at least six months following the last dose of bevacizumab.

Females of Reproductive Potential
Contraception
Harm to the foetus may result if bevacizumab is administered to a pregnant woman. Female patients of reproductive potential should be advised to use effective contraception during treatment with bevacizumab and for 6 months following the last dose of bevacizumab *[see Pregnancy in this section]*

Infertility
The risk of ovarian failure increases with bevacizumab, and fertility may be impaired. Prior to starting treatment with bevacizumab, female patients of reproductive potential must be informed of the risk of ovarian failure. The long term effects on fertility are unknown. In some patients, ovarian function recovered after bevacizumab (Reference Product) treatment was discontinued *[see Sections Warnings and Precautions, Undesirable Effects].*

Paediatric Use
Bevacizumab is not approved for use in patients under the age of 18. The safety, effectiveness and pharmacokinetic profile of bevacizumab in paediatric patients is not known. There are reports in the literature of non-mandibular osteonecrosis in bevacizumab (Reference Product)-treated patients under 18 years.

There is insufficient data on the safety and efficacy of bevacizumab in children with glioblastoma.

Summary of Animal Data
After 4 to 26 weeks exposure of bevacizumab (Reference Product) at 0.4 to 20 times the recommended human dose of bevacizumab (based on mg/kg and exposure), physeal dysplasia was observed in juvenile cynomolgus monkeys with open growth plates. The physeal dysplasia was partially reversible after stopping treatment, and incidence and severity were related to dose. Arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles, were seen in female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose.

Geriatric Use
In patients aged ≥65 years given bevacizumab (Reference Product), the following severe adverse events occurred more frequently (≥2%) than in younger patients: asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhoea, constipation, anorexia, leukopenia, anaemia, dehydration, hypokalaemia, hypernatremia, arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs); Grade 3-4 thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, nausea, headache and fatigue.

Bevacizumab (Reference Product) had a similar effect on overall survival in elderly patients and younger patients.

CONTRAINDICATIONS [1,2]
- Hypersensitivity to the active substance or to any of the excipients (see Section Composition)
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Pregnancy

WARNINGS AND PRECAUTIONS [1,2]
General
Initiate bevacizumab therapy under the supervision of a physician experienced in cancer treatment/oncologist.

Gastrointestinal Perforations and Fistulae
There is increased risk of developing gastrointestinal perforation (serious and sometimes fatal) and gall bladder perforation when treated with bevacizumab. Gastrointestinal perforation, some fatal, was reported in 0.3% to 3.2% of bevacizumab (Reference Product)-treated patients. Caution should be exercised in patients with metastatic carcinoma of the colon or rectum, as intra-abdominal inflammatory processes may be a risk factor for gastrointestinal perforations. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab.

Bevacizumab should be permanently discontinued in patients with gastrointestinal perforation.

Gastrointestinal-vaginal fistulae
Patients treated with bevacizumab for persistent, recurrent, or metastatic cervical cancer have a higher 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. An additional important risk factor for the development of GI-vaginal fistulae is recurrence of cancer within the field of prior radiation. Patients developing GI vaginal fistulas may also develop bowel obstructions and may require surgical intervention and diverting ostomies *[see Boxed Warning, Section Dose and Method of Administration].*

Non-Gastrointestinal Fistulae
Bevacizumab treatment may increase the risk of patients developing fistulae.
Bevacizumab should be permanently discontinued in patients with tracheoesophageal fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. There is limited information on the continued use of bevacizumab in patients with other fistulae.
Consider discontinuation of bevacizumab for internal fistula not arising in the GI tract.

Wound Healing Complications
Bevacizumab may have adverse effects on wound healing. Serious complications, including anastomotic complications, have occurred; with fatal outcomes. Do not start therapy for at least 28 days after major surgery, or till the surgical wound has healed completely. If a patient experiences wound healing complications, withhold bevacizumab till the wound is fully healed. Patients undergoing elective surgery should have therapy withheld.

Rare cases of necrotising fasciitis have been reported in patients treated with bevacizumab (Reference Product), some of which were fatal. Usually necrotising fasciitis is secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue bevacizumab therapy in patients with necrotising fasciitis. Initiate the appropriate treatment without delay.

Hypertension
Bevacizumab (Reference Product)-treated patients showed a higher incidence of hypertension. Before bevacizumab treatment is initiated, pre-existing hypertension should be properly controlled. No information is available on the effect of bevacizumab in patients who have uncontrolled hypertension at the time of start of therapy. In general, it is recommended that blood pressure be monitored during bevacizumab treatment.

If a patient is receiving cisplatin, the use of diuretics to manage hypertension is not advised. Discontinue bevacizumab permanently if treatment with antihypertensives is not able to control medically significant hypertension, or in cases of hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)
In rare cases, bevacizumab (Reference Product)-treated patients have developed signs and symptoms consistent with the rare neurologic disorder PRES. These include: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The diagnosis of PRES should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Specific symptoms, should be treated, and hypertension should be controlled, along with discontinuation of bevacizumab. There is no information on the safety of reinitiating bevacizumab therapy in patients who have experienced PRES.

Proteinuria
Patients who have had hypertension may have a higher risk of proteinuria if treated with bevacizumab. Proteinuria should be monitored by appropriate urinanalyis, preferably by dipstick, before starting bevacizumab treatment, and during the treatment. If patients develop nephrotic syndrome (NCI-CTCAE v.3) permanently discontinue bevacizumab treatment.

Arterial thromboembolism
Arterial thromboembolic reactions such as cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) had a higher incidence in patients treated with bevacizumab (Reference Product) in combination with chemotherapy, than in patients receiving chemotherapy alone.
Patients who are on bevacizumab plus chemotherapy and have risk factors such as a history of arterial thromboembolism, diabetes or age >65 years are at higher risk of developing arterial thromboembolic reactions. Exercise caution when treating such patients with bevacizumab.
Permanently discontinue bevacizumab in patients with arterial thromboembolic reactions.

Venous thromboembolism
The risk of venous thromboembolic reactions, including pulmonary embolism, is higher in patients under bevacizumab treatment.

Persistent, recurrent, or metastatic cervical cancer patients under treatment with bevacizumab in combination with paclitaxel and cisplatin may have increased risk of venous thromboembolic events.
Discontinue bevacizumab in patients with life-threatening (Grade 4, NCI-CTCAE v.3) thromboembolic reactions, including pulmonary embolism; and closely monitor patients with thromboembolic reactions ≤Grade 3 (NCI-CTCAE v.3).

Haemorrhage
Bevacizumab treatment increases the risk of haemorrhage, especially tumour-associated haemorrhage. Severe or fatal haemorrhage, including haemoptysis, gastrointestinal bleeding, CNS haemorrhage, epistaxis, and vaginal bleeding occurred up to 5 times more frequently in bevacizumab (Reference Product)-treated patients. Discontinued bevacizumab permanently in patients with Grade 3 or 4 bleeding (NCI-CTCAE v.3) during treatment.

Monitor patients for signs and symptoms of CNS bleeding, and discontinue bevacizumab treatment in cases of intracranial bleeding.

Exercise caution when initiating bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or who are receiving a full dose of anticoagulants for the treatment of thromboembolism; as there is no information on the safety profile of bevacizumab in such patients. However, no increase occurred in the rate of ≥Grade 3 bleeding (NCI-CTCAE v.3) in patients who developed venous thrombosis and who were treated with a full dose of warfarin and bevacizumab (Reference Product) concomitantly.

Pulmonary haemorrhage/haemoptysis
There may be a risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis in patients with non-small cell lung cancer treated with bevacizumab. Do not administer bevacizumab to patients with recent pulmonary haemorrhage/haemoptysis (>2.5 ml of red blood).

Congestive heart failure (CHF)
Both asymptomatic and symptomatic CHF has been reported with bevacizumab (Reference Product) treatment. Exercise caution when administering bevacizumab to patients with clinically significant cardiovascular disease, such as pre-existing coronary artery disease, or congestive heart failure.
Patients with risk factors for CHF, treatment with anthracyclines, or radiotherapy to the left chest may be at a higher risk to exhibit CHF with bevacizumab therapy.

Reactions ranging from asymptomatic decline in left ventricular ejection fraction to symptomatic CHF requiring hospitalization have been reported with bevacizumab (Reference Product).

Neutropenia and Infection
Patients treated with some myelotoxic chemotherapy regimens plus bevacizumab (Reference Product) had increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia, in comparison to patients treated with chemotherapy alone. Some cases were fatal. A greater proportion of patients with persistent, recurrent, or metastatic cervical cancer treated with bevacizumab (Reference Product) plus paclitaxel and topotecan experienced grade 3-5 infections than patients treated with paclitaxel and topotecan.

Hypersensitivity reactions/infusion reactions
There is a risk of infusion/hypersensitivity reactions in patients treated with bevacizumab. As recommended for infusions of any therapeutic humanised monoclonal antibody, patients must be closely observed for such reactions during and following administration of bevacizumab. Discontinue therapy and administer appropriate treatment if such reactions occur. A systematic pre-medication is not warranted.

Osteonecrosis of the jaw (ONJ)
Patients treated with bevacizumab (Reference Product) have experienced ONJ. The majority of cases occurred in patients who had prior or concomitant treatment with intravenous bisphosphonates (for which ONJ is an identified risk). Exercise caution when administering bevacizumab and intravenous bisphosphonates (simultaneously or sequentially).

Another identified risk factor is invasive dental procedures. Before starting bevacizumab, a dental examination with appropriate preventive dentistry should be considered. Patients who have received or are receiving intravenous bisphosphonates should be avoid such procedures where possible.

Eye disorders
Unapproved intravitreal use of bevacizumab (Reference Product) has been reported to cause serious ocular adverse reactions including infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in multiple degrees of visual loss, up to and including permanent blindness.

Systemic effects following intravitreal use
Anti-VEGF therapies have been reported to reduce circulating serum VEGF concentration with intravitreal injection. Non-ocular events include haemorrhage and thromboembolic reactions

Ovarian failure/fertility
Bevacizumab may impair fertility in female patients. Before initiating treatment in women of child-bearing potential, discuss fertility preservation strategies.

Laboratory abnormalities
Grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities that occurred with greater incidence in patients treated with bevacizumab (Reference Product) than in the corresponding control groups were hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, and increased international normalised ratio (INR).
Bevacizumab (Reference Product) was associated with transient increases in serum creatinine, with and without proteinuria. The increase in serum creatinine was not associated with more frequent clinical manifestations of renal impairment in bevacizumab (Reference Product)-treated patients.
Bevacizumab treatment may be associated with decreased neutrophil count, decreased white blood cell count and presence of urine protein.

DRUG INTERACTIONS[1,2]
No clinically relevant interaction of co-administered chemotherapy on bevacizumab (Reference Product) pharmacokinetics was observed. No clinically relevant interaction of bevacizumab (Reference Product) was observed on the pharmacokinetics of co-administered interferon alpha 2a, erlotinib (or its active metabolite OSI-420), or the chemotherapies irinotecan (and its metabolite SN38[a]), capecitabine, oxaliplatin, and cisplatin.
In patients with NSCLC, there was no apparent difference in the mean exposure of either carboplatin or paclitaxel, when each was administered alone or in combination with bevacizumab (Reference Product).
In some patients with mRCC, treated with bevacizumab (Reference Product) in combination with sunitinib malate microangiopathic haemolytic anaemia (MAHA) was reported; MAHA was fully reversible upon discontinuation of bevacizumab (Reference Product) and sunitinib malate.

No studies investigating the interaction of anti-EGFR antibodies and bevacizumab have been conducted. Observations suggest increased toxicity with concomitant use of anti-EGFR antibodies compared to bevacizumab plus chemotherapy alone.

Interactions between bevacizumab and radiotherapy have not been established. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy.

UNDESIRABLE EFFECTS [1,2,3]
Summary of the safety profile
Data used for the overall safety profile of bevacizumab (Reference Product) was collected from patients with various types of cancer. These patients were predominantly treated with bevacizumab (Reference Product) in combination with chemotherapy.

The appropriate sections of this document discuss the following serious adverse reactions in greater detail:
- Gastrointestinal Perforations and Fistulae *[see Boxed Warning, Dose and Method of Administration, and Warnings and Precautions]*
- Non-Gastrointestinal Fistula *[see Dose and Method of Administration and Warnings and Precautions]*
- Wound Healing Complications *[see Boxed Warning, Dose and Method of Administration, and Warnings and Precautions]*
- Haemorrhage *[see Boxed Warning, Dose and Method of Administration, and Warnings and Precautions]*
- Arterial Thromboembolism *[see Dose and Method of Administration and Warnings and Precautions]*
- Venous Thromboembolism *[see Dose and Method of Administration and Warnings and Precautions]*
- Hypertension *[see Dose and Method of Administration and Warnings and Precautions]*
- Posterior Reversible Encephalopathy Syndrome *[see Dose and Method of Administration and Warnings and Precautions]*
- Proteinuria *[see Dose and Method of Administration and Warnings and Precautions]*
- Hypersensitivity Reactions/Infusion Reactions *[see Dose and Method of Administration and Warnings and Precautions]*
- Ovarian Failure *[see Warnings and Precautions and Use in Specific Populations]*

The most common adverse reactions (those with incidence >10% and at least twice as frequent as in the control arm) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal haemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Though some of the adverse reactions are commonly seen with chemotherapy, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel. Hypertension, fatigue or asthenia, diarrhoea and abdominal pain were the most frequently observed adverse reactions in patients.

In some patients, adverse reactions led to the discontinuation of bevacizumab (Reference Product).

The occurrence of hypertension and proteinuria are likely to be dose-dependent, according to the clinical safety data.

The following sections categorise adverse reactions by frequency category.
Very common (≥1/10): Febrile neutropenia, paronychia, leukopenia, neutropenia, thrombocytopenia, anorexia, peripheral sensory neuropathy, dysarthria, headache, dysguesia, eye disorder, lacrimation increased, hypertension, thromboembolism (venous), dyspnoea, rhinitis, rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, abdominal pain, wound healing complications, exfoliative dermatitis, dry skin, skin discoloration, arthralgia, proteinuria, ovarian failure, asthenia, fatigue, pyrexia, pain, mucosal inflammation, weight decreased.

Common (≥1/100 to <1/10): Sepsis, abscess, cellulitis, infection, urinary tract infection, anaemia, lymphopenia, hypersensitivity, infusion reactions, dehydration, cerebrovascular accident, syncope, somnolence, congestive heart failure, supraventricular tachycardia, thromboembolism (arterial), pulmonary haemorrhage/haemoptysis, pulmonary embolism, epistaxis, hypoxia, dysphonia, gastrointestinal perforation, intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae, gastrointestinal disorder, proctalgia, palmar-plantar erythrodysaesthesia syndrome, fistula, myalgia, muscular weakness, back pain, pelvic pain, lethargy, dry mouth, haemorrhage, deep vein thrombosis.

Uncommon (≥1/1,000 to <1/100): biliary fistula, bronchopleural fistula

Rare (≥1/10,000 to <1/1,000): Necrotising fasciitis, posterior reversible encephalopathy syndrome

Very rare (<1/10,000): Hypertensive encephalopathy

Not known (cannot be estimated from the available data): Renal thrombotic microangiopathy; pulmonary hypertension; nasal septum perforation; gastrointestinal ulcer; gallbladder perforation; osteonecrosis of the jaw; non-mandibular osteonecrosis; foetal abnormalities; comanifestations of hypersensitivity/infusion reactions (dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting); polyserositis; mesenteric venous occlusion; eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): permanent loss of vision, endophthalmitis (infectious and sterile), intraocular inflammation, retinal detachment, increased intraocular pressure, haemorrhage including conjunctival, vitreous haemorrhage or retinal haemorrhage, vitreous floaters, ocular hyperaemia, ocular pain or discomfort; intestinal necrosis; anastomotic ulceration; pancytopenia, acne, anaphylactic and anaphylactoid-type reactions, angina, anxiety, bladder fistula, blurred vision, cerebral infarction, deafness, decreased appetite, dizziness, dyspepsia, gastritis, gastroesophageal reflux disease, gastrointestinal hemorrhage, melaena, gingival hemorrhage, gingival pain, gingivitis, hemolytic anemia, hemorrhagic stroke, hypoalbuminemia, hypomagnesemia, intra-abdominal thrombosis, neutropenic infections, peripheral edema, pneumonitis, rectal fistula, renal failure, renal fistula, thrombosis, tinnitus, upper respiratory tract infection, vaginal fistula, tracheo-esophageal fistula, vitreous opacity.

Immunogenicity
Bevacizumab, like all therapeutic proteins, has the potential to induce an immune response. In colon carcinoma patients treated with bevacizumab (Reference Product), a small number of patients were positive for anti-bevacizumab antibodies, of whom some were positive for neutralizing antibodies. These antibody responses have unknown clinical significance.

In a double-blind, randomized, active-controlled, parallel-arm, comparative PK, efficacy, safety and immunogenicity study of **KRABEVA®** and bevacizumab (Reference Product), both in combination with capecitabine and oxaliplatin in patients with metastatic colorectal cancer (mCRC), the immunogenicity of **KRABEVA®** and bevacizumab (Reference Product) were found to be similar.

OVERDOSE[1,2]
20 mg/kg IV is the highest dose tested in humans, and was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

SHELF-LIFE
Please refer to carton/label.

STORAGE AND HANDLING INFORMATION
Store vials at 2°C - 8°C. Keep out of reach of children.
Keep vial in the outer carton in order to protect from light.

KRABEVA® does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.
KRABEVA® is stable in and compatible with sterile saline solution (0.9% sodium chloride solution) for 48 hours under aseptic conditions and 24 hours under standard laboratory conditions at room temperature. From a microbiological point of view, the product should be used immediately.

- Administer/mix **KRABEVA®** using normal saline solution only.
- Do not prepare or administer in dextrose solution.
- **KRABEVA®** must not be administered as an intravenous push or bolus.
- To ensure the prepared solution is sterile, a healthcare professional should prepare **KRABEVA®** using aseptic technique.
- As with all parenteral medicinal products, **KRABEVA®** should be inspected visually for particulate matter and discolouration prior to administration.
- Withdraw the necessary amount of **KRABEVA®** and dilute to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection.
- Keep the concentration of the final **KRABEVA®** solution within the range of 1.4 mg/ml to 16.5 mg/ml.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- **KRABEVA®** is not for intravitreal administration.

Incompatibilities
No incompatibilities have been observed between **KRABEVA®** and polyvinyl chloride or polyolefine bags or infusion sets. Dilute **KRABEVA®** using normal saline solution only. Do not prepare or administer in dextrose solution.

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

PACKAGING INFORMATION
KRABEVA® 100 mg/4mL – Pack of 1 Vial (4 mL):
KRABEVA® 100 mg (25 mg/ml) is filled in a 6 mL USP type 1 glass vial, plugged with a 20 mm flurotec chlorobutyl serum rubber stopper, and sealed with flip-off seal of aluminium and plastic (polypropylene).

KRABEVA® 400 mg/16mL- Pack of 1 Vial (16 mL):
KRABEVA® 400 mg (25 mg/mL) is filled in a 20 mL USP type 1 glass vial, plugged with a 20 mm flurotec chlorobutyl serum rubber stopper, and sealed with flip-off seal of aluminium and plastic (polypropylene).

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **DrugSafety@biocon.com.**

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Note: Unless otherwise stated, material contained herein related to studies, tests, treatment and applications are taken from publicly available information.