AUSTRALIAN PRODUCT INFORMATION

CYRAMZA® (RAMUCIRUMAB) CONCENTRATE FOR INTRAVENOUS INFUSION

1. NAME OF THE MEDICINE

Ramucirumab [rmc].

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYRAMZA is available as a concentrate in 10 mL or 50 mL single-use vials. Each vial contains either 100 mg ramucirumab in 10 mL (10 mg/mL) or 500 mg ramucirumab in 50 mL (10 mg/mL). CYRAMZA contains the excipients histidine, histidine hydrochloride monohydrate, glycine, sodium chloride, polysorbate 80 and water for injections.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for intravenous infusion vial.

CYRAMZA is a sterile, clear to slightly opalescent and colourless to slightly yellow solution without visible particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CYRAMZA, in combination with paclitaxel, is indicated for the treatment of adult patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.

CYRAMZA, as monotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy when treatment in combination with paclitaxel is not appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Do not administer ramucirumab as an intravenous push or bolus.

After dilution and preparation, CYRAMZA is administered as an intravenous infusion.

Only use sterile sodium chloride (0.9%) solution for injection as a diluent. Do not use dextrose as a diluent.

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

Premedication

Premedication is recommended with a histamine H1 antagonist (e.g. promethazine) intravenously prior to administration of ramucirumab.

If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR), premedication **must** be given for all subsequent infusions. If a patient has a second Grade 1 or 2 IRR, administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medications: promethazine hydrochloride (intravenously), paracetamol, and dexamethasone (see **Section 4.2 Dose and method of administration, Dose or Infusion Rate Adjustments**).

Gastric Adenocarcinoma

Ramucirumab in combination with paclitaxel

The recommended dose of ramucirumab is 8 mg/kg on Days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28-day cycle. Prior to each paclitaxel infusion, patients should have a complete blood count and blood chemistry performed to evaluate hepatic function. Criteria to be met prior to each paclitaxel administration are provided in Table 1.

Table 1. Criteria to be Met Prior to Each Paclitaxel Administration

	CRITERIA
Neutrophils	**Day 1**: ≥ 1.5 x 10^9/L **Days 8 and 15**: ≥ 1.0 x 10^9/L
Platelets	**Day 1**: ≥ 100 x 10^9/L **Days 8 and 15**: ≥ 75 x 10^9/L
Bilirubin	≤ 1.5 x upper limit of normal value (ULN)
AST/ALT	**No liver metastases**: ALT/AST ≤ 3 x ULN **Liver metastases**: ALT/AST ≤ 5 x ULN

Ramucirumab single agent

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks administered as an intravenous infusion over approximately 60 minutes (maximum infusion rate 25 mg/min).

Dose or Infusion Rate Adjustments

Infusion-related Reactions

Reduce the ramucirumab infusion rate by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a Grade 1 or 2 IRR [per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (see **Section 4.2 Dose and method of administration; Premedication**). Immediately and permanently discontinue ramucirumab for Grade 3 or 4 IRRs (see **Section 4.4 Special warnings and precautions for use**).

Hypertension

Monitor blood pressure during treatment with ramucirumab and treat as clinically indicated. Temporarily suspend ramucirumab for severe hypertension until controlled with medical management (see **Section 4.4 Special warnings and precautions for use**).

Posterior Reversible Encephalopathy Syndrome

Permanently discontinue ramucirumab in patients who experience Posterior Reversible Encephalopathy Syndrome (PRES) (see **Section 4.4 Special warnings and precautions for use**).

Proteinuria

Monitor for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein level is ≥ 2+, perform a 24-hour urine collection. Temporarily discontinue ramucirumab administration if the urine protein level is ≥ 2 g/24 hours. Resume treatment at a reduced dose level (to 6 mg/kg every two weeks) once the urine protein level returns to <2 g/24 hours. A second dose reduction to 5 mg/kg every two weeks) is recommended if a urine protein level ≥ 2 g/24 hours reoccurs.

Permanently discontinue ramucirumab therapy if the urine protein level is >3 g/24 hours or in the setting of nephrotic syndrome (see **Section 4.8 Adverse effects (Undesirable Effects)**).

Paclitaxel

Paclitaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. For NCI-CTCAE Grade 4 haematological toxicity or Grade 3 paclitaxel-related nonhaematological toxicity, it is recommended to reduce the paclitaxel dose by 10 mg/m2 for all following cycles. A second reduction of 10 mg/m2 is recommended if these toxicities persist or reoccur. See paclitaxel prescribing information for additional dosage and administration recommendations.

See paclitaxel prescribing information for premedication requirements.

Impaired Wound Healing

Ramucirumab therapy should be temporarily discontinued for at least 4 weeks prior to elective surgery. Ramucirumab therapy should be temporarily discontinued if there are wound healing complications, until the wound is fully healed (see **Section 4.4 Special warnings and precautions for use**).

Permanently discontinue ramucirumab therapy in the event of:

Severe arterial thromboembolic events, gastrointestinal perforations, NCI CTCAE Grade 3 or 4 bleeding (see **Section 4.4 Special warnings and precautions for use**).

Fistula

Ramucirumab therapy should be permanently discontinued in the event of spontaneous development of fistula (see **Section 4.4 Special warnings and precautions for use**).

Use in Renal Impairment

There have been no formal studies with ramucirumab in patients with renal impairment. No dose reductions are recommended.

Use in Hepatic Impairment

There have been no formal studies with ramucirumab in patients with hepatic impairment. No dose reductions are recommended (see **Section 4.4 Special warnings and precautions for use**).

Instructions for Use/Handling

Do not administer or mix with dextrose solution.

1. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.
2. Each vial is intended for use in one patient on one occasion only and discard any residue. Inspect the content of the vials prior to dilution for particulate matter and discolouration (see **Section 3 Pharmaceutical Form** for description). If particulate matter or discolourations are identified, discard the vial.
3. Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL concentrate of ramucirumab. Dilute ramucirumab as required to achieve a final volume of 250 mL. Only use sterile sodium chloride (0.9%) solution for injection as a diluent.

<u>In case of prefilled intravenous infusion container usage:</u>

Based on the calculated volume of ramucirumab, remove the corresponding volume of sterile sodium chloride (0.9%) solution for injection from the prefilled 250 mL intravenous container. Aseptically transfer the calculated volume of ramucirumab to the intravenous container. The final volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

<u>In case of empty intravenous infusion container usage:</u>

Aseptically transfer the calculated volume of ramucirumab into an empty intravenous container. Add a sufficient quantity of sterile sodium chloride (0.9%) solution for injection to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medication.

4. Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.
5. Discard any unused portion of ramucirumab left in a vial, as the product contains no preservatives.
6. Administer via infusion pump. A separate line with a protein sparing 0.22 micron filter must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

4.3 CONTRAINDICATIONS

CYRAMZA is contraindicated in patients with known hypersensitivity to ramucirumab or to any of the excipients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Neutropenia

Severe neutropenia has been reported in clinical trials with ramucirumab in combination with chemotherapy. Blood counts should be monitored in patients receiving ramucirumab in combination with chemotherapy.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischaemia have been reported in clinical trials. Permanently discontinue ramucirumab in patients who experience a severe ATE (see **Section 4.2 Dose and method of administration**).

Hypertension

An increased incidence of severe hypertension was observed in clinical trials. Patients with uncontrolled hypertension were excluded from the clinical trials and ramucirumab should not be commenced until their hypertension is controlled. Monitor blood pressure regularly, and withhold ramucirumab for patients who develop hypertension until it is adequately controlled. In clinical trials, hypertension was controlled in most instances with standard antihypertensives. Permanently discontinue ramucirumab if medically significant hypertension cannot be controlled with antihypertensive therapy (see **Section 5.2 Pharmacokinetic properties**).

Aneurysms and artery dissections

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

Heart Failure

In pooled data from ramucirumab clinical trials, heart failure was reported at a numerically higher incidence in patients receiving ramucirumab in combination with a variety of chemotherapy regimens, or erlotinib, compared to chemotherapy or erlotinib alone.

Patients should be monitored for clinical signs and symptoms of heart failure during treatment, and suspension of treatment should be considered if clinical manifestations develop.

Gastrointestinal Perforations

Cases, sometimes fatal, of gastrointestinal perforation have been reported in patients treated with ramucirumab. Permanently discontinue ramucirumab in patients who experience gastrointestinal perforations (see **Section 4.2 Dose and method of administration**).

Severe Bleeding

Severe gastrointestinal haemorrhage including fatal events were reported in patients with gastric adenocarcinoma treated with ramucirumab in combination with paclitaxel. Ramucirumab is an antiangiogenic therapy and may increase the risk of severe bleeding. Ramucirumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding (see **Section 4.2 Dose and method of administration**). Blood counts and

coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding.

Infusion-Related Reactions

Infusion-related reactions (IRR) were reported in clinical trials with ramucirumab. The majority of events occurred during or following a first or second ramucirumab infusion. Monitor patients during the infusion for signs of hypersensitivity reactions with resuscitation equipment readily available. Symptoms included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnoea, wheezing, hypoxia, and paraesthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Immediately and permanently discontinue ramucirumab for Grade 3 or 4 IRRs (see **Section 4.2 Dose and method of administration**).

Impaired Wound Healing

The impact of ramucirumab has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, ramucirumab did not impair wound healing in monkeys. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld for at least 4 weeks prior to scheduled surgery. The decision to resume ramucirumab following surgical intervention should be based on clinical judgement of adequate wound healing.

If a patient develops wound healing complications during therapy, discontinue ramucirumab until the wound is fully healed (see **Section 4.2 Dose and method of administration**).

Posterior reversible encephalopathy syndrome (PRES)/ Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of PRES, including fatal cases, have been rarely reported in patients receiving ramucirumab.

PRES (or RPLS) has been reported with a rate of <0.1% in clinical studies and in the post-market setting with ramucirumab (see **Section 4.8 Adverse effects (Undesirable Effects)**). PRES is a neurological disorder which can present with seizures, headache, nausea/vomiting, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal.

Confirm the diagnosis of PRES with MRI and discontinue ramucirumab in patients who develop PRES. Permanently discontinue ramucirumab in patients who experience PRES.

Fistula

Patients may be at increased risk for the development of fistula when treated with ramucirumab. Ramucirumab treatment should be discontinued in patients who develop fistula (see **Section 4.2 Dose and method of administration**).

Use in hepatic impairment

Ramucirumab should be used with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. In these patients, ramucirumab should only be used if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure

(see **Section 4.2 Dose and method of administration** and **Section 5.2 Pharmacokinetic properties**).

Use in renal impairment

There are no safety data available for patients with severe renal impairment (eGFR < 30 ml/min) treated with ramucirumab (see **Section 4.2 Dose and method of administration**).

Use in the elderly

In the REGARD and RAINBOW studies there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No reduction in starting dose is recommended

Paediatric use

The safety and effectiveness of ramucirumab has not been established in patients under 18 years of age.

In cynomolgus monkeys that received 5-50 mg/kg IV ramucirumab weekly for 39 weeks, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested. At the lowest dose the relative exposure in monkeys was less than the anticipated clinical exposure based on AUC.

Effects on laboratory tests

Changes in laboratory test parameters (including hyponatraemia, hypokalaemia, liver function disturbances and myelosupression) may occur with ramucirumab therapy as a single agent or in combination with chemotherapy. Electrolyte, liver function tests and a full blood count should be monitored, including during monotherapy (see also **Section 4.4 Special warnings and precautions for use; Neutropenia** and **Section 4.4 Special warnings and precautions for use; Use in hepatic impairment**).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interactions were observed between ramucirumab and paclitaxel. The pharmacokinetics (PK) of paclitaxel was not affected when coadministered with ramucirumab and the PK of ramucirumab was not affected when coadministered with paclitaxel.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reproductive toxicity studies with ramucirumab have not been performed, however, animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction. Based on ramucirumab's mechanism of action, it is likely that ramucirumab will inhibit angiogenesis and result in adverse effects on fertility, including impaired ovulation, endometrial and placental function, and corpus luteum development. Treatment-related increases in follicular mineralisation of the ovary were also observed in monkeys that received ramucirumab weekly for 39 weeks at clinically relevant exposures.

There are no data on the effect of ramucirumab on human fertility. Female fertility is likely to be compromised during treatment with ramucirumab based on studies in animals.

Use in pregnancy

Pregnancy Category D

There are no adequate or well controlled studies of the use of ramucirumab in pregnant women or animals. IgG antibodies cross the placental barrier and ramucirumab may therefore inhibit angiogenesis in the developing foetus. As angiogenesis is critical to maintenance of pregnancy and to foetal development, this inhibition of angiogenesis may result in adverse effects on pregnancy, including foetal death and impaired heart, lung and kidney development. Ramucirumab is not recommended during pregnancy, and women of childbearing potential should be advised to use effective contraception. Women of childbearing potential or women who become pregnant during treatment should be counselled as to the potential risks of ramucirumab to the foetus and for maintaining pregnancy. Based on the half-life of ramucirumab, women of childbearing potential should be advised to avoid becoming pregnant while receiving ramucirumab and for at least 3 months after the last dose of ramucirumab.

Use in lactation.

It is unknown whether ramucirumab is excreted in human milk. Excretion in milk and oral absorption is expected to be low. As a risk to newborns/infants cannot be excluded, breast-feeding should be discontinued during treatment with ramucirumab and for at least 3 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on ability to drive or use machinery have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Ramucirumab in combination with Paclitaxel for Gastric Adenocarcinoma

The following table provides the frequency and severity of adverse drug reactions (ADRs) reported in ≥ 5% of ramucirumab-treated patients in RAINBOW, a Phase 3 gastric adenocarcinoma study of ramucirumab in combination with paclitaxel. Frequency of Adverse Drug Reactions – Very Common ≥ 10%. Refer to NCI CTCAE Criteria (Version 4.0) for each Grade of toxicity.

Table 2. ADRs occurring at incidence rate ≥ 5% in patients receiving ramucirumab in combination with paclitaxel for gastric adenocarcinoma

System Organ Class	Frequency	Event	Ramucirumab Plus Paclitaxel (N=327)		Placebo Plus Paclitaxel (N=329)	
			All Grades Toxicity (%)	Grade ≥ 3 Toxicity (%)	All Grades Toxicity (%)	Grade ≥ 3 Toxicity (%)
Blood and Lymphatic System Disorders	Very Common	Leucopenia	33.9	17.4	21.0	6.7
	Very Common	Neutropenia	54.4	40.7	31.0	18.8
	Very Common	Thrombocytopenia	13.1	1.5	6.1	1.8
Gastrointestinal Disorders	Very Common	Diarrhoea	32.4	3.7	23.1	1.5
	Very Common	Gastrointestinal Haemorrhage Events[a]	10.1	3.7	6.1	1.5
	Very Common	Stomatitis	19.6	0.6	7.3	0.6
General Disorders and Administration Site Disorders	Very Common	Fatigue/Asthenia	56.9	11.9	43.8	5.5
	Very Common	Oedema Peripheral	25.1	1.5	13.7	0.6
Metabolism and Nutrition Disorders	Very Common	Hypoalbuminaemia	11.0	1.2	4.9	0.9
Renal and Urinary Disorders	Very Common	Proteinuria	16.8	1.2	6.1	0.0
Respiratory, Thoracic, and Mediastinal Disorders	Very Common	Epistaxis	30.6	0.0	7.0	0.0
Vascular Disorder	Very Common	Hypertension[b]	25.1	14.7	5.8	2.7

[a] MedRA preferred terms included anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.

[b] Includes hypertensive cardiomyopathy.

Clinically relevant ADRs reported in ≥ 1% and <5% of the ramucirumab plus paclitaxel-treated patients in RAINBOW were gastrointestinal perforation (1.2% ramucirumab plus paclitaxel versus 0.3% for placebo plus paclitaxel) and sepsis (3.1% ramucirumab plus paclitaxel versus 1.8% placebo plus paclitaxel).

Single-agent Ramucirumab for Gastric Adenocarcinoma

The following table provides the frequency and severity of adverse drug reactions (ADRs) reported in ≥ 5% of ramucirumab-treated patients in REGARD, a single-agent, placebo-controlled Phase 3 gastric adenocarcinoma study.

Frequency of Adverse Drug Reactions – Very common ≥ 10%; Common ≥ 1% and <10%. Refer to NCI CTCAE Criteria (Version 4.0) for each Grade of toxicity.

Table 3. ADRs occurring at incidence rate ≥ 5% in patients receiving single-agent ramucirumab for gastric adenocarcinoma

System Organ Class	Frequency	Event	Ramucirumab (N=236)		Placebo (N=115)	
			All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Gastrointestinal Disorders	Very Common	Abdominal Pain[a]	28.8	5.9	27.8	2.6
	Very Common	Diarrhoea	14.4	0.8	8.7	1.7
Metabolism and Nutrition Disorders	Common	Hypokalaemia	5.9	2.1	5.2	0.9
	Common	Hyponatremia	5.5	3.4	1.7	0.9
Nervous System Disorders	Common	Headache	9.3	0	3.5	0
Vascular Disorders	Very Common	Hypertension	16.1	7.6	7.8	2.6

[a] Includes hepatic pain.

Clinically relevant ADRs reported in ≥ 1% and <5% of the ramucirumab-treated patients in REGARD were: neutropenia, arterial thromboembolic events, intestinal obstruction, epistaxis, and rash.

Clinically relevant reactions (including Grade ≥ 3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical trials were proteinuria, infusion-related reactions, and gastrointestinal perforations (see **Section 4.2 Dose and method of administration** and **Section 4.4 Special warnings and precautions for use**).

Post-marketing Experience

Nervous system disorders - Rare (< 0.1% and > 0.01%): Posterior reversible encephalopathy syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

Spontaneous Data

The following adverse drug reactions are based on postmarketing reports.

Blood and lymphatic system disorders:

Thrombotic microangiopathy: Rare (≥0.01% - <0.1%)

Neoplasms benign, malignant and unspecified:

Haemangioma: Common (≥1.0% - <10%)

Nervous system disorders:

Posterior reversible encephalopathy syndrome: Rare (≥0.01% - <0.1%) (See **Section 4.2 Dose and method of administration** and **Section 4.4 Special warnings and precautions for use**).

Respiratory, thoracic and mediastinal disorders:

Dysphonia: Common (≥1.0% - <10%)

Endocrine disorders:

Hypothyroidism: Common (≥1.0% - <10%)

Vascular disorders

Cases of aneurysms and artery dissections, sometimes fatal, have been reported with VEGFR pathway inhibitors.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no data on overdose in humans. Ramucirumab has been administered in a Phase 1 study up to 10 mg/kg every two weeks without reaching a maximum tolerated dose. In case of overdose, use supportive therapy. There is no known antidote to ramucirumab overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

VEGF Receptor 2 is the key mediator of VEGF induced angiogenesis. Ramucirumab is a human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells.

Immunogenicity

Overall, there was a low incidence of both treatment emergent anti-drug antibodies and neutralising antibodies among ramucirumab-treated patients, and no correlation with safety outcomes in these patients. There was no relationship between immunogenicity and infusion-related reactions (IRRs) or treatment emergent adverse events. There is insufficient data to evaluate the effects of anti-drug antibodies (ADAs) on the efficacy or safety of ramucirumab.

Clinical trials

RAINBOW

RAINBOW, a multinational , randomised, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel, was conducted in 665 patients with locally advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the gastro-oesophageal junction [GEJ]) following platinum- or fluoropyrimidine-containing chemotherapy with or

without anthracycline. The primary endpoint was overall survival (OS) and secondary endpoints included progression-free survival (PFS) and overall response rate (ORR). Patients were required to have experienced disease progression during, or within 4 months after the last dose of first-line therapy with ECOG performance status (PS) 0-1.

Patients were randomised in a 1:1 ratio to receive ramucirumab plus paclitaxel (n=330) or placebo plus paclitaxel (n=335). Randomisation was stratified by geographic region, time to progression from the start of first-line therapy (<6 months versus ≥6 months) and disease measurability. Ramucirumab at 8 mg/kg or placebo was administered by intravenous infusion every 2 weeks (on days 1 and 15) of a 28-day cycle. Paclitaxel at 80 mg/m2 was administered by intravenous infusion on days 1, 8 and 15 of each 28-day cycle.

A majority (75%) of patients randomised in the study received prior platinum/fluoropyrimidine combination therapy without an anthracycline. The remainder (25%) received prior platinum/fluoropyrimidine combination therapy with an anthracycline. Two-thirds of the patients experienced disease progression while still on first-line therapy (66.8%). Baseline patient demographics and disease characteristics were generally balanced between the study arms. The median age was 61 years; 71% of the patients were male; 61% were Caucasian, 35% Asian; the ECOG PS was 0 for 39% of patients, 1 for 61% of patients; 81% of patients had measurable disease and 79% had gastric adenocarcinoma; 21% had GEJ adenocarcinoma. The majority of patients (76%) had experienced disease progression within 6 months from the start of first-line therapy.

For patients treated with ramucirumab plus paclitaxel the median duration of therapy was 19 weeks, and for patients treated with placebo plus paclitaxel the median duration of therapy was 12 weeks. The median relative dose intensity of ramucirumab was 98.6% and of placebo was 99.6%. The median relative dose intensity of paclitaxel was 87.7% for the ramucirumab plus paclitaxel arm and 93.2% for the placebo plus paclitaxel arm. A similar percentage of patients discontinued treatment due to adverse events: 12% of patients treated with ramucirumab plus paclitaxel compared with 11% of patients treated with placebo plus paclitaxel. Post discontinuation systemic anti-cancer therapy was given to 47.9% of patients receiving ramucirumab plus paclitaxel and 46.0% of patients receiving placebo plus paclitaxel.

Refer to Table 4 shown below for efficacy outcomes on Overall Survival (OS), Progression Free Survival (PFS) and Objective Response Rate (ORR).

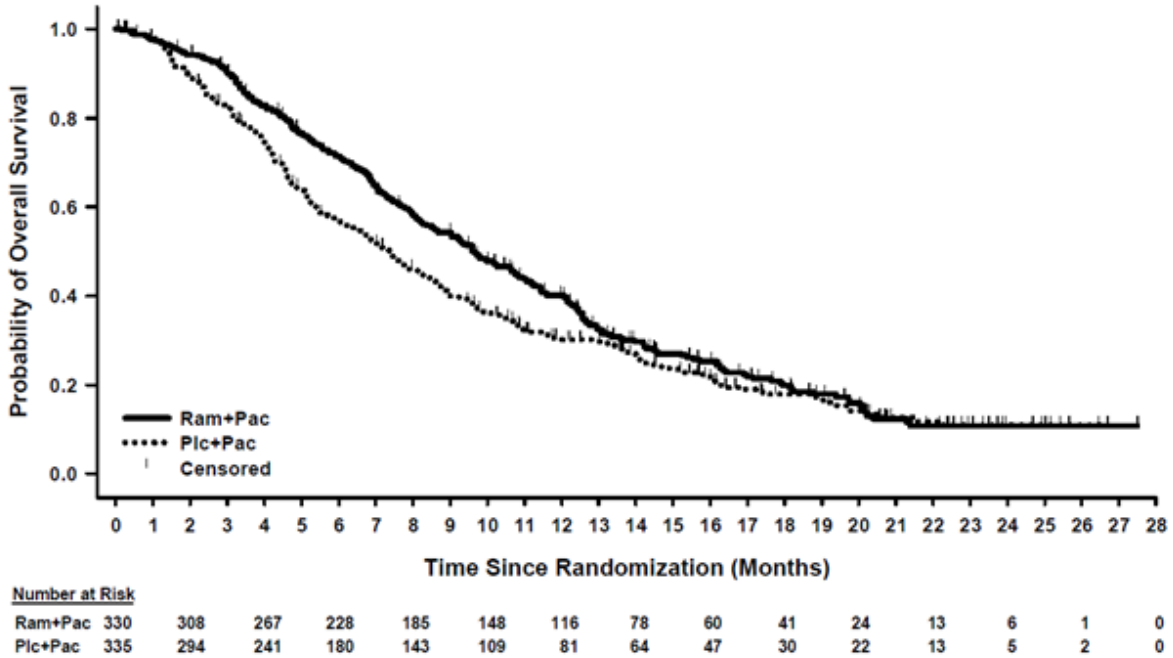
Table 4. Summary of Efficacy Data – Intent to Treat (ITT) Population

	Ramucirumab + Paclitaxel N = 330	**Placebo + Paclitaxel N = 335**
Overall Survival, months		
Median (95% CI)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)
Hazard Ratio (95% CI)	0.807 (0.678, 0.962)	
Stratified Log-rank p-value	0.0169	
Progression-Free Survival, months		
Median (95% CI)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)
Hazard Ratio (95% CI)	0.635 (05.36, 0.752)	
Stratified Log-rank p-value	<0.0001	
Objective Response		
Objective Response Rate (CR+PR) 95% CI	27.9% (23.3%, 33.0%)	16.1% (12.6%, 20.4%)
Odds Ratio (95% CI)	2.14 (1.45, 3.16)	
Stratified CMH p=value	0.0001	

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response, CMH = Cochran-Mantel-Haenszel
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥2 patients.

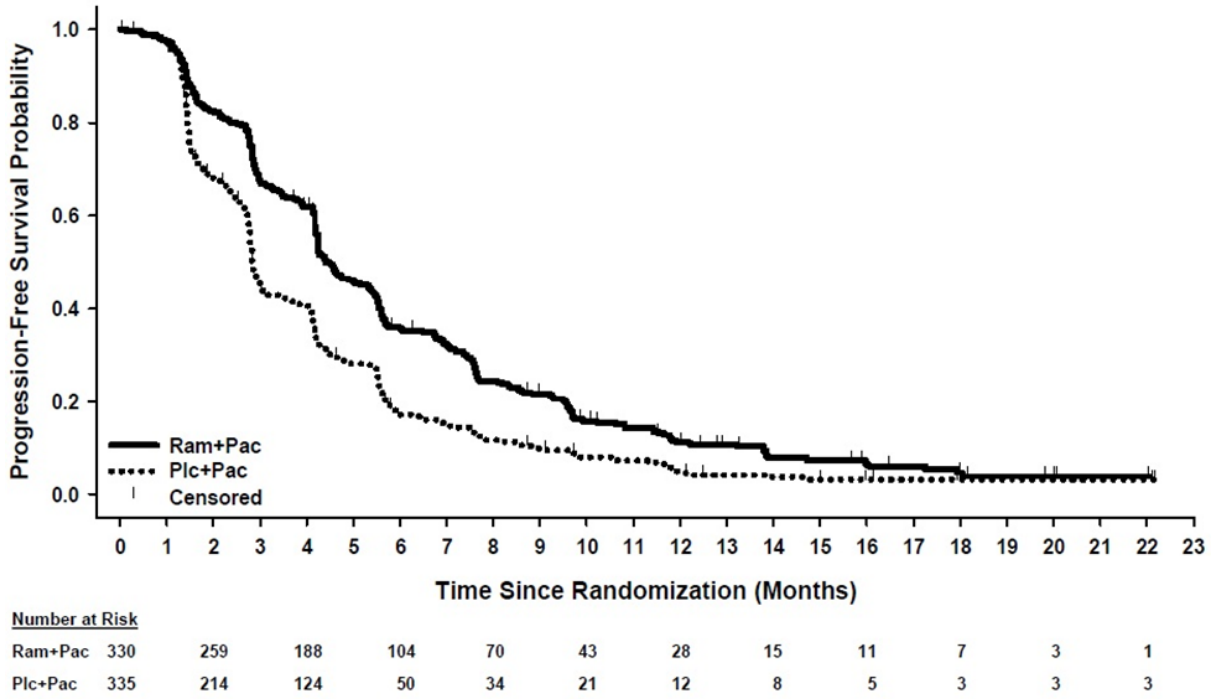
Patients with ECOG score ≥2 were excluded from the pivotal studies, therefore the safety and efficacy of Cyramza in this patient population is unknown.

Figure 1. Kaplan-Meier Curves of Overall Survival for Ramucirumab plus Paclitaxel versus Placebo plus Paclitaxel in RAINBOW



Abbreviations: Pac = paclitaxel; Plc = placebo; Ram = ramucirumab.

Figure 2. Kaplan-Meier Curves of Progression-free Survival for Ramucirumab plus Paclitaxel versus Placebo plus Paclitaxel in RAINBOW



Abbreviations: Pac = paclitaxel; Plc = placebo; Ram = ramucirumab.

REGARD

REGARD, a multinational, randomised, double-blind, multicentre study of ramucirumab plus best supportive care (BSC) versus placebo plus BSC, was conducted in 355 patients with locally advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the gastro-oesophageal junction [GEJ]) following platinum- or fluoropyrimidine-containing chemotherapy. The primary endpoint was overall survival (OS) and secondary endpoints included progression-free survival (PFS) and 12 week PFS rate. Patients were required to have experienced disease progression during first-line treatment or within 4 months after the last dose of first-line therapy for metastatic disease, or during adjuvant treatment or within 6 months after the last dose of adjuvant therapy, and had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1. Patients were randomised in a 2:1 ratio to receive an intravenous infusion of ramucirumab 8 mg/kg (n=238) or placebo (n=117) every 2 weeks. Randomisation was stratified by weight loss over the prior 3 months (≥10% versus <10%), geographic region, and location of the primary tumour (gastric versus GEJ).

Patients enrolled in the study received prior platinum/fluoropyrimidine combination therapy (81%), fluoropyrimidine-containing regimens without platinum (15%), or platinum-containing regimens without fluoropyrimidine (4%). With respect to baseline demographics and disease characteristics: the median age was 60 years; 70% of patients were male; 77% were Caucasian, 16% Asian; the ECOG PS was 0 for 28% of patients and 1 for 72% of patients; 91% of patients had measurable disease; and 75% of patients had gastric adenocarcinoma, 25% adenocarcinoma of the GEJ. The majority of patients (85%) had experienced disease progression during first-line treatment or following first-line therapy

and the remainder during or following adjuvant therapy. Patients received a median of 4 cycles (range 1-34) of ramucirumab and 3 cycles (range 1-30) of placebo.

The median relative dose intensity of ramucirumab was 99.6%. Eleven percent of patients treated with ramucirumab and 6% of patients on placebo discontinued therapy due to adverse events. Overall survival was statistically significantly improved in patients receiving ramucirumab as compared with patients receiving placebo (hazard ratio [HR] 0.776; 95% CI: 0.603 to 0.998; p=0.0473), corresponding to a 22% reduction in the risk of death and an increase in median survival to 5.2 months for ramucirumab from 3.8 months for placebo. Progression-free survival was statically significantly improved in patients receiving ramucirumab as compared with patients receiving placebo (HR 0.483; 95% CI: 0.376 to 0.620; p<0.0001), corresponding to a 52% reduction in the risk of progression or death and an increase in median PFS to 2.1 months for ramucirumab from 1.3 months for placebo. Efficacy results are shown in Table 2.

Table 5. Summary of Efficacy Data – Intent to Treat (ITT) Population

	Ramucirumab N=238	**Placebo N=117**
Overall Survival, months		
Median (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
Hazard Ratio (95% CI)	0.776 (0.603, 0.998)	
Stratified Log-rank p-value	0.0473	
Progression-Free Survival, months		
Median (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
Hazard Ratio (95% CI)	0.483 (0.376, 0.620)	
Stratified Log-rank p-value	<0.0001	
12-week PFS rate % (95% CI)	40.1 (33.6, 46.4)	15.8 (9.7, 23.3)

Abbreviations: CI = confidence interval

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥2 patients

Patients with ECOG score ≥2 were excluded from the pivotal studies, therefore the safety and efficacy of Cyramza in this patient population is unknown.

Figure 3. Kaplan-Meier Curves of Overall Survival for Ramucirumab versus Placebo in REGARD

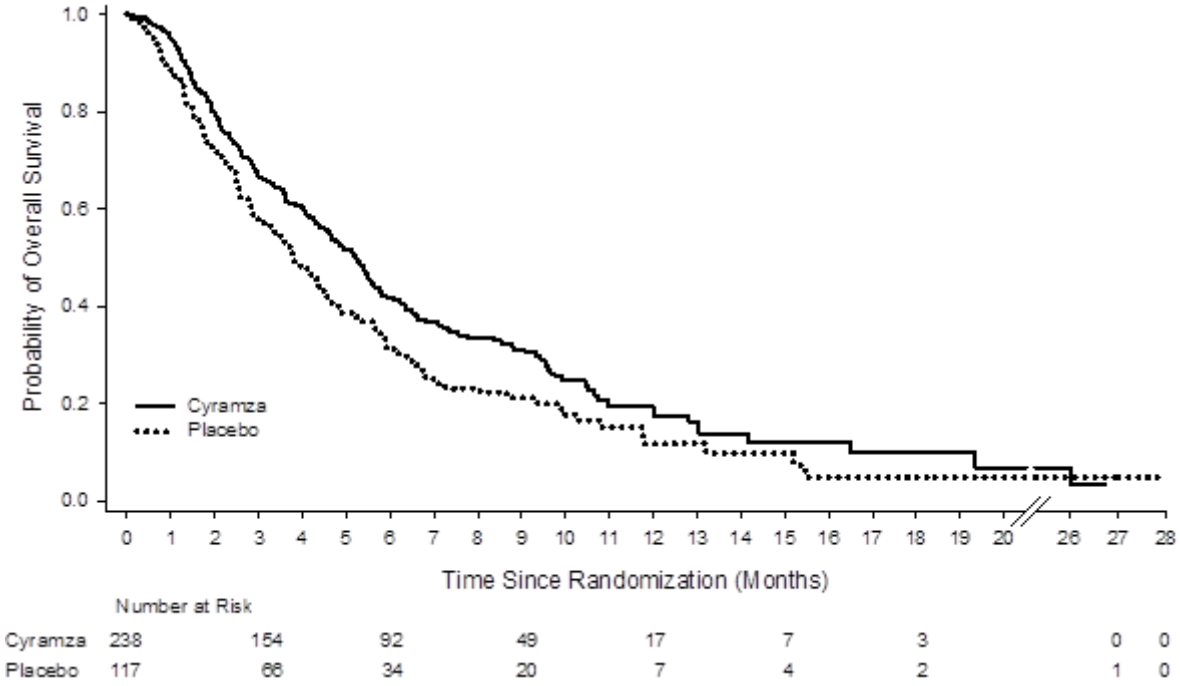
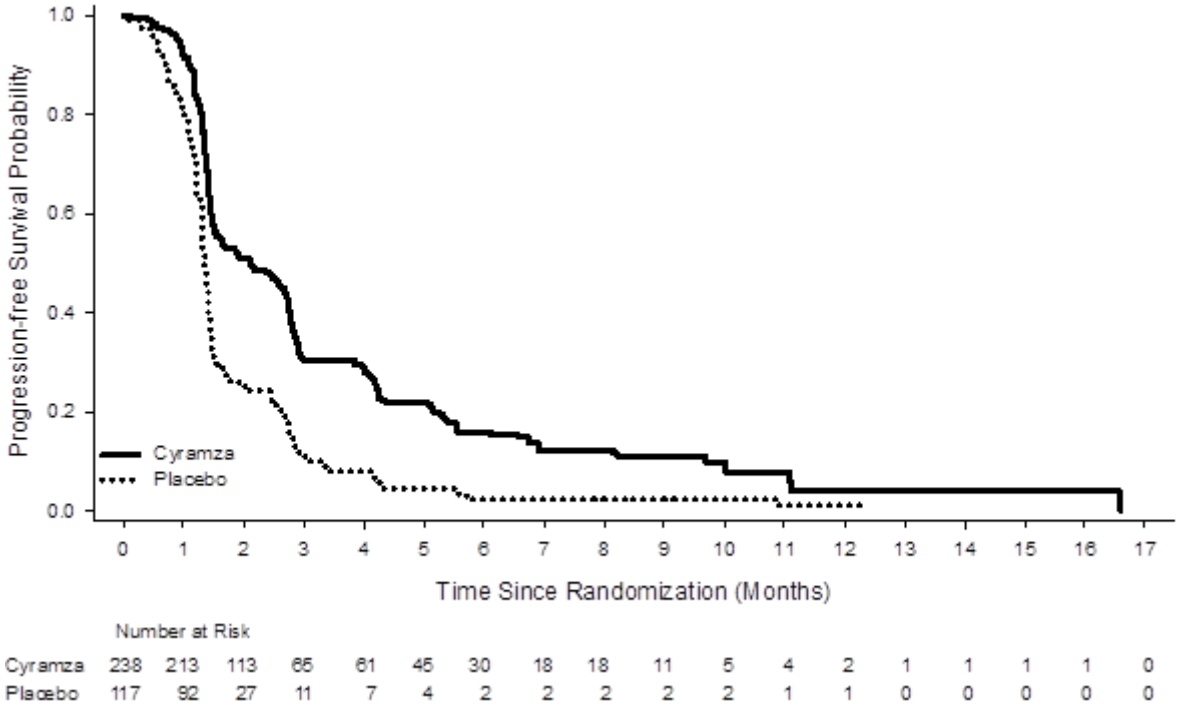


Figure 4. Kaplan-Meier Curves of Progression-free Survival for Ramucirumab versus Placebo in REGARD



5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ramucirumab is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

Following the dose regimen of 8 mg/kg ramucirumab (single agent) every 2 weeks, the geometric means of ramucirumab C_{min} were 49.5 µg/mL (range of 6.3-228 µg/mL) and 74.4 µg/mL (range of 13.8-234 µg/mL) prior to administration of the fourth and seventh dose, respectively, in serum from patients with advanced gastric adenocarcinoma. Based on population pharmacokinetic approach (PopPK) on patients with various types of cancers, the mean (% coefficient of variation [CV%]) volume of distribution of ramucirumab at steady state (V_{ss}) was 5.4 L (15%).

Metabolism

The metabolism of ramucirumab has not been studied. Antibodies are principally cleared by catabolism.

Excretion

Based on a PopPK analysis, the mean (CV%) clearance of ramucirumab was 0.015 L/hour (30%) and the mean elimination half-life was 14 days (20%).

Special Populations

PopPK analysis suggested age, gender, body weight, and race had no effect on the PK of ramucirumab.

Elderly Patients

Based on the results of the PopPK analysis, there was no difference in ramucirumab exposure in patients ≥65 years of age compared to patients <65 years old.

Renally Impaired Patients

Based on the results of the PopPK analysis, ramucirumab exposure was similar in patients with mild renal impairment (calculated creatinine clearance [CrCl] ≥60 to <90 mL/min), moderate renal impairment (CrCl ≥30 to <60 mL/min), or severe renal impairment (CrCl ≥15 to <30 mL/min) as compared to patients with normal renal function (CrCI ≥90 mL/min).

Hepatically Impaired patients

Based on the results of the PopPK analysis, ramucirumab exposure was similar in patients with mild hepatic impairment (total bilirubin >1.0-1.5 times upper limit of normal [ULN] and any AST, or total bilirubin ≤1.0 ULN and AST> ULN) or moderate hepatic impairment (total bilirubin >1.5-3.0 times ULN and any AST) compared to patients with normal hepatic function (total bilirubin and AST ≤ULN). No PK data were available from patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

Exposure response relationships: RAINBOW

Exposure-response analyses indicated that efficacy and specific measures of safety of ramucirumab were correlated with ramucirumab exposure. Increased efficacy, as measured

by improvements in OS and PFS, was associated with increasing ramucirumab exposure range which was produced by 8 mg/kg ramucirumab given on days 1 and 15 of a 28 day cycle. The incidences of Grade ≥3 hypertension, neutropenia, and leucopenia were also increased with higher ramucirumab exposure (see **Section 4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use**).

Exposure response relationship: REGARD

Based on limited PK data, exposure-response analysis suggested that efficacy of ramucirumab was correlated with ramucirumab exposure.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No animal studies have been performed to test ramucirumab for potential genotoxicity.

Carcinogenicity

No animal studies have been performed to test ramucirumab for potential carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

See **Section 2 Qualitative and Quantitative Composition**.

6.2 INCOMPATIBILITIES

Do not administer or mix with dextrose solution.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

CYRAMZA should be stored in a refrigerator between 2 to 8 °C. Do not freeze. Do not shake the vial.

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

Chemical and physical in-use stability of CYRAMZA in sodium chloride 9 mg/mL (0.9%) solution for injection has been demonstrated for: 24 hours at 2 to 8 °C or for 4 hours at 25 °C. Do not freeze or shake the infusion solution.

6.5 NATURE AND CONTENTS OF CONTAINER

CYRAMZA is available as 10 mL and 50 mL concentrates in a vial (Type I glass) with a chlorobutyl rubber stopper, an aluminium seal and polypropylene cap.

CYRAMZA is available in packs* of 1 of 10 mL and 1 vial of 50 mL.

*Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

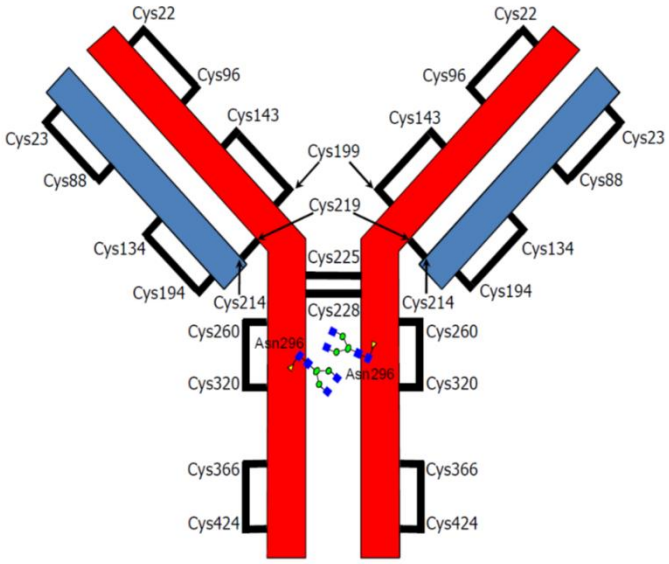
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Ramucirumab is a human IgG1 monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology.

Ramucirumab is a human monoclonal antibody composed of 2 heavy chain (γ1-chain) molecules consisting of 446 amino acid residues each and 2 light chain (κ-chain) molecules consisting of 214 amino acid residues each.



The average molecular mass of ramucirumab with the predominant form of N-linked glycosylation is 146,756 Da.

CAS number
947687-13-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Medicine

8. SPONSOR

Eli Lilly Australia Pty. Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

9. DATE OF FIRST APPROVAL

23 July 2015

10. DATE OF REVISION

21 September 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor address update

CYRAMZA® is a registered trademark of Eli Lilly and Company