S4

1. NAME OF THE MEDICINE

Cyramza 100 mg, 10 mg/ml, concentrate for solution for infusion

Cyramza 500 mg, 10 mg/ml, concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 10 mg ramucirumab.

Each 10 ml vial contains 100 mg of ramucirumab.

Each 50 ml vial contains 500 mg of ramucirumab.

Ramucirumab is a human IgG1 monoclonal antibody produced by recombinant DNA technology.

Excipient with known effect:

Each 10 ml vial contains approximately 17 mg sodium.

Each 50 ml vial contains approximately 85 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear to slightly opalescent and colourless to slightly yellow solution, pH 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastric cancer

Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy (see section 5.1).

Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate (see section 5.1).

Colorectal cancer (CRC)

Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

Non-small cell lung cancer (NSCLC)

Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations (see section 5.1).

Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy.

Hepatocellular carcinoma (HCC)

Cyramza monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

4.2 Posology and method of administration

Cyramza therapy must be initiated and supervised by physicians experienced in oncology.

Posology

Gastric cancer and gastro-oesophageal junction (GEJ) adenocarcinoma

Cyramza in combination with paclitaxel

The recommended dose of Cyramza 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/m^2 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 infusion 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)
Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT)	**No liver metastases:** ALT/AST ≤3 x ULN **Liver metastases:** ALT/AST ≤5 x ULN

Cyramza as a single agent

The recommended dose of Cyramza as a single agent is 8 mg/kg every 2 weeks.

Colorectal cancer

The recommended dose of Cyramza is 8 mg/kg every 2 weeks administered by intravenous infusion, prior to FOLFIRI administration. Prior to chemotherapy, patients should have a complete blood count. Criteria to be met prior to FOLFIRI are provided in Table 2.

Table 2: Criteria to be met prior to FOLFIRI administration

	Criteria
Neutrophils	≥1,5 x 10^9/L
Platelets	≥100 x 10^9/L
Chemotherapy-related gastrointestinal toxicity	≤ Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE])

Non-small cell lung cancer

Cyramza in combination with erlotinib for the treatment of NSCLC with activating EGFR mutations

The recommended dose of ramucirumab in combination with erlotinib is 10 mg/kg every two weeks.

EGFR mutation status should be determined prior to initiation of treatment with ramucirumab and erlotinib using a validated test method. See erlotinib prescribing information for the posology and method of administration of erlotinib.

Cyramza in combination with docetaxel for the treatment of NSCLC after platinum-based chemotherapy.

The recommended dose of Cyramza is 10 mg/kg on day 1 of a 21 day cycle, prior to docetaxel infusion.

The recommended dose of docetaxel is 75 mg/m^2 administered by intravenous infusion over

approximately 60 minutes on day 1 of a 21 day cycle. For East Asian patients, a reduced docetaxel starting dose of 60 mg/m^2 on day 1 of a 21 day cycle should be considered. See docetaxel prescribing information for specific dosing advice.

Hepatocellular carcinoma

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks.

Alpha fetoprotein (AFP) testing in HCC

Patients with HCC should be selected based on a serum AFP concentration of ≥ 400 ng/ml with a validated AFP test prior to ramucirumab treatment (see section 5.1).

Duration of treatment

It is recommended that treatment be continued until disease progression or until unacceptable toxicity has occurred.

Premedication

Premedication is recommended with a histamine H1 antagonist (for example diphenhydramine) prior to infusion of Cyramza. If a patient experiences a Grade 1 or 2 infusion-related reaction premedication must be given for all subsequent infusions. If a patient experiences a second Grade 1 or 2 infusion-related reaction (IRR) administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medicinal products: an intravenous histamine H1 antagonist (for example diphenhydramine hydrochloride), paracetamol and dexamethasone.

See professional information for paclitaxel, for components of FOLFIRI and for docetaxel, as applicable, for premedication requirements and additional information.

***Posology adjustments for* Cyramza**

Infusion-related reactions

The infusion rate of Cyramza should be reduced by 50 % for the duration of the infusion and all subsequent infusions if the patient experiences a grade 1 or 2 IRR. Cyramza should be immediately and permanently discontinued in the event of a grade 3 or 4 IRR (see section 4.4).

Hypertension

The blood pressure of patients should be monitored prior to each Cyramza administration and treated as clinically indicated. Cyramza therapy should be temporarily discontinued in the event of severe hypertension, until controlled with medical management. If there is medically significant hypertension that cannot be controlled safely with antihypertensive therapy, Cyramza therapy should be permanently discontinued (see section 4.4).

Proteinuria

Patients should be monitored for the development or worsening of proteinuria during Cyramza therapy. If the urine protein is ≥2+ on a dipstick, a 24 hour urine collection should be performed. Cyramza therapy should be temporarily discontinued if the urine protein level is ≥2 g/24 hours. Once the urine protein level returns to <2 g/24 hours, treatment should be resumed at a reduced dose level (see Table 3). A second dose reduction (see Table 3) is recommended if a urine protein level ≥2 g/24 hours reoccurs.

Cyramza therapy should be permanently discontinued if the urine protein level is >3 g/24 hours or in the event of nephrotic syndrome.

Table 3: Cyramza dose reductions for proteinuria

Initial Cyramza dose:	First dose reduction to:	Second dose reduction to:
8 mg/kg	6 mg/kg	5 mg/kg
10 mg/kg	8 mg/kg	6 mg/kg

Elective surgery or impaired wound healing

Cyramza therapy should be temporarily discontinued for at least 4 weeks prior to elective surgery. Cyramza therapy should be temporarily discontinued if there are wound healing complications, until the wound is fully healed (see section 4.4).

Permanent discontinuation

Cyramza therapy should be permanently discontinued in the event of:

Severe arterial thromboembolic events (see section 4.4).

Gastrointestinal perforations (see section 4.4).

Severe bleeding: NCI CTCAE Grade 3 or 4 bleeding (see section 4.4).

Spontaneous development of fistula (see section 4.4).

Hepatic encephalopathy or hepatorenal syndrome (see section 4.4).

Paclitaxel dose adjustments

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 non-haematological

toxicity, it is recommended to reduce the paclitaxel dose by 10 mg/m^2 for all following cycles. A second reduction of 10 mg/m^2 is recommended if these toxicities persist or reoccur.

FOLFIRI dose adjustments

Dose reductions for individual components of FOLFIRI may be made for specific toxicities. Dose modifications of each component of FOLFIRI should be made independently and are provided in Table 4. Table 5 provides details of dose delays or dose reductions of components of FOLFIRI at the next cycle based on maximum grade of specific adverse events.

Table 4: FOLFIRI dose reductions

FOLFIRI component[a]	Dose level			
	Initial dose	-1	-2	-3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	100 mg/m^2
5-FU bolus	400 mg/m^2	200 mg/m^2	0 mg/m^2	0 mg/m^2
5-FU infusion	2,400 mg/m^2 over 46-48 hours	2,000 mg/m^2 over 46-48 hours	1,600 mg/m^2 over 46-48 hours	1,200 mg/m^2 over 46-48 hours

[a] 5-FU = 5-fluorouracil.

Table 5: Dose modification of FOLFIRI components due to specific Adverse Events (AEs)

AE	NCI CTCAE grade	Dose modification at day 1 of cycle subsequent to AE
Diarrhoea	2	If diarrhoea has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. For recurrent Grade 2 diarrhoea, reduce by 1 dose level for 5-FU and irinotecan.
	3	If diarrhoea has recovered to Grade ≤1, reduce by 1 dose level for 5-FU and irinotecan.
	4	If diarrhoea has recovered to Grade ≤1, reduce by 2 dose levels for 5-FU and irinotecan. If Grade 4 diarrhoea does not resolve to Grade ≤1, withhold 5-FU and irinotecan for a maximum of 28* days until resolution *to Grade ≤1.

Neutropenia or Thrombocytopenia		Haematological criteria in Table 2 are met	Haematological criteria in Table 2 are not met
	2	No dose modification.	Reduce by 1 dose level for 5-FU and irinotecan.
	3	Reduce by 1 dose level for 5-FU and irinotecan.	Delay 5-FU and irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 1 level for 5-FU and irinotecan.
	4	Reduce by 2 dose levels for 5-FU and irinotecan.	Delay 5-FU and irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU and irinotecan.
Stomatitis/Mucositis	2	If stomatitis/mucositis has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. For recurrent Grade 2 stomatitis, reduce by 2 dose levels for 5-FU.	
	3	If stomatitis/mucositis has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. If Grade 3 mucositis/stomatitis does not resolve to Grade ≤1, delay 5-FU for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU.	
	4	Withhold 5-FU for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 dose levels for 5-FU.	
Febrile neutropenia		Haematological criteria in Table 2 are met and fever resolved	Haematological criteria in Table 2 are not met and fever resolved
		Reduce by 2 dose levels for 5-FU and irinotecan.	Delay 5-FU and irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU and

			irinotecan. Consider use of colony-stimulating factor prior to next cycle.

*The 28 day time period begins on day 1 of the cycle subsequent to the AE.

Docetaxel dose adjustments

Docetaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3 or 4 non-haematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity. It is recommended to reduce the docetaxel dose by 10 mg/m^2 for all following cycles. A second reduction of 15 mg/m^2 is recommended if these toxicities persist or reoccur. In this case, East Asian patients with a starting dose of 60 mg/m^2 should have docetaxel treatment discontinued (see Posology).

Special populations

Elderly

In the pivotal studies there is limited evidence that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions are recommended (see sections 4.4 and 5.1).

Renal impairment

There have been no formal studies with Cyramza in patients with renal impairment. Clinical data suggest that no dose adjustments are required in patients with mild, moderate or severe renal impairment (see sections 4.4 and 5.2). No dose reductions are recommended.

Hepatic impairment

There have been no formal studies with Cyramza in patients with hepatic impairment. Clinical data suggest that no dose adjustments are required in patients with mild or moderate hepatic impairment. There are no data regarding Cyramza administration in patients with severe hepatic impairment (see sections 4.4 and 5.2). No dose reductions are recommended.

Paediatric population

The safety and efficacy of Cyramza in children and adolescents (<18 years) has not been established. There are no data available.

There is no relevant use of ramucirumab in the paediatric population for the indications of advanced gastric cancer or gastro-oesophageal adenocarcinoma, adenocarcinoma of the colon and rectum, lung carcinoma, and hepatocellular carcinoma.

Method of administration

Cyramza is for intravenous use. After dilution, Cyramza is administered as an intravenous infusion over approximately 60 minutes. It should not be administered as an intravenous bolus or push. To achieve the required infusion duration of approximately 60 minutes, the maximum infusion rate of 25 mg/minute should not be exceeded, instead the infusion duration should be increased. The patient should be monitored during infusion for signs of infusion-related reactions (see section 4.4) and the availability of appropriate resuscitation equipment should be ensured.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In patients with NSCLC, Cyramza is contraindicated where there is tumour cavitation or tumour involvement of major vessels (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 studies. Cyramza should be permanently discontinued in patients who experience a severe ATE (see section 4.2).

Gastrointestinal perforations

Cyramza is an antiangiogenic therapy and may increase the risk of gastrointestinal perforations. Cases of gastrointestinal perforation have been reported in patients treated with Cyramza. Cyramza should be permanently discontinued in patients who experience gastrointestinal perforations (see section 4.2).

Severe bleeding

Cyramza is an antiangiogenic therapy and may increase the risk of severe bleeding.

Cyramza should be permanently discontinued in patients who experience Grade 3 or 4 bleeding (see section 4.2). 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. For HCC patients with evidence of portal hypertension or prior history of oesophageal variceal bleeding, screening for and treatment of oesophageal varices should be performed as per standard of care before starting Cyramza treatment.

Severe gastrointestinal haemorrhage, including fatal events, were reported in patients with gastric cancer treated with Cyramza in combination with paclitaxel, and in patients with mCRC treated with Cyramza in combination with FOLFIRI.

Pulmonary haemorrhage in NSCLC

Patients with squamous histology are at higher risk of developing serious pulmonary bleeding, however, no excess of Grade 5 pulmonary haemorrhage was observed in Cyramza treated patients with squamous histology in REVEL. NSCLC patients with recent pulmonary bleeding (>2,5 ml or bright red blood) as well as patients with evidence of baseline tumour cavitation, regardless of histology, or those with any evidence of tumour invasion or encasement of major blood vessels have been excluded from clinical trials (see section 4.3). Patients receiving any kind of therapeutic anticoagulation were excluded from the REVEL NSCLC clinical trial and patients receiving chronic therapy with non-steroidal anti-inflammatory drugs or anti-platelet agents were excluded from the REVEL and RELAY NSCLC clinical trials. Aspirin use at doses up to 325 mg/day was permitted (see section 5.1).

Infusion-related reactions

Infusion-related reactions were reported in clinical studies with Cyramza. The majority of events occurred during or following a first or second Cyramza infusion. Patients should be monitored during the infusion for signs of hypersensitivity. Symptoms included rigors/tremors, backpain/spasms, chest pain and/or tightness, chills, flushing, dyspnoea, wheezing, hypoxia, and paraesthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Cyramza should be immediately and permanently discontinued in patients who experience a Grade 3 or 4 IRR (see section 4.2).

Hypertension

An increased incidence of severe hypertension was reported in patients receiving Cyramza as compared to placebo. In most cases hypertension was managed using standard antihypertensive treatment. Patients with uncontrolled hypertension were excluded from the trials: Cyramza treatment should not be initiated in such patients until and unless their pre-existing hypertension is controlled. Patients who are treated with Cyramza should have their blood pressure monitored. Cyramza should be temporarily discontinued for severe hypertension until controlled with medical management. Cyramza should be permanently discontinued if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.2).

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES), including fatal cases, have been rarely reported in patients receiving ramucirumab. PRES symptoms may include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. A diagnosis of PRES can be confirmed by brain imaging (e.g., magnetic resonance imaging).

Discontinue ramucirumab in patients who experience PRES. The safety of reinitiating ramucirumab in patients who develop PRES and recover is not known.

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 Cyramza, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Impaired wound healing

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

If a patient develops wound healing complications during therapy, Cyramza should be discontinued until the wound is fully healed (see section 4.2).

Hepatic impairment

Cyramza 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. There are very limited efficacy and safety data available in these patients. Cyramza should only be used in these patients if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure.

In HCC patients, hepatic encephalopathy was reported at a higher rate in the Cyramza-treated patients compared to the placebo-treated patients (see section 4.8). Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy. Cyramza should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome (see section 4.2).

Fistula

Patients may be at increased risk for the development of fistula when treated with Cyramza. Cyramza treatment should be discontinued in patients who develop fistula (see section 4.2).

Proteinuria

An increased incidence of proteinuria was reported in patients receiving_Cyramza as compared to placebo. Patients should be monitored for the development or worsening of proteinuria during Cyramza therapy. If the urine protein is ≥2+ on a dipstick, a 24 hour urine collection should be performed. Cyramza therapy should be temporarily discontinued if the urine protein level is ≥2 g/24 hours. Once the urine protein level returns to <2 g/24 hours, treatment should be resumed at a reduced dose level. A second dose reduction is recommended if a urine protein level ≥2 g/24 hours reoccurs. Cyramza therapy should be permanently discontinued if the urine protein level is >3 g/24 hours or in the event of nephrotic syndrome (see section 4.2).

Stomatitis

An increased incidence of stomatitis was reported in patients receiving Cyramza in combination with chemotherapy as compared to patients treated with placebo plus chemotherapy. Symptomatic treatment should be instituted promptly if stomatitis occurs.

Renal impairment

There are limited safety data available for patients with severe renal impairment (creatinine clearance 15 to 29 ml/min) treated with Cyramza (see sections 4.2 and 5.2).

Sodium restricted diet

Each 10 ml vial contains less than 1 mmol sodium (23 mg), essentially 'sodium free'. Each 50 ml vial contains approximately 85 mg sodium. This is equivalent to approximately 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Elderly patients with NSCLC

A trend towards less efficacy with increasing age has been observed in patients receiving Cyramza plus docetaxel for the treatment of advanced NSCLC with disease progression after platinum-based chemotherapy (see section 5.1). Comorbidities associated with advanced age, performance status and the likely tolerability to chemotherapy should therefore be thoroughly evaluated prior to the initiation of treatment in the elderly (see sections 4.2 and 5.1).

For Cyramza used in combination with erlotinib for the first line treatment of NSCLC with activating EGFR mutations, patients aged 70 years and older compared to patients under 70 years of age, experienced a higher incidence of grade ≥3 adverse events and all grade serious adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interactions were observed between Cyramza and paclitaxel. The pharmacokinetics of paclitaxel were not affected when co-administered with Cyramza and the pharmacokinetics of Cyramza were not affected when co-administered with paclitaxel. The pharmacokinetics of irinotecan and its active metabolite, SN-38, were not affected when co-administered with Cyramza. The pharmacokinetics of docetaxel or erlotinib were not affected when co-administered with Cyramza.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to avoid becoming pregnant while on Cyramza and should be informed of the potential hazard to the pregnancy and foetus. Women of childbearing potential should use effective contraception during and up to 3 months after the last dose of Cyramza treatment.

Pregnancy

There are no data from the use of Cyramza in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). As angiogenesis is critical to maintenance of pregnancy and to foetal development, the inhibition of angiogenesis following Cyramza administration may result in adverse effects on pregnancy, including the foetus. Cyramza should only be used if the potential benefit

to the mother justifies the potential risk during pregnancy. If the patient becomes pregnant while being treated with Cyramza, she should be informed of the potential risk to the maintenance of pregnancy and the risk to the foetus. Cyramza is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether Cyramza 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, breastfeeding should be discontinued during treatment with Cyramza and for at least 3 months after the last dose.

Fertility

There are no data on the effect of Cyramza on human fertility. Female fertility is likely to be compromised during treatment with Cyramza based on studies in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Cyramza has no or negligible influence on the ability to drive and use machines. If patients experience 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 Undesirable effects

Summary of the safety profile

The most serious adverse reactions associated with Cyramza treatment (as a single agent or in combination with cytotoxic chemotherapy) were:

- Gastrointestinal perforation (see section 4.4)
- Severe gastrointestinal haemorrhage (see section 4.4)
- Arterial thromboembolic events (see section 4.4)
- Posterior reversible encephalopathy syndrome (see section 4.4)

The most common adverse reactions observed in patients treated with Cyramza as monotherapy are: peripheral oedema, hypertension, diarrhoea, abdominal pain, headache, proteinuria and thrombocytopenia.

The most common adverse reactions observed in patients treated with Cyramza in combination with chemotherapy are: fatigue/asthenia, neutropenia, diarrhoea, epistaxis, and stomatitis.

The most common adverse reactions observed in patients treated with Cyramza in combination with erlotinib are: infections, diarrhoea, hypertension, stomatitis, proteinuria, alopecia and epistaxis.

Tabulated list of adverse reactions

Tables 6 and 7 below list the adverse drug reactions (ADRs) from placebo controlled phase III clinical trials associated with Cyramza used either as a monotherapy treatment for gastric cancer and HCC or in combination with different chemotherapy regimens or erlotinib for the treatment of gastric cancer, mCRC and NSCLC. ADRs are listed below by MedDRA body system organ class. The following convention has been used for classification of frequency:

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

Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 6: ADRs reported in patients treated with Cyramza as monotherapy in phase 3 clinical trials (REGARD, REACH-2 and REACH patients with alpha fetoprotein ≥ 400 ng/ml)

System Organ Class (MedDRA)	**Very Common**	**Common**	**Uncommon**
Blood and lymphatic system disorders	Thrombocytopenia[a]	Neutropenia[a]	
Metabolism and nutrition disorders		Hypokalaemia[a,b] (hypokalaemia and decreased blood potassium) Hyponatraemia[a] Hypoalbuminaemia[a]	
Nervous system disorders	Headache	Hepatic encephalopathy[c] (hepatic encephalopathy and hepatic coma)	

Vascular disorders	Hypertension[a,d] (increased blood pressure and hypertension)	Arterial thromboembolic events[a]	
Respiratory, thoracic, and mediastinal disorders		Epistaxis	
Gastrointestinal disorders	Abdominal pain[a,e] (abdominal pain, lower abdominal pain, upper abdominal pain, and hepatic pain.) Diarrhoea	Intestinal obstruction[a]	Gastrointestinal perforation[a]
Skin and subcutaneous tissue disorders		Rash[a]	
Renal and urinary disorders	Proteinuria[a,f] (includes one case of nephrotic syndrome)		
General disorders and administration site disorders	Peripheral oedema	Infusion-related reactions[a]	

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.

[b] Includes: hypokalaemia and blood potassium decreased.

[c] Based on study REACH-2 and REACH (single-agent ramucirumab in HCC). Includes hepatic encephalopathy and hepatic coma.

[d] Includes: blood pressure increased and hypertension.

[e] Includes: abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.

[f] Includes one case of nephrotic syndrome

Table 7: ADRs reported in patients treated with Cyramza in combination with chemotherapy in phase 3 clinical trials (RAINBOW, REVEL, RAISE and RELAY)

System Organ Class (MedDRA)	**Very Common**	**Common**

Infections and infestations	Infections[j,k]	Sepsis[a,b]
Blood and lymphatic system disorders	Neutropenia[a] Leukopenia[a,c] (leukopenia and white cell count decreased) Thrombocytopenia[a] Anaemia[j]	Febrile neutropenia[d]
Metabolism and nutrition disorders		Hypoalbuminaemia[a] Hyponatraemia[a]
Nervous system disorders	Headache[j]	
Vascular disorders	Hypertension[a,e] (increased blood pressure, hypertension, and hypertensive cardiomyopathy)	
Respiratory, thoracic, and mediastinal disorders	Epistaxis	Pulmonary haemorrhage[j,l]
Gastrointestinal disorders	Stomatitis Diarrhoea	Gastrointestinal haemorrhage events[a,f] (anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage) Gastrointestinal perforation[a] Gingival bleeding[j]

Skin and subcutaneous tissue disorders	Alopecia[j]	Palmar-plantar erthyrodysaesthesia syndrome[g]
Renal and urinary disorders	Proteinuria[a] (Includes cases of nephrotic syndrome)	
General disorders and administration site disorders	Fatigue[a,i] (fatigue and asthenia) Mucosal inflammation[d] Peripheral oedema	

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.

[b] Based on study RAINBOW (ramucirumab plus paclitaxel).

[c] Based on study RAINBOW (ramucirumab plus paclitaxel). Includes: leukopenia and white blood cell count decreased.

[d] Based on study REVEL (ramucirumab plus docetaxel).

[e] Includes: blood pressure increased, hypertension, and hypertensive cardiomyopathy.

[f] Based on study RAINBOW (ramucirumab plus paclitaxel) and study RAISE (ramucirumab plus FOLFIRI). Includes: anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.

[g] Based on study RAISE (ramucirumab plus FOLFIRI). [h] Includes cases of nephrotic syndrome.

[i] Based on study RAINBOW (ramucirumab plus paclitaxel) and study REVEL (ramucirumab plus docetaxel). Includes: fatigue and asthenia.

[j] Based on study RELAY (ramucirumab plus erlotinib).

[k] Infections includes all preferred terms that are part of the System Organ Class Infections and infestations. Most common (≥1%) Grade ≥3 infections include pneumonia, cellulitis, paronychia, skin infection, and urinary tract infection.

[l] Includes haemoptysis, laryngeal haemorrhage, haemothorax (a fatal event occurred) and pulmonary haemorrhage.

Clinically relevant reactions (including Grade ≥3) associated with antiangiogenic therapy observed in Cyramza-treated patients across clinical studies were: gastrointestinal perforations, infusion-related reactions and proteinuria (see sections 4.2 and 4.4).

Colorectal cancer

Cyramza *in combination with FOLFIRI*

In the RAISE study, in mCRC patients treated with Cyramza plus FOLFIRI, the most frequent (≥1%) ADR that led to the discontinuation of Cyramza was proteinuria (1,5%). The most frequent (≥1%) ADRs leading to discontinuation of one or more components of FOLFIRI were: neutropenia (12,5%), thrombocytopenia

(4,2%), diarrhoea (2,3%) and stomatitis (2,3%). The most frequent component of FOLFIRI to be discontinued was the 5-FU bolus.

Adverse reactions from other sources

Table 8: Post-marketing ADRs associated with Cyramza reported in clinical trials and through post-marketing reporting

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Haemangioma			
Blood and lymphatic system disorders			Thrombotic microangiopathy	
Nervous system disorders			Posterior reversible encephalopathy syndrome	
Vascular disorders				Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dysphonia			

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternately, report suspected adverse reactions to the company at ade_za@lilly.com

4.9 Overdose

There is no data on overdose in humans. Cyramza 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, supportive therapy should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies ATC code: L01XC21.

Mechanism of action

Vascular Endothelial Growth Factor (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.

Clinical efficacy and safety

Clinical efficacy and safety were established in the following phase 3 clinical studies:

- REGARD, a global, multicenter, randomised, double-blind study that compared single-agent ramucirumab plus best supportive care (BSC) with placebo plus BSC in the treatment of patients with advanced gastric cancer whose disease has progressed during or following prior combination chemotherapy. REGARD met the primary endpoint of overall survival (OS), with consistent improvements also observed in other secondary endpoints, including progression-free survival.
- RAINBOW, a global, multicenter, randomised, double-blind study that compared ramucirumab in combination with paclitaxel with placebo plus paclitaxel in the treatment of patients with advanced gastric cancer whose disease progressed during or following prior combination chemotherapy. RAINBOW met the primary endpoint of overall survival (OS), with consistent improvements also observed in other secondary endpoints, including progression-free survival.
- RAISE, a global, multicenter, randomised, double-blind study, which demonstrated statistically significant and clinically meaningful efficacy and a tolerable and manageable safety profile of

ramucirumab in combination with FOLFIRI in patients with metastatic CRC whose disease had progressed during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

- RELAY was a global, randomised, double-blind, phase 3 study of ramucirumab plus erlotinib versus placebo plus erlotinib that randomised (1:1) 449 previously untreated patients with metastatic nonsmall cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) activating mutations at study entry. Eligible patients were ECOG PS 0 or 1. Patients with CNS metastases or known T790M EGFR mutations at baseline were excluded from the study. Patients at a high risk of bleeding, cardiovascular events, including those who had experienced any arterial thrombotic event within 6 months of enrolment, were also excluded from the study.
- REVEL, a global, multicenter, randomised, double-blind study, which demonstrated statistically significant and clinically meaningful efficacy and a tolerable and manageable safety profile of ramucirumab in combination with docetaxel in patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy. The primary endpoint was OS. Patients were randomised in a 1:1 ratio to receive ramucirumab plus docetaxel (n=628) or placebo plus docetaxel (n=625). Randomisation was stratified by geographic region, gender, prior maintenance, and ECOG PS. Ramucirumab at 10 mg/kg or placebo and docetaxel at 75 mg/m^2 were each administered by intravenous infusion on day 1 of a 21-day cycle. Sites in East Asia administered a reduced dose of docetaxel at 60 mg/m^2 every 21 days. Patients with recent serious pulmonary, gastrointestinal, or postoperative bleeding, evidence of CNS haemorrhage, tumour involvement of major airway or blood vessel, intra-tumour cavitation, and history of significant bleeding or uncontrolled thrombotic disorders were excluded. Also, patients receiving any kind of therapeutic anticoagulation and/or chronic therapy with non-steroidal anti-inflammatory drugs or other anti-platelets agents or those with untreated, clinically unstable brain/CNS metastases were excluded Aspirin use at doses up to 325 mg/day was permitted. (see section 4,4). A limited number of non-Caucasian, especially Black patients (2,6%) were included. Therefore there is limited experience with the combination of ramucirumab and docetaxel in these patients with advanced NSCLC as well as in patients with renal impairment, cardiovascular disease and obesity.
- REACH-2, was a global, randomised, double-blind study of ramucicumab plus basic supportive care (BSC) versus placebo plus BSC that randomised (2:1) 292 patients with HCC who had a serum AFP ≥ 400 ng/ml at study entry. Patients enrolled into the study had disease progression on or after prior

sorafenib therapy or were intolerant to sorafenib. Eligible patients were Child Pugh A (score < 7), had creatinine clearance ≥ 60 ml/min, and ECOG PS of 0 or 1. In addition, patients were either Barcelona Clinic Liver Cancer (BCLC) stage B and no longer amenable to locoregional therapy, or were BCLC stage C. Patients with brain metastases, leptomeningeal disease, uncontrolled spinal cord compression, a history of or current hepatic encephalopathy or clinically meaningful ascites, severe variceal bleeding in the 3 months prior to treatment, or gastric or oesophageal varices at high risk of bleeding were excluded from the study. The primary endpoint was overall survival. The threshold for the elevated AFP study entry requirement for REACH-2 was determined based on the survival results from a pre-specified subgroup, exploratory analysis from REACH, a previously completed, supportive phase 3 clinical study in 565 HCC patients randomised (1:1) to either ramucirumab plus BSC or placebo plus BSC that had disease progression on or after prior sorafenib therapy.

Immunogenicity

Overall, there was a low incidence of both treatment-emergent anti-drug antibodies and neutralising antibodies among Cyramza treated patients, and no correlation with safety outcomes in these patients. There was no relationship between immunogenicity and IRRs or treatment emergent adverse events

5.2 Pharmacokinetic properties

Following the dose regimen of 8 mg/kg every 2 weeks, the geometric means of ramucirumab C_{min} prior to administration of the fourth and seventh dose of ramucirumab given as a single agent in advanced gastric cancer patients' serum were 49,5 µg/ml (range of 6,3-228 µg/ml) and 74,4 µg/ml (range of 13,8-234 µg/ml), respectively. In HCC patients' serum the geometric means of ramucirumab C_{min} prior to administration of the second, fourth and seventh dose of ramucirumab were 23,5 µg/ml (range of 2,9-76,5 µg/ml), 44,1 µg/ml (range of 4,2-137 µg/ml) and 60,2 µg/ml (range of 18,3-123 µg/ml), respectively.

Following the dose regimen of 8 mg/kg ramucirumab every 2 weeks in combination with FOLFIRI, the geometric means of ramucirumab C_{min} were 46,3 µg/ml (range of 7,7-119 µg/ml) and 65,1 µg/ml (range of 14,5-205 µg/ml) prior to administration of the third and fifth dose, respectively, in serum from patients with mCRC.

Following the dose regimen of 10 mg/kg ramucirumab every 3 weeks, the geometric means of ramucirumab C_{min} were 28,3 µg/ml (range of 2,5-108 µg/ml) and 38,4 µg/ml (range of 3,1-128 µg/ml) prior to administration of the third and fifth dose, respectively of ramucirumab given in combination with docetaxel, in serum from patients with NSCLC.

Following the dose regimen of 10 mg/kg ramucirumab every 2 weeks, the geometric means of ramucirumab C_{min} were 68,5 µg/ml (range of 20,3-142 µg/ml) and 85,7 µg/ml (range of 36,0-197 µg/ml) prior to administration of the fourth and seventh dose, respectively of ramucirumab given in combination with erlotinib, in serum from patients with NSCLC.

Absorption

Ramucirumab is administered as an intravenous infusion only.

Distribution

Based on population pharmacokinetic approach (PopPK), the mean (% coefficient of variation [CV%]) volume of distribution at steady state for ramucirumab was 5,4L (15%).

Biotransformation

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

Elimination

Based on PopPK, the mean (CV%) clearance of ramucirumab was 0,015 L/hour (30%) and the mean half-life was 14 days (20%).

Time and dose dependency

There was no clear deviation from dose proportionality in pharmacokinetics of ramucirumab from 6 mg/kg to 20 mg/kg. An accumulation ratio of 1,5 was observed for ramucirumab when dosed every 2 weeks. Based on simulations using the PopPK model, steady state would be attained by the sixth dose.

Elderly

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

Renal impairment

No formal studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of ramucirumab. Based on PopPK, ramucirumab exposure was similar in patients with mild renal impairment (creatinine clearance [CrCl] ≥60 to <90 ml/min), moderate renal impairment (CrCl

≥30 to <60 ml/min) or severe renal impairment (CrCl 15 to 29 ml/min) as compared to patients with normal renal function (CrCl ≥90 ml/min).

Hepatic impairment

No formal studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ramucirumab. Based on PopPK, ramucirumab exposure in patients with mild hepatic impairment (total bilirubin >1,0-1,5 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 ULN and any AST) was similar to patients with normal hepatic function (total bilirubin and AST ≤ ULN). Ramucirumab has not been studied in patients with severe hepatic impairment (total bilirubin >3,0 ULN and any AST).

Other special Populations

Based on PopPK, the following covariates were found to have no impact on ramucirumab disposition: age, sex, race, albumin levels. These and other factors investigated had < 20 % effect on ramucirumab disposition. Body weight is considered a significant co-variate of ramucirumab pharmacokinetics supporting the dosing based on body weight.

Exposure response relationships

Efficacy

Exposure-response analyses indicated that efficacy was correlated with ramucirumab exposure across pivotal studies. Efficacy, as measured by improvements in OS, was associated with increasing ramucirumab exposure range produced by 8 mg/kg ramucirumab given every 2 weeks and by 10 mg/kg ramucirumab given every 3 weeks. An improvement in PFS was also associated with increasing ramucirumab exposure for advanced gastric cancer, NSCLC with disease progression after platinum-based chemotherapy and mCRC.

In the REACH-2 study for HCC, a relevant exposure-efficacy association was observed for ramucirumab which showed that only patients with above-median exposure experienced an improvement in OS, compared to placebo, and these exposure-efficacy relationships remained after attempts to adjust for other prognostic factors. A treatment effect on PFS was observed for all exposure levels produced by 8 mg/kg ramucirumab given every 2 weeks. No such relation was observed in the RELAY study for NSCLC with 10 mg/kg ramucirumab plus erlotinib given every 2 weeks.

Safety

In RAINBOW, the incidences of Grade ≥3 hypertension, neutropenia, and leukopenia were increased with higher ramucirumab exposure.

In RAISE, the incidence of Grade ≥3 neutropenia was increased with higher ramucirumab exposure.

In RELAY, no exposure-safety relationship was identified for the selected safety endpoints, including Grade ≥3 hypertension, diarrhoea, proteinuria and dermatitis acneiform.

In REVEL, the incidences of Grade ≥3 febrile neutropenia and hypertension were increased with higher ramucirumab exposure.

In the pooled data from REACH-2 and REACH (patients with alpha fetoprotein ≥ 400 ng/ml), the incidences of Grade ≥ 3 hypertension was increased with higher ramucirumab exposure.

5.3 Preclinical safety data

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

The target organs identified in repeated dose cynomolgus monkey toxicity studies were kidney (glomerulonephritis), bone (thickening and abnormal endochondral ossification of the epiphyseal growth plate) and female reproductive organs (decreased weight of ovaries and uterus). A minimal grade of inflammation and/or mononuclear cell infiltration was seen in several organs.

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, embryo-foetal development, and postnatal development. Based on ramucirumab's mechanism of action, it is likely that in animals, ramucirumab will inhibit angiogenesis and result in adverse effects on fertility (ovulation), placental development, developing foetuses and postnatal development.

A single dose of ramucirumab did not impair wound healing in monkeys using a full-thickness incisional model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine monohydrochloride

Sodium chloride

Glycine (E640)

Polysorbate 80 (E433)

Water for injections

6.2 Incompatibilities

Cyramza should not be administered or mixed with dextrose solutions.

Cyramza must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial 24 months

After dilution

When prepared as directed, infusion solutions of Cyramza contain no antimicrobial preservatives. 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 ºC to 8 ºC or for 4 hours below 30 ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, inuse storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC to 8 ºC).

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The concentrate for solution for infusion is a clear to slightly opalescent and colourless to slightly yellow liquid without visible particles.

10 ml solution in a Type I clear tubing glass vial sealed with a grey chlorobutyl rubber stopper, grey aluminium seal and a slate grey polypropylene cap.

50 ml solution in a Type I clear tubing glass vial sealed with a grey chlorobutyl rubber stopper, grey aluminium seal and a slate grey polypropylene cap.

Pack of 1 vial of 10 ml.

Pack of 2 vials of 10 ml.

Pack of 1 vial of 50 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not shake the vial.

Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discolouration (the concentrate for solution for infusion should be clear to slightly opalescent and colourless to slightly yellow without visible particles) prior to dilution. If particulate matter or discolouration is identified, discard the vial.

Calculate the dose and volume of Cyramza needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/ml solution of Cyramza. Only use sodium chloride 9 mg/ml (0,9%) solution for injection as a diluent.

In case of prefilled intravenous infusion container usage

Based on the calculated volume of Cyramza, remove the corresponding volume of sodium chloride 9 mg/ml (0,9%) solution for injection from the prefilled 250 ml intravenous container. Aseptically transfer the calculated volume of Cyramza to the intravenous container. The final total 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 medicinal products.

In case of empty intravenous infusion container usage

Aseptically transfer the calculated volume of Cyramza into an empty intravenous infusion container. Add a sufficient quantity of sodium chloride 9 mg/ml (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 medicinal products.

Parenteral medicinal products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.

Discard any unused portion of Cyramza left in a vial, as the product contains no antimicrobial preservatives.

Administer via infusion pump. A separate infusion line with a protein sparing 0,22 micron filter must be used for the infusion and the line must be flushed with sodium chloride 9 mg/ml (0,9%) solution for injection at the end of the infusion.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

First Floor, Golden Oak House

Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston, 2191

8. REGISTRATION NUMBER(S)

Cyramza 100 mg: 52/30.1/0116

Cyramza 500 mg: 52/30.1/0117

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2020

10. DATE OF REVISION OF THE TEXT

17 February 2021