SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RIQVIVA 100 (concentrate for solution for intravenous infusion)

RIQVIVA 400 (concentrate for solution for intravenous infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains bevacizumab 25 mg/mL.

RIQVIVA 100 contains 100 mg bevacizumab per 4 mL

RIQVIVA 400 contains 400 mg bevacizumab per 16 mL

Contains sugar (α, α trehalose dihydrate) .

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RIQVIVA is a clear or opalescent, colourless to slightly brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RIQVIVA is indicated for:

Metastatic colorectal cancer

RIQVIVA in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic adenocarcinoma of the colon or rectum.

Locally recurrent or metastatic breast cancer

RIQVIVA in combination with paclitaxel is indicated for first-line treatment of adult patients with locally recurrent or metastatic cancer of the breast.

RIQVIVA in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic adenocarcinoma of the breast in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with RIQVIVA in combination with capecitabine.

Advanced, metastatic or recurrent adenocarcinoma of the lung

RIQVIVA in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent adenocarcinoma of the lung.

RIQVIVA, in combination with erlotinib, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

Advanced and/or metastatic Renal Cell Cancer (mRCC)

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

Cervical cancer

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

Malignant Glioma (WHO Grade IV)- Glioblastoma

RIQVIVA , in combination with radiotherapy and temozolomide is indicated for the treatment of adult patients with newly diagnosed glioblastoma. RIQVIVA , as a single agent, or in combination with irinotecan, is indicated for the treatment of patients with glioblastoma after relapse or disease progression.

4.2 Posology and method of administration

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of RIQVIVA, administered as an intravenous infusion, is as follows:

First-line treatment:

5 mg/kg of body weight given once every 2 weeks or 7,5 mg/kg of body weight given once every 3 weeks.

Second-line treatment:

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.

Metastatic breast cancer (mBC)

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

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

Adenocarcinoma of the lung

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

The recommended dose of RIQVIVA is 7,5 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

The recommended dose of RIQVIVA when used in addition to carboplatin chemo therapy is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Advanced and/or metastatic renal cell cancer (mRCC)

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

Malignant glioma (WHO Grade IV)- Glioblastoma

The recommended dose of RIQVIVA, administered as an intravenous infusion, is as follows:

Newly diagnosed glioblastoma: RIQVIVA (10 mg/kg of body weight given once every 2 weeks) is administered in combination with temozolomide and radiotherapy for 6 weeks.

Following a 4 week treatment break, RIQVIVA (10 mg/kg of body weight given once every 2 weeks) is re-initiated in combination with temozolomide for up to 6 cycles of 4 week duration:
After administration of up to 6 cycles of combined RIQVIVA and temozolomide, RIQVIVA (15 mg/kg of body weight given once every 3 weeks) is continued as a single agent until disease progression.

Cervical Cancer

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

Special populations

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 with hepatic impairment.
Paediatric population: The safety and efficacy have not been studied in children.

Method of administration:

RIQVIVA must be prepared ,using the aseptic technique to ensure the sterility, and administered under the supervision of a healthcare professional experienced in the use of antineoplastic medicines.
Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration. The safety and efficacy of alternating or switching between RIQVIVA and products that are biosimilar but not deemed interchangeable have not been established. Therefore, the benefit-risk of alternating or switching need to be carefully considered.
The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

The initial dose of RIQVIVA should be administered following chemotherapy; all subsequent doses can be given before or after chemotherapy.

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. It is recommended that RIQVIVA treatment be continued until progression of the underlying causes.

4.3 Contraindications

- Hypersensitivity to:
    - the active substance (bevacizumab) or to any of the excipients,
    - Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy and lactation (see section 4.6).
- Concomitant use with sunitinib (see section 4.5).
- Intravitreal use.

4.4 Special warnings and precautions for use

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 (see section 4.8).

GI-vaginal Fistulae in study GOG-0240

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

Non-GI Fistulae

Patients may be at increased risk for the development of fistulae when treated with bevacizumab.

Permanently discontinue RIQVIVA. in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of RIQVIVA in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of RIQVIVA 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. RIQVIVA 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. Safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting RIQVIVA treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. RIQVIVA 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 RIQVIVA. The safety of reinitiating RIQVIVA 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 (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1,4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism

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 RIQVIVA.

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

Venous thromboembolism

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment.

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

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

Haemorrhage

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

Patients with untreated CNS metastases were routinely excluded from studies 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 trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and RIQVIVA 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 RIQVIVA treatment, as such patients were excluded from trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly (NCI-CTCAE v.3).

Pulmonary haemorrhage/haemoptysis

Patients with non-small cell lung cancer treated with bevacizumab may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2,5 mL of red blood) should not be treated with RIQVIVA.

Aneurysms and artery dissections

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

Congestive heart failure (CHF)/ Cardiomyopathy

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with RIQVIVA (see section 4.8).

Neutropenia

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

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 humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (ONJ)

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

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

Eye disorders

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

Systemic effects following intravitreal use

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

Ovarian failure/fertility

Bevacizumab may impair female fertility Therefore, fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with RIQVIVA (see sections 4.6 and 4.8).

Paediatric use

Bevacizumab is not approved for use in patients under the age of 18 years. The safety and efficacy of bevacizumab in this population have not been established. Addition of bevacizumab to standard of care did not demonstrate clinical benefit in paediatric patients in two phase II clinical trials: one in paediatric high-grade glioma and one in paediatric metastatic rhabdomyosarcoma or nonrhabdomyosarcoma soft tissue sarcoma.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab.

Traceability

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

4.5 Interaction with other medicines and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

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

Combination of bevacizumab and sunitinib malate

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

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

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

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

Radiotherapy

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

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use highly effective contraception during and for up to 6 months after treatment.

Pregnancy

RIQVIVA is contraindicated during pregnancy (see section 4.3).

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Angiogenesis has been shown to be critically important to foetal development.

The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. IgGs are known to cross the placental barrier, and RIQVIVA may inhibit angiogenesis in the foetus.

In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8).

Lactation

As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development, women must discontinue breastfeeding during therapy and not breastfeed for at least six months following the last dose of RIQVIVA.

Fertility

Bevacizumab may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with RIQVIVA.

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see "Ovarian failure/fertility" under sections 4.4 and 4.8). A sub-study with 295 premenopausal women has shown a higher incidence (32/82 patients) of new cases of ovarian failure in the bevacizumab group compared to the control group (2/78 patients). After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients (25/29). Long term effects of the treatment with bevacizumab on fertility are unknown. Ovarian failure was defined as the presence of all of the following for females who were premenopausal at randomisation: a negative serum β-HCG pregnancy test, ≥ 3 months of amenorrhea, and serum follicle-stimulating hormone (FSH) of ≥ 30 MIU/mL.

Men should be advised not to father a child while receiving treatment with RIQVIVA and must use effective contraception during and for at least 3 months after treatment with RIQVIVA.

4.7 Effects on ability to drive and use machines

There is evidence that bevacizumab treatment may result in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

4.8 Undesirable effects

a. Summary of the safety profile:

The most serious adverse reactions were:

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

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

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

b. Tabulated list of adverse reactions

Table 1 lists adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class. Side effects are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping side effects are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1: Tabulated list of adverse reaction-Adverse Reactions by Frequency

System organ class	**Frequency**
Infections and infestations	
Paronychia, Sepsis, Abscess Cellulitis, Infection, Urinary tract infection.	Frequent
Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (see section 4.4)	Frequency unknown
Blood and lymphatic system disorders	
Febrile neutropenia, Leukopenia, Thrombocytopenia, Neutropenia, Anaemia, Lymphopenia.	Frequent
Immune system disorders	

Hypersensitivity and infusion reactions: with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting. (See also hypersensitivity, infusion reactions below).	Frequency unknown
Metabolism and nutrition disorders	
Anorexia, Hypomagnesaemia, Hyponatraemia, Dehydration.	Frequent
Nervous system disorders	
Peripheral sensory neuropathy, Dysarthria, Headache, Dysguesia, Cerebrovascular accident, Syncope, Somnolence.	Frequent
Hypertensive encephalopathy, Posterior reversible encephalopathy syndrome (PRES) (see section 4.4).	Less Frequent
Eye disorders	
Eye disorder, Lacrimation increased.	Frequent
Cardiac disorders	
Congestive heart failure, Supraventricular tachycardia.	Frequent
Vascular disorders	
Hypertension, Thrombo-embolism (arterial), Haemorrhage, Deep vein thrombosis.	Frequent
Renal thrombotic microangiopathy, clinically manifested as proteinuria (For further information on proteinuria see section 4.4)	Frequency unknown

Respiratory, thoracic and mediastinal disorders	
Dyspnoea, Rhinitis, Epistaxis, Cough, Pulmonary embolism, Hypoxia.	Frequent
Pulmonary hypertension, Nasal septum perforation, Dysphonia.	Frequency unknown
Gastrointestinal disorders	
Diarrhoea, Nausea, Vomiting, Abdominal pain, Constipation, Stomatitis, Rectal haemorrhage, Intestinal perforation,	Frequent
Ileus, Intestinal obstruction, Recto-vaginal fistulae, Gastrointestinal disorder, Proctalgia.	
Gastrointestinal ulcer.	Frequency unknown
Endocrine disorders	
Ovarian failure.	Frequent
Hepatobiliary disorders	
Gallbladder perforation.	Frequency unknown
Skin and subcutaneous tissue disorders	
Exfoliative dermatitis, Dry skin, Skin discoloration, Palmar-plantar erythrodysaesthesia syndrome.	Frequent

Musculoskeletal and connective tissue disorders	
Arthralgia, Myalgia, Muscular weakness, Back pain.	Frequent
Osteonecrosis of the jaw have been observed in bevacizumab treated patients mainly in association with prior or concomitant use of bisphosphonates (see section 4.4). Cases of osteonecrosis at sites other than the jaw, have been observed in bevacizumab treated paediatric patients (see section 4.4).	Frequency unknown
Renal and urinary disorders	
Proteinuria, Urinary tract infection.	Frequent
Congenital, familial, and genetic disorder	
Foetal abnormalities, treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.5).	Frequency unknown
General disorders and administration site conditions	
Asthaenia, Fatigue, Pyrexia, Pain, Mucosal inflammation, Lethargy.	Frequent
Reproductive System and Breast disorder	
Pelvic pain.	Frequent
Investigations	
Weight decreased.	Frequent

Osteonecrosis observed in paediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the tabulated adverse effect section as neither CTC grade nor reporting rate were available from published data.

c. Further information on selected serious side effects:

Gastro-intestinal perforations and Fistulae (also refer to section 4.4):

Bevacizumab has been associated with serious cases of gastro-intestinal (GI) perforation or fistulae (see also below, under heading Fistulae). Gastro-intestinal perforation have been reported in clinical trials with an incidence of less than 1 % in patients with metastatic adenocarcinoma of the breast or lung, up to 2,0 % in metastatic renal cell cancer, newly diagnosed glioblastoma, or ovarian cancer and up to 2,7 % (including gastrointestinal fistula and abscess) in patients with

metastatic colorectal adenocarcinoma. Cases of GI perforations have also been observed in patients with relapsed glioblastoma.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, GI perforations, (all grades) were reported in 3,2 % of patients, all of whom had a history of prior pelvic radiation.

Fatal outcome was reported in approximately a third of serious cases of gastro-intestinal perforations, which represents between 0,2 to 1 % of all bevacizumab treated patients. 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.

Non-GI Fistulae (see section 4.4):

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 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. Less frequent reports of other types of fistulae that involve areas of the body other than the gastro-intestinal tract (e.g., bronchopleural, and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Wound healing (see section 4.4):

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials. In clinical trials of metastatic adenocarcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery 28 to 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). Cases of serious wound healing complications have been reported during bevacizumab use, some of which had a fatal outcome (see section 4.4). In trials in locally recurrent and metastatic adenocarcinoma of the breast, Grade 3 -to 5 wound healing complications were observed in 1,1 % of patients receiving bevacizumab compared with up to 0,9 % of patients in the control arms. In a study of patients with relapsed glioblastoma (study AVF3708g), the incidence of postoperative wound healing complications (including craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3,6 % in patients treated with single-agent bevacizumab . In patients with newly diagnosed glioblastoma the incidence of Grade 3 to 5 post-operative wound healing complications (including complications following craniotomy) was 3,3 % when treated with bevacizumab in combination with chemotherapy and radiotherapy, compared with 1,6 % when treated with chemotherapy and radiotherapy alone.

Nasal Septum Perforations:

Cases of nasal septum perforations have been reported in patients treated with bevacizumab (see section 4.4).

Hypertension:

In clinical trials, the overall incidence of hypertension (all grades) ranged up to 42,1 % in bevacizumab treated patients in clinical trials compared with up to 14 % in those treated with

comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medication) 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 a study on patients who received bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, all grade hypertension was observed in 77,3 % compared to 14,3 % of patients treated with erlotinib alone. Grade 3 hypertension was 60,0 % in patients treated with bevacizumab in combination with erlotinib compared to 11,7 % in patients

treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

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

Cases of hypertensive encephalopathy have been reported, some of which were fatal. The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephaolopathy Syndrome (see section 4.4):

There have been reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephaolopathy Syndrome (PRES), a rare neurological disorder, see section 4.4.

Proteinuria (see section 4.4):

In clinical trials, proteinuria has been reported within the range of 0,7 % to 54,7 % of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. 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 studies urine protein levels of 2 g /24 hrs led to the holding of bevacizumab until recovery to < 2 g/24 hrs.

Haemorrhage (see section 4.4):

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 to 5 bleeding events ranged from 0,4 % to 6,9 % in bevacizumab treated patients, compared with up to 4,5 % of patients in chemotherapy control group. The haemorrhagic events that have been observed in clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g., epistaxis).

Tumour-associated haemorrhage (see section 4.4):

Major or massive pulmonary haemorrhage/ haemoptysis has been observed primarily in studies in patients with adenocarcinoma of the lung. Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab , 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 studies, while patients with unknown tumour histology were included.

In patients with adenocarcinoma of the lung, all grade events 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 to 5 events have been observed in up to 2,3 % of patients treated with bevacizumab plus chemotherapy as compared with < 1 % with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.3) and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical studies. Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In a study, CNS haemorrhage was reported in 2,4 % (2/84) of patients in the bevacizumab alone arm (Grade 1); and in 3,8 % (3/79) of patients treated with bevacizumab and irinotecan (Grades 1, 2 and 4).

Mucocutaneous haemorrhage:

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50 % of bevacizumab treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g., epistaxis) may be dose-dependent. There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival or vaginal bleeding.

Thromboembolism (see section 4.4):

Arterial thromboembolism:

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

In clinical trials, the overall incidence of arterial thromboembolic events ranged up to 5,9 % in the bevacizumab containing arms compared with up to 1,7 % 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 a clinical trial, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan, arterial thromboembolic events were observed in 11 % (11/100) of patients compared to 5,8 % (6/104) in the chemotherapy control group.

In an uncontrolled clinical trial in patients with relapsed glioblastoma, arterial thromboembolic events were observed in up to 6,3 % (5/79) of patients who received bevacizumab in combination with irinotecan compared to up to 4,8 % (4/84) of patients who received bevacizumab alone.

Venous thromboembolism:

The incidence of venous thromboembolic events in clinical trials was similar in patients receiving bevacizumab in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis. In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2,8 % to 17,3 % of bevacizumab-treated patients compared with 3,2 % to 15,6 % in the controls. In the clinical trials in NSCLC an increase of the overall incidence of venous thromboembolic events with Grade 3 to 5 severity was observed of up to 7,8 % in the bevacizumab containing arm compared with 4,9 % in the chemotherapy control arm. One event (0,2 %) was fatal on the bevacizumab containing arm compared to none in the carboplatin-paclitaxel arm.

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, Grade 3 to 5 venous thromboembolic events have been reported in up to 10,6 % of patients treated with chemotherapy and bevacizumab compared with up to 5,4% in patients with chemotherapy alone.

In a clinical trial in patients with newly diagnosed glioblastoma, Grade 3 to 5 venous thromboembolic events were observed in 7,3 % of patients treated with bevacizumab in combination with chemotherapy and radiotherapy, compared to 8,0 % of patients treated with chemotherapy and radiotherapy alone.

Hypersensitivity, infusion reactions:

Patients may be at risk of developing infusion/hypersensitivity reactions (see section 4.8). Close observation of the patient during and following the administration of bevacizumab is recommended. If a reaction occurs, the infusion should be discontinued and appropriate medical therapy administered. A systemic premedication is not warranted.

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5 % in bevacizumab -treated patients) – see section 4.8.

Congestive Heart Failure (CHF):

In clinical trials with bevacizumab , congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. 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 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.

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 (see section 4.5).

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 i.v. bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when bevacizumab and i.v. 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 i.v. bisphosphonates invasive dental procedures should be avoided, if possible.

Infections:

In a clinical trial of bevacizumab in combination with chemotherapy plus radiotherapy for the treatment of patients with newly diagnosed glioblastoma, the incidence of all Grade and Grade 3 to 5 infections was 54,4 % and 12,8 % in the bevacizumab plus chemotherapy and radiotherapy arm versus 39,1 % and 7,8 % in the chemotherapy plus radiotherapy only arm, respectively.

Elderly Patients:

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events, 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 to 4 leucopenia and thrombocytopenia; and all grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see sections 4.4 and 4.8, Thromboembolism sections). No increase in the incidence of other reactions, including gastro-intestinal perforation, wound healing complications, congestive heart failure, and haemorrhage was observed in elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

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 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 PT (prothrombin time), international normalised ratio (INR).

Clinical trials have shown that increases in serum creatinine (ranging between 1,5 to 1,9 times baseline level), both with and without proteinuria, are associated with the use of bevacizumab . The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis (some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness; including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for intravenous administration) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment; Retinal pigment epithelial tear; Increased intraocular pressure; Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage; Conjunctival haemorrhage.

An observational claims database study comparing unapproved intravitreal bevacizumab to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for bevacizumab (adjusted HR: 1,82; 99 % CI: 1,20, 2,76) (Incidence 0,46 events per 100 patients per year; comparator 0,26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1,11; 99 % CI: 1,01, 1,23) (Incidence 6,33 events per 100 patients per year; comparator 5,64 events per 100 patients per year).

Following variable and non-validated methods in compounding, storage, and handling of bevacizumab , serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

Systemic Events (reported from unapproved intravitreal use)

An observational claims database study comparing unapproved intravitreal bevacizumab to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of haemorrhagic stroke for bevacizumab (adjusted HR: 1,57; 99 % CI: 1,04, 2,37) (Incidence 0,41 events per 100 patients per year; comparator 0,26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1,11; 99 % CI: 1,01, 1,23)

(Incidence 6,03 events per 100 patients per year; comparator 5,51 events per 100 patients per year).

A second observational study found similar results for all-cause mortality. A randomised controlled clinical trial comparing unapproved bevacizumab to an approved treatment for patients with wet age-related macular degeneration has reported an increased risk of serious systemic adverse events for bevacizumab, most of which resulted in hospitalisation (adjusted risk ratio 1,29; 95 % CI: 1,01, 1,66) (Incidence 24,1 %; comparator 19,0 %).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

The side effects profile will be exaggerated and aggravated. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01F G01

5.1 Pharmacodynamic properties

Mechanism of action

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumours thereby inhibiting tumour growth.
Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

5.2 Pharmacokinetic properties

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

Absorption

Not applicable.

Distribution

The typical value for central volume (V_C) was 2,73 L and 3,28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1,69 L and 2,35 L for female and male patients respectively, when bevacizumab is co-administered with anti- neoplastic agents. After correcting for body weight, male patients had a larger V_C (+ 20 %) than female patients.

Metabolism

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

Elimination

The value for clearance is, on average, equal to 0,188 and 0,220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+17 %) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

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

Pharmacokinetics in special populations

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

Renal or hepatic impairment:

No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with renal or hepatic impairment, since the kidneys and the liver are not a major organs for bevacizumab metabolism or excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

α, α-trehalose dihydrate

polysorbate 20

sodium phosphate (monobasic, monohydrate)

sodium phosphate (dibasic, anhydrous)

water for injection

6.2 Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5 %). Therefore RIQVIVA infusions should not be administered or mixed with glucose solutions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Storage of unopened vials

Store in a refrigerator (between 2 °C to 8 °C).

DO NOT FREEZE. DO NOT SHAKE.

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

Storage of diluted product

RIQVIVA does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution**.**

Chemical and physical in-use stability has been demonstrated at 5 ± 3 °C or 30 ± 2 °C up to 48 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

RIQVIVA 100: 5 mL clear tubular USP Type I glass vial with a 20 mm butyl rubber stopper with fluorotic coating and a blue 20 mm flip-off aluminium seal containing 100 mg of bevacizumab.

RIQVIVA 400: 20 mL clear tubular USP Type I glass vial with a 20 mm butyl rubber stopper with fluorotic coating and a blue 20 mm flip-off aluminium seal containing 400 mg of bevacizumab**.**

6.6 Special precautions for disposal <and other handling>

RIQVIVA infusions should not be administered or mixed with dextrose or glucose solutions (see "Incompatibilities" section 6.2 above).

Do not administer as an intravenous push or bolus.

RIQVIVA should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare RIQVIVA. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0,9 % sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1,4 to 16,5 mg/mL.

Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Disposal of unused/expired medicines:

The release of pharmaceuticals in the environment should be minimised. 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.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

RIQVIVA 100: 56/26/0604

RIQVIVA 400: 56/26/0605

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 November 2023

10. DATE OF REVISION OF TEXT

15 August 2024