# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Cyramza 10 mg/ml concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 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 in murine (NS0) cells by recombinant DNA technology.

Excipient with known effect

Each 10 ml vial contains approximately 17 mg sodium and 1 mg polysorbate 80.
Each 50 ml vial contains approximately 85 mg sodium and 5 mg polysorbate 80.

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

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

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

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

Ramucirumab 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 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/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<br>**Days 8 and 15:** ≥ 1.0 x $10^9$/L |
| Platelets | **Day 1:** ≥ 100 x $10^9$/L<br>**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<br>**Liver metastases:** ALT/AST ≤ 5 x ULN |

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

*Colorectal cancer*

The recommended dose of ramucirumab 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 | $\geq 1.5 \times 10^9$/L |
| Platelets | $\geq 100 \times 10^9$/L |
| Chemotherapy-related gastro-intestinal toxicity | ≤ Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]) |

*Non-small cell lung cancer (NSCLC)*

*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 ramucirumab 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 (HCC)*

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 ramucirumab. 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 prescribing information for paclitaxel, for components of FOLFIRI and for docetaxel, as applicable, for premedication requirements and additional information.

*Posology adjustments for ramucirumab*

*Infusion-related reactions*
The infusion rate of ramucirumab 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. Ramucirumab 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 ramucirumab administration and treated as clinically indicated. Ramucirumab 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, ramucirumab therapy should be permanently discontinued (see section 4.4).

*Proteinuria*
Patients should be monitored for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein is ≥ 2+ on a dipstick, a 24 hour urine collection should be performed. Ramucirumab 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.

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

**Table 3: Ramucirumab dose reductions for proteinuria**

| Initial ramucirumab 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*
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).

*Permanent discontinuation*
Ramucirumab 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 drug reactions.

**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 drug reactions (ADRs)**

| **ADR** | **NCI CTCAE grade** | **Dose modification at day 1 of cycle subsequent to ADR** | |
|---|---|---|---|
| Diarrhoea | 2 | If diarrhoea has recovered to Grade ≤1, reduce by 1 dose level for 5-FU.<br>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.<br>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.<br>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 ADR.

*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/m² 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 ramucirumab 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. Currently available data are described in section 4.8, 5.1 and 5.2. Due to limited data no recommendation on posology can be made.

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.

For patients with NSCLC, ramucirumab 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 ischemia have been reported in clinical studies. Ramucirumab should be permanently discontinued in patients who experience a severe ATE (see section 4.2).

Gastrointestinal perforations

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

Severe bleeding

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). 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 ramucirumab treatment.

Severe gastrointestinal haemorrhage, including fatal events, were reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel, and in patients with mCRC treated with ramucirumab 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 ramucirumab 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 ramucirumab. The majority of events occurred during or following a first or second ramucirumab infusion. Patients should be monitored during the infusion for signs of hypersensitivity. 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. Ramucirumab 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 ramucirumab as compared to placebo. In most cases hypertension was managed using standard antihypertensive treatment. Patients with uncontrolled hypertension were excluded from the trials: ramucirumab treatment should not be initiated in such patients until and unless their pre-existing hypertension is controlled. Patients who are treated with ramucirumab should have their blood pressure monitored. Ramucirumab should be temporarily discontinued for severe hypertension until controlled with medical management. Ramucirumab 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 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. 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 judgment of adequate wound healing.

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

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. There are very limited efficacy and safety data available in these patients. Ramucirumab 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 ramucirumab-treated patients compared to the placebo-treated patients (see section 4.8). Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy. Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome (see section 4.2).

Cardiac Failure

In pooled data from ramucirumab clinical trials, cardiac 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. This increased incidence was not observed in patients receiving ramucirumab compared to placebo from single agent clinical trials. In the post-marketing setting, cardiac failure was observed for ramucirumab, mostly in combination with paclitaxel. Patients should be monitored for clinical signs and symptoms of cardiac failure during treatment, and suspension of treatment should be considered if clinical signs and symptoms of cardiac failure develop. See section 4.8.

Fistula

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

Proteinuria

An increased incidence of proteinuria was reported in patients receiving ramucirumab as compared to placebo. Patients should be monitored for the development, or worsening of proteinuria during ramucirumab therapy. If the urine protein is $\geq$ 2+ on a dipstick, a 24 hour urine collection should be performed. Ramucirumab therapy should be temporarily discontinued if the urine protein level is $\geq$ 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 $\geq$ 2 g/24 hours reoccurs. Ramucirumab 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 ramucirumab 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 ramucirumab (see sections 4.2 and 5.2).

Elderly patients with NSCLC

A trend towards less efficacy with increasing age has been observed in patients receiving ramucirumab 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 ramucirumab 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.

Sodium

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

Polysorbate

This medicinal product contains approximately 1 mg of polysorbate 80 in each 10 ml, and 5 mg of polysorbate 80 in each 50 ml vial.

## 4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interactions were observed between ramucirumab and paclitaxel. The pharmacokinetics of paclitaxel were not affected when co-administered with ramucirumab and the pharmacokinetics of ramucirumab 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 ramucirumab. The pharmacokinetics of docetaxel or erlotinib were not affected when co-administered with ramucirumab.

## 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 ramucirumab treatment.

Pregnancy

There are no data from the use of ramucirumab 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 ramucirumab administration may result in adverse events 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 ramucirumab, 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.

Breast-feeding

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 breast-fed newborns/infants cannot be excluded, breast-feeding 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 ramucirumab on human fertility. Female fertility is likely to be compromised during treatment with ramucirumab 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 ramucirumab 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 ramucirumab as monotherapy are: peripheral oedema, hypertension, diarrhoea, abdominal pain, headache, proteinuria and thrombocytopenia.

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

The most common adverse reactions observed in patients treated with ramucirumab 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 ramucirumab 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 for ADR tables:

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)
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 ramucirumab 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]<br>Hyponatraemia[a]<br>Hypoalbuminaemia[a] | |
| Nervous system disorders | Headache | Hepatic encephalopathy[c] | |
| Vascular disorders | Hypertension[a,d] | Arterial thromboembolic events[a] | |
| Respiratory, thoracic, and mediastinal disorders | | Epistaxis | |
| Gastrointestinal disorders | Abdominal pain[a,e]<br>Diarrhoea | Intestinal obstruction[a] | Gastrointestinal perforation[a] |
| Skin and subcutaneous tissue disorders | | Rash[a] | |
| Renal and urinary disorders | Proteinuria[a,f] | | |
| 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 ramucirumab in combination with chemotherapy or erlotinib in phase 3 clinical trials (RAINBOW, REVEL, RAISE and RELAY)**

| System Organ Class (MedDRA) | Very Common | Common | Uncommon |
|---|---|---|---|
| Infections and infestations | Infections[j,k] | Sepsis[a,b] | |
| Blood and lymphatic system disorders | Neutropenia[a]<br>Leukopenia[a,c]<br>Thrombocytopenia[a]<br>Anaemia[j] | Febrile neutropenia[d] | |
| Metabolism and nutrition disorders | | Hypoalbuminaemia[a]<br>Hyponatraemia[a] | |
| Nervous system disorders | Headache[j] | | |
| Cardiac disorders | | | Cardiac failure |
| Vascular disorders | Hypertension[a,e] | Arterial thromboembolic events[a] | |
| Respiratory, thoracic, and mediastinal disorders | Epistaxis | Pulmonary haemorrhage[j,l] | |
| Gastrointestinal disorders | Stomatitis<br>Diarrhoea | Gastrointestinal haemorrhage events[a,f]<br>Gastrointestinal perforation[a]<br>Gingival bleeding[j] | |
| Skin and subcutaneous tissue disorders | Alopecia[j] | Palmar-plantar erthyrodysaesthesia syndrome[g] | |
| Renal and urinary disorders | Proteinuria[a,h] | | |
| General disorders and administration site disorders | Fatigue[a,i]<br>Mucosal inflammation[d]<br>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), study REVEL (ramucirumab plus docetaxel) 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 ramucirumab-treated patients across clinical studies were: gastrointestinal perforations, infusion-related reactions and proteinuria (see sections 4.2 and 4.4).

Colorectal cancer

*Ramucirumab in combination with FOLFIRI*

In the RAISE study, in mCRC patients treated with ramucirumab plus FOLFIRI, the most frequent (≥ 1 %) ADR that led to the discontinuation of ramucirumab 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: ADRs associated with ramucirumab 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 | |
| Endocrine disorders | Hypothyroidism | | | |
| Nervous system disorders | | | Posterior reversible encephalopathy syndrome | |
| Cardiac disorders | | | | Cardiac failure[a] |
| Vascular disorders | | | | Aneurysms and artery dissections |
| Respiratory, thoracic and mediastinal disorders | Dysphonia | | | |

[a] In the post-marketing setting, cardiac failure has been observed for ramucirumab mostly in combination with paclitaxel. See section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

Paediatric population

No new safety concerns were identified based on the limited number of paediatric patients treated with ramucirumab monotherapy in study I4T-MC-JVDA (see section 5.1). One patient in this study had

progressive widening of distal femoral growth plate. The impact of this finding on growth is not known. No new safety concerns were reported in the limited number of paediatric patients treated with ramucirumab in combination therapy in studies J1S-MC-JV01 and J1S-MC-JV02 (see section 5.1).

### 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, VEGF/VEGFR (Vascular Endothelial Growth Factor) inhibitors, ATC code: L01FG02.

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

*Gastric cancer*

*RAINBOW*
RAINBOW, a global, randomised, double-blind, study of Cyramza plus paclitaxel versus placebo plus paclitaxel, was conducted in 665 patients with locally recurrent and unresectable or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline. The primary endpoint was overall survival (OS) and the 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 and with ECOG PS 0-1. Patients were randomised in a 1:1 ratio to receive Cyramza 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. Cyramza 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/m$^2$ 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 and fluoropyrimidine combination therapy without anthracycline. The remainder (25 %) received prior platinum and fluoropyrimidine combination therapy with 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 arms: the median age was 61 years; 71 % of 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 cancer; 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 Cyramza 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 Cyramza was 98.6 %

and of placebo was 99.6 %. The median relative dose intensity of paclitaxel was 87.7 % for the Cyramza 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 Cyramza 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 Cyramza plus paclitaxel and 46.0 % of patients receiving placebo plus paclitaxel.

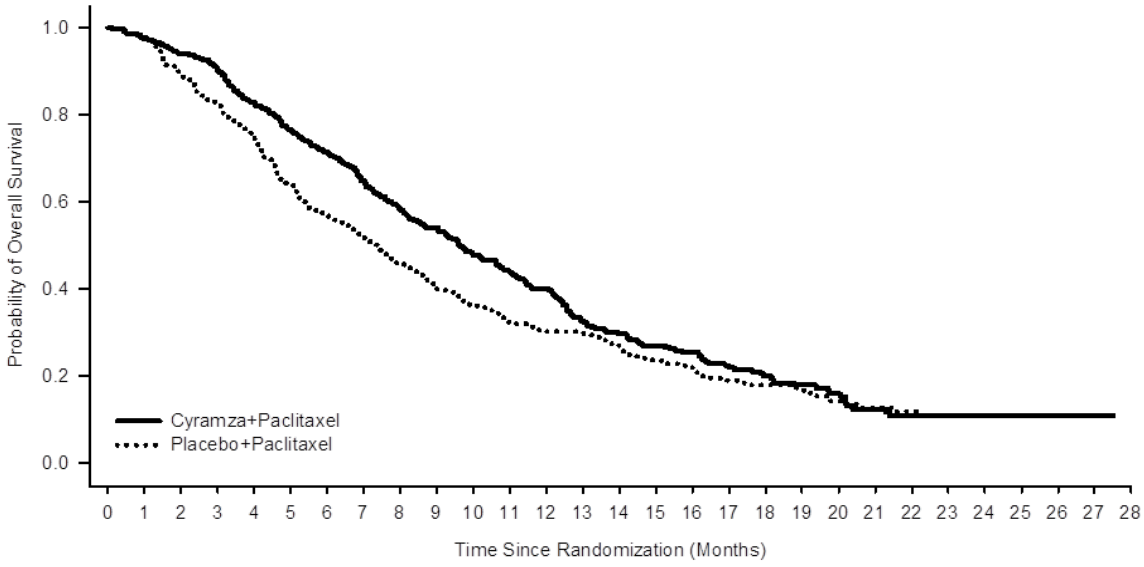
Overall survival was statistically significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (HR 0.807; 95 % CI: 0.678 to 0.962; p = 0.0169). There was an increase in median survival of 2.3 months in favour of the Cyramza plus paclitaxel arm: 9.63 months in the Cyramza plus paclitaxel arm and 7.36 months in the placebo plus paclitaxel arm. Progression-free survival was statistically significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (HR 0.635; 95 % CI: 0.536 to 0.752; p < 0.0001). There was an increase in median PFS of 1.5 months in favour of the Cyramza plus paclitaxel arm: 4.4 months in the Cyramza plus paclitaxel arm and 2.9 months in the placebo plus paclitaxel arm. Objective response rate [ORR(complete response [CR] + partial response [PR])] was significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (Odds ratio 2.140; 95 % CI: 1.499 to 3.160; p = 0.0001). The ORR in the Cyramza plus paclitaxel arm was 27.9 % and in the placebo plus paclitaxel arm was 16.1 %. Improvements in OS and PFS were consistently observed in pre-specified subgroups based on age, sex, race and in most other pre-specified subgroups. Efficacy results are shown in Table 9.

**Table 9: Summary of efficacy data – Intent to treat (ITT) population**

| | **Cyramza plus paclitaxel N = 330** | **Placebo plus 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 (0.536, 0.752) | |
| Stratified log-rank p-value | < 0.0001 | |
| Objective response rate (CR +PR) | | |
| Rate- percent (95 % CI) | 27.9 (23.3, 33.0) | 16.1 (12.6, 20.4) |
| Odd ratio | 2.140 (1.449, 3.160) | |
| Stratified CMH p-value | 0.0001 | |

Abbreviations: CI = confidence interval, CR= complete response, PR= partial response, CMH= Cochran-Mantel-Haenszel

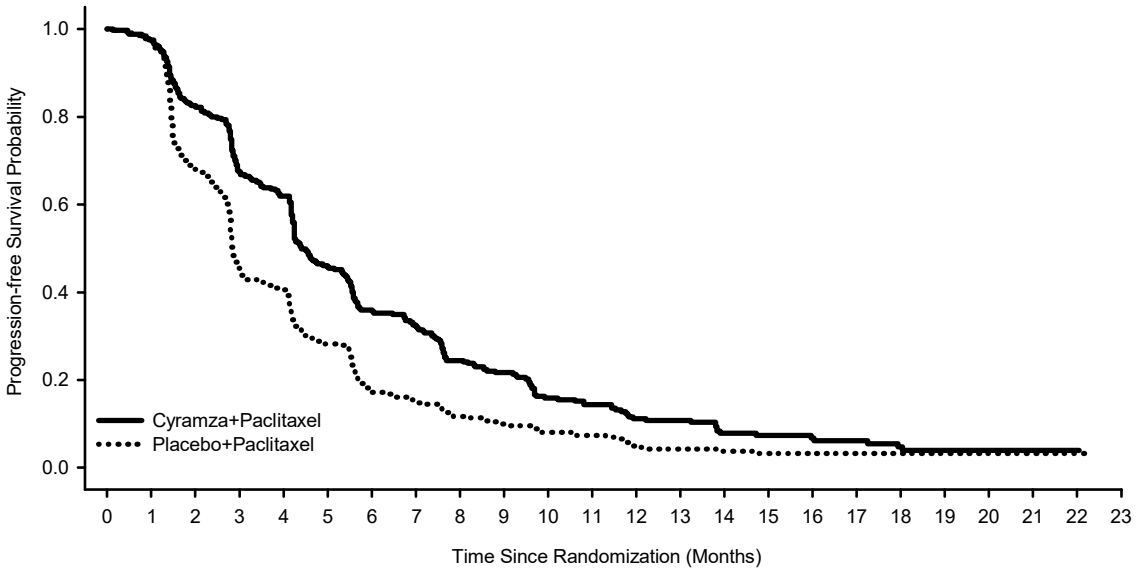
**Figure 1: Kaplan-Meier curves of overall survival for Cyramza plus paclitaxel versus placebo plus paclitaxel in RAINBOW**




Number at Risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyramza+Paclitaxel | 330 | 308 | 267 | 228 | 185 | 148 | 116 | 78 | 60 | 41 | 24 | 13 | 6 | 1 | 0 |
| Placebo+Paclitaxel | 335 | 294 | 241 | 180 | 143 | 109 | 81 | 64 | 47 | 30 | 22 | 13 | 5 | 2 | 0 |

**Figure 2: Kaplan-Meier curves of progression-free survival for Cyramza plus paclitaxel versus placebo plus paclitaxel in RAINBOW**




Number at Risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyramza+Paclitaxel | 330 | 259 | 188 | 104 | 70 | 43 | 28 | 15 | 11 | 7 | 3 | 1 |
| Placebo+Paclitaxel | 335 | 214 | 124 | 50 | 34 | 21 | 12 | 8 | 5 | 3 | 3 | 3 |

*REGARD*

REGARD, a multinational, randomised, double-blind study of Cyramza plus BSC versus placebo plus BSC, was conducted in 355 patients with locally recurrent and unresectable, or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- or fluoropyrimidine-containing chemotherapy. The primary endpoint was OS and secondary endpoints included PFS. Patients were required to have experienced disease progression during, 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 ECOG PS 0-1. To be included in the study, patients were required

to have total bilirubin of ≤1.5 mg/dl and AST and ALT ≤ 3 times ULN, or ≤ 5 times ULN if liver metastases were present.

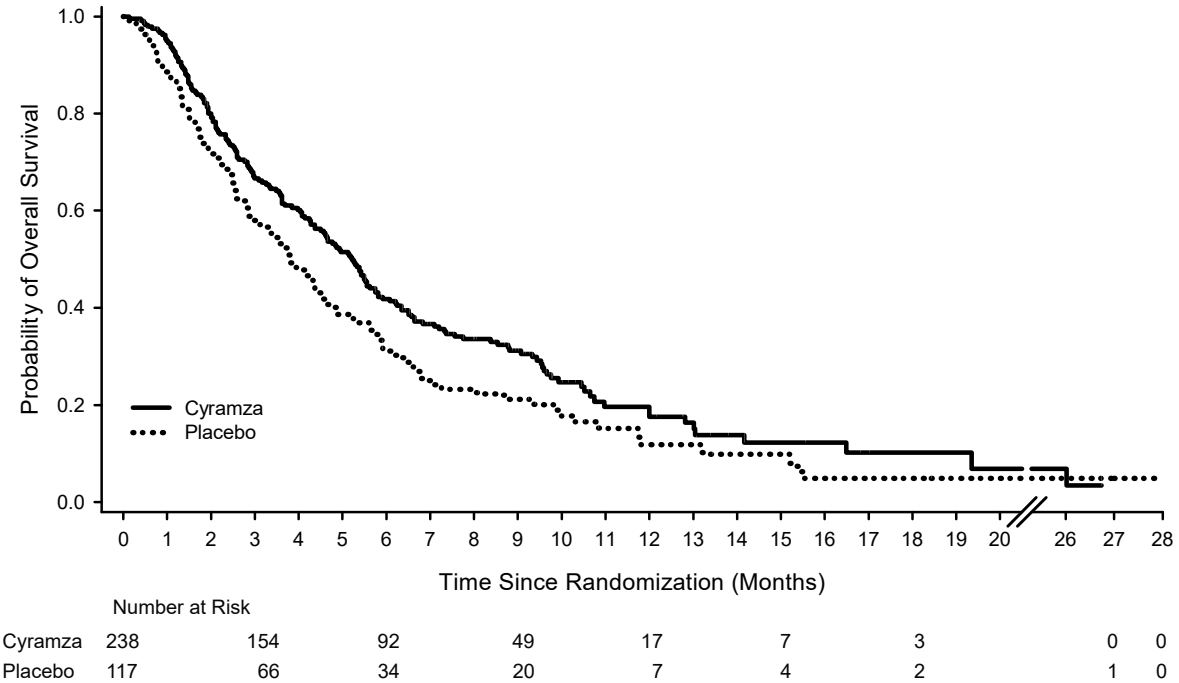
Patients were randomised in a 2:1 ratio to receive an intravenous infusion of Cyramza 8 mg/kg (n = 238) or placebo (n = 117) every 2 weeks. Randomisation was stratified by weight loss over the prior 3 months (≥ 10 % versus < 10 %), geographic region, and location of the primary tumour (gastric versus GEJ). Baseline demographics and disease characteristics were balanced. The ECOG PS was 1 for 72 % of patients. There were no patients with Child-Pugh B or C liver cirrhosis enrolled in REGARD. 11 % of patients treated with Cyramza and 6 % of patients on placebo discontinued therapy due to adverse events. Overall survival was statistically significantly improved in patients receiving Cyramza 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 Cyramza from3.8 months for placebo. Progression-free survival was statistically significantly improved in patients receiving Cyramza 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 Cyramza from 1.3 months for placebo. Efficacy results are shown in Table 10.

**Table 10: Summary of efficacy data – ITT population**

| | **Cyramza 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

**Figure 3: Kaplan-Meier curves of overall survival for Cyramza versus placebo in REGARD**



Based on limited data from REGARD patients with HER2-positive gastric or GEJ adenocarcinoma and patients previously treated with trastuzumab (in RAINBOW), it is considered unlikely that Cyramza has a detrimental effect or that it has no effect in patients with HER2-positive gastric cancer. *Post hoc* unstratified subgroup analyses from RAINBOW patients previously treated with trastuzumab (n = 39) suggested a survival benefit in such patients (HR 0.679, 95 % CI 0.327, 1.419) and demonstrated a benefit for progression free survival (PFS) (HR 0.399, 95 % CI 0.194, 0.822).

*Colorectal cancer*

*RAISE*
RAISE was a global, randomised, double-blind, study of Cyramza plus FOLFIRI versus placebo plus FOLFIRI, in patients with mCRC, who had disease progression on or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients were required to have ECOG PS 0 or 1 and to have disease progression within 6 months of the last dose of first-line therapy. Patients were required to have adequate hepatic, renal and coagulation function. Patients with a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders, a recent history of severe (Grade ≥3) bleeding or who had experienced an arterial thrombotic event (ATE) in the 12 months prior to randomisation were excluded. Patients were also excluded if they had experienced any of: an ATE, Grade 4 hypertension, Grade 3 proteinuria, a Grade 3-4 bleeding event, or bowel perforation during first-line bevacizumab therapy.

A total of 1072 patients were randomised (1:1) to receive either Cyramza (n = 536) at 8 mg/kg or placebo (n = 536), in combination with FOLFIRI. All medicinal products were administered intravenously. The FOLFIRI regimen was: irinotecan 180 mg/m$^2$ administered over 90 minutes and folinic acid 400 mg/m$^2$ administered, simultaneously over 120 minutes; followed by bolus 5-fluorouracil(5-FU) 400 mg/m$^2$ over 2 to 4 minutes; followed by 5-FU 2400 mg/m$^2$ administered by continuous infusion over 46 to 48 hours. Treatment cycles on both arms were repeated every 2 weeks. Patients who discontinued one or more components of treatment because of an adverse event were permitted to continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity. The primary endpoint was OS and the secondary endpoints included PFS, objective response rate (ORR) and quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30. Randomisation was stratified by geographic region, tumour KRAS status (mutant or wild-type), and time to disease progression (TTP) after commencing first-line treatment (< 6 months versus ≥ 6 months).

Demographic and baseline characteristics for the ITT population were similar between treatment arms. Median age was 62 years and 40 % of patients were ≥ 65 years; 57 % of patients were male; 76 % were White and 20 % Asian; 49 % had ECOG PS 0; 49 % of patients had KRAS mutant tumours; and 24 % of patients had TTP < 6 months after commencing first-line treatment. Post discontinuation systemic anti-cancer therapy was given to 54 % of patients receiving Cyramza plus FOLFIRI and 56 % of patients receiving placebo plus FOLFIRI.

Overall survival was statistically significantly improved in patients receiving Cyramza plus FOLFIRI compared with those receiving placebo plus FOLFIRI (HR 0.844; 95 % CI: 0.730 to 0.976; p = 0.0219). There was an increase in median survival of 1.6 months in favour of the Cyramza plus FOLFIRI arm: 13.3 months in the Cyramza plus FOLFIRI arm and 11.7 months in the placebo plus FOLFIRI arm. Progression-free survival was statistically significantly improved in patients receiving Cyramza plus FOLFIRI compared with those receiving placebo plus FOLFIRI (HR 0.793; 95 % CI: 0.697 to 0.903; p = 0.0005). There was an increase in median PFS of 1.2 months in favour of the Cyramza plus FOLFIRI arm: 5.7 months in the Cyramza plus FOLFIRI arm and 4.5 months in the placebo plus FOLFIRI arm. Efficacy results are shown in Table 11 and Figures 4 and 5.

Pre-specified analyses for OS and PFS by stratification factors were performed. The HR of OS was 0.82 (95 % CI: 0.67 to 1.0) in patients with a KRAS wild type tumour, and 0.89 (95 % CI: 0.73 to 1.09) in patients with a KRAS mutant tumour. For patients with TTP ≥ 6 months after commencing first-line treatment the HR of OS was 0.86 (95 % CI: 0.73 to 1.01), and 0.86 (95 % CI: 0.64 to 1.13) in patients with TTP < 6 months after commencing first-line treatment. Pre-specified subgroup analyses for both PFS and OS according to age (< 65 and ≥ 65 years), gender, race, ECOG PS (0 or ≥ 1), number of organs involved, liver metastases only, site of primary tumour (colon or rectum), carcinoembryonic antigen levels (< 200 µg/L, ≥ 200 µg/L), all showed a treatment effect favouring Cyramza plus FOLFIRI treatment over placebo plus FOLFIRI. In 32 of the 33 pre-specified sub-group analyses for OS, the HR was < 1.0. The one sub-group with HR > 1 was for patients with disease progression from start of first-line bevacizumab treatment of < 3 months (HR 1.02 [95 % CI: 0.68 to 1.55]). This one sub-group is a group which can be considered to have aggressive disease that is relatively refractory to first-line treatment. In both treatment arms, patients who experienced neutropenia had a longer median OS compared to patients who did not experience neutropenia. The median OS in patients with any grade neutropenia was greater in the ramucirumab arm (16.1 months) than in the placebo arm (12.6 months). Median OS in patients who did not experience neutropenia was 10.7 months in both arms.

**Table 11: Summary of efficacy data – ITT population**

| | **Cyramza plus FOLFIRI N = 536** | **Placebo plus FOLFIRI N = 536** |
|---|---|---|
| Overall survival, months | | |
| Median (95 % CI) | 13.3 (12.4, 14.5) | 11.7 (10.8, 12.7) |
| Hazard ratio (95 % CI) | 0.84 (0.73, 0.98) | |
| Stratified log-rank p-value | 0.022 | |
| Progression free survival, months | | |
| Median (95 % CI) | 5.7 (5.5, 6.2) | 4.5 (4.2, 5.4) |
| Hazard ratio (95 % CI) | 0.79 (0.70, 0.90) | |
| Stratified log-rank p-value | < 0.001 | |

Abbreviations: CI = confidence interval

**Figure 4: Kaplan-Meier curves of overall survival for Cyramza plus FOLFIRI versus placebo plus FOLFIRI in RAISE**

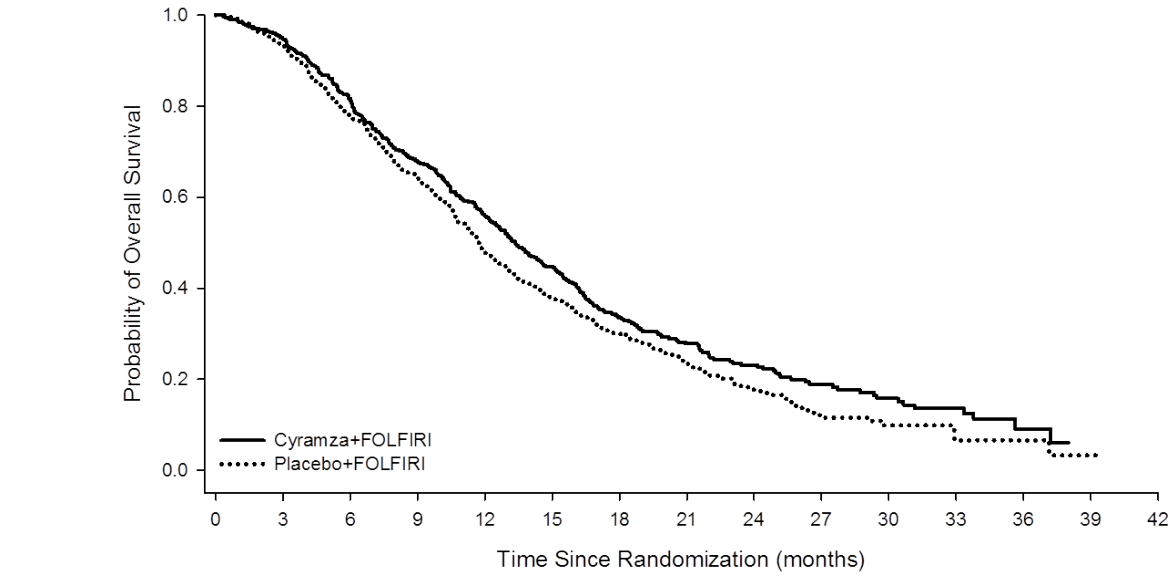
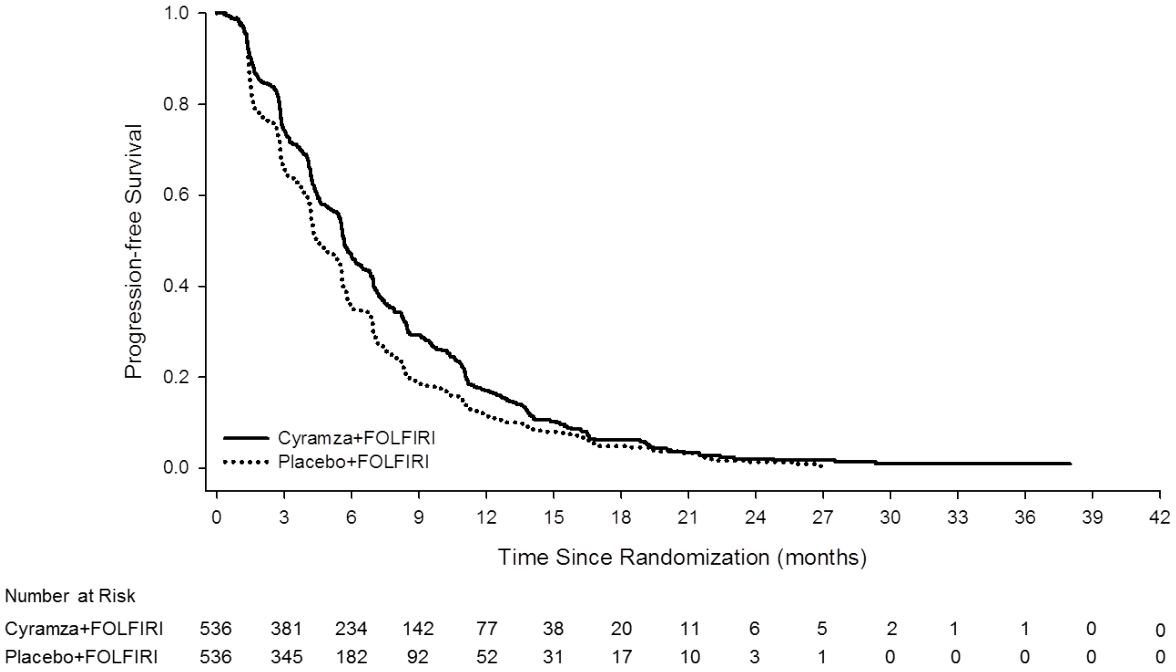


**Figure 5: Kaplan-Meier curves of progression -free survival for Cyramza plus FOLFIRI versus placebo plus FOLFIRI in RAISE**




Number at Risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyramza+FOLFIRI | 536 | 381 | 234 | 142 | 77 | 38 | 20 | 11 | 6 | 5 | 2 | 1 | 1 | 0 | 0 |
| Placebo+FOLFIRI | 536 | 345 | 182 | 92 | 52 | 31 | 17 | 10 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |

The ORR was similar for both treatment arms (13.4 % versus 12.5 %, ramucirumab plus FOLFIRI versus placebo plus FOLFIRI, respectively). The disease control rate (complete response plus partial response plus stable disease) was numerically higher in patients on the ramucirumab plus FOLFIRI arm as compared to the placebo plus FOLFIRI arm (74.1 % versus 68.8 %, respectively). For the EORTC QLQ-C30, patients in the ramucirumab plus FOLFIRI treatment arm reported a transient decrease in QoL compared to the patients in the placebo plus FOLFIRI treatment arm in most of the scales. Few between-arm differences were reported after the first month of treatment.

*NSCLC*

*RELAY*

RELAY was a global, randomised, double-blind, phase 3 study of Cyramza plus erlotinib versus placebo plus erlotinib that randomised (1:1) 449 previously untreated patients with metastatic non-small 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.

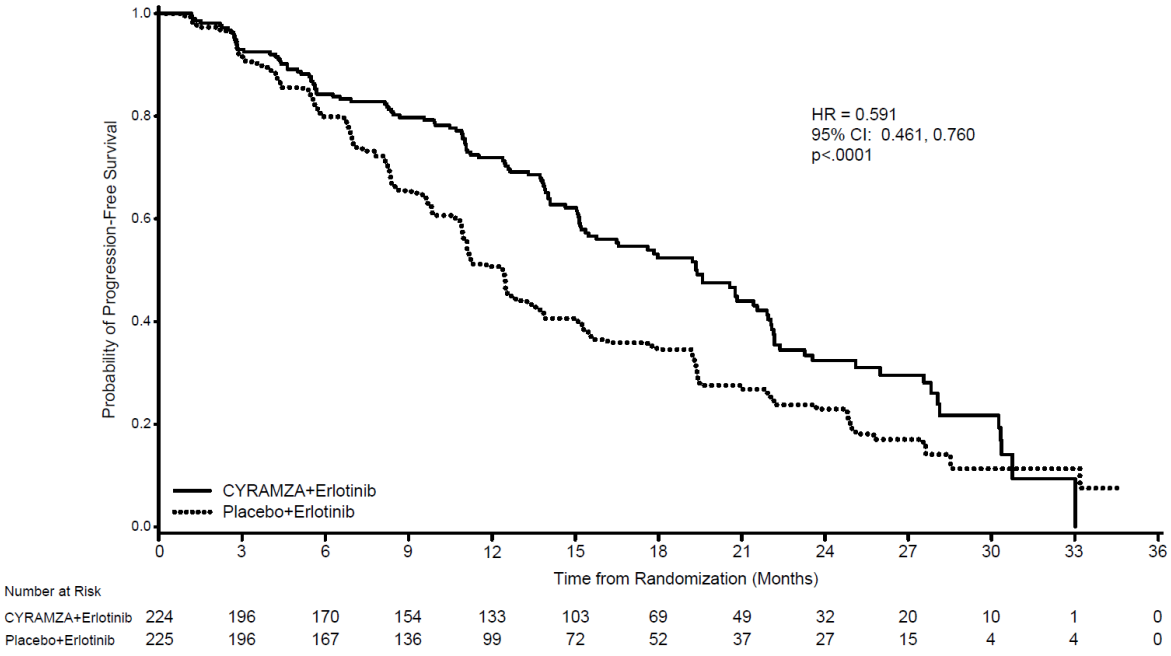
Demographics and baseline characteristics were balanced between arms. 77 % of patients were Asian and 22 % were Caucasian. Patients treated with Cyramza plus erlotinib experienced a statistically significant improvement in progression-free survival (PFS) compared to patients treated with placebo plus erlotinib (Table 12). Consistent results were observed across subgroups including exon 19 deletions and exon 21 (L858R) substitution, age, race (Caucasian HR: 0.618, Asian HR: 0.638), smokers and never smokers. Overall survival data were immature at the time of the primary PFS analysis (17.6 % maturity). RELAY efficacy results are shown in Table 12 and Figure 6.

**Table 12: Summary of efficacy data in RELAY – Intent to treat (ITT) population**

| | **Cyramza plus erlotinib N = 224** | **Placebo plus erlotinib N = 225** |
|---|---|---|
| **Progression-free Survival** | | |
| Number of events (%) | 122 (54.5) | 158 (70.2) |
| Median – months (95 % CI) | 19.4 (15.38, 21.55) | 12.4 (10.97, 13.50) |
| Hazard Ratio (95 % CI) | 0.591 (0.461, 0.760) | |
| Stratified Log-rank p-value | < 0.0001 | |
| **Objective Response Rate (Complete Response + Partial Response)** | | |
| Rate – percent (95 % CI) | 76 (70.8, 81.9) | 75 (69.0, 80.3) |
| CR, n (%) | 3 (1.3) | 2 (0.9) |
| PR, n (%) | 168 (75.0) | 166 (73.8) |
| **Duration of Response** | **N = 171** | **N = 168** |
| Number of events (%) | 101 (59.1) | 128 (76.2) |
| Median – months (95 % CI) | 18.0 (13.86, 19.78) | 11.1 (9.69, 12.29) |
| Hazard Ratio (95 % CI) | 0.619 (0.477, 0.805) | |
| Unstratified Log-rank p-value | 0.0003 | |

Abbreviations: CI = confidence interval, NR= not reached, CR = complete response, PR = partial response. Endpoints were alpha-protected.

**Figure 6: Kaplan-Meier curves of progression free survival for Cyramza plus erlotinib versus placebo plus erlotinib in RELAY**




A final analysis of OS, for which the study was not powered, was performed at 297 events (maturity 66.1 %). The stratified OS HR was 0.98 [95 % CI 0.78 – 1.24, p = 0.864] with a median OS of 51.1 months [95 % CI 44.85 - 57.26] for Cyramza plus erlotinib vs 46.0 months [95 % CI 43.56 - 53.03] for placebo plus erlotinib.

*REVEL*

REVEL, a randomised, double-blind study of Cyramza plus docetaxel versus placebo plus docetaxel, was conducted in 1253 patients with locally advanced or metastatic squamous or non-squamous NSCLC with disease progression on or after one platinum-based therapy. The primary endpoint was OS. Patients were randomised in a 1:1 ratio to receive Cyramza plus docetaxel (n = 628) or placebo

plus docetaxel (n = 625). Randomisation was stratified by geographic region, gender, prior maintenance, and ECOG PS. Cyramza 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.

Baseline patient demographics and disease characteristics were generally balanced between arms: the median age was 62 years; 67 % of patients were male; 82 % were Caucasian, 13 % Asian; the ECOG PS was 0 for 32 % of patients, 1 for 67 % of patients; 73 % of patients had non-squamous histology and 26 % had squamous histology. The most common prior therapies included pemetrexed (38 %), gemcitabine (25 %), taxane (24 %), and bevacizumab (14 %); 22 % of patients received prior maintenance therapy. The median duration of docetaxel therapy was 14.1 weeks for the ramucirumab plus docetaxel arm (with a median of 4.0 infusions received) and 12.0 weeks for the placebo plus docetaxel arm (with a median of 4.0 infusions received).

OS was statistically significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (HR 0.857; 95 % CI: 0.751 to 0.979; p = 0.024). There was an increase in median survival of 1.4 months in favour of the Cyramza plus docetaxel arm: 10.5 months in the Cyramza plus docetaxel arm and 9.1 months in the placebo plus docetaxel arm. PFS was statistically significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (HR 0.762; 95 % CI: 0.677 to 0.859; p < 0.001). There was an increase in median PFS of 1.5 months in favour of the Cyramza plus docetaxel arm: 4.5 months in the Cyramza plus docetaxel arm and 3 months in the placebo plus docetaxel arm. ORR was significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (22.9 % vs. 13.6 %, p < 0.001). The primary QoL analysis showed similar time to deterioration for all Lung Cancer Symptom Scale (LCSS) scores between treatment arms.

A consistent improvement (ramucirumab plus docetaxel vs placebo plus docetaxel) was observed in important subgroups for PFS and OS. OS subgroup results included the following: non-squamous histology (HR 0.83; 95 % CI: 0.71 to 0.97; median OS [mOS]: 11.1 vs 9.7 months) and squamous histology (HR 0.88; 95 % CI: 0.69 to 1.13; mOS: 9.5 vs 8.2 months); patients with prior maintenance (HR 0.69; 95 % CI: 0.51 to 0.93; mOS: 14.4 vs 10.4 months); time since start of prior therapy < 9 months (HR 0.75; 95 % CI: 0.64 to 0.88; mOS: 9.3 vs 7.0 months); patients < 65 years old (HR 0.74, 95 % CI: 0.62, 0.87; mOS: 11.3 vs 8.9 months). A trend towards less efficacy with increasing age has been observed in patients receiving ramucirumab plus docetaxel for the treatment of advanced NSCLC with disease progression after platinum-based chemotherapy (see section 5.1). No differences in efficacy between treatment arms have been observed in the subgroups of patients ≥ 65 years old (OS HR 1.10, 95 % CI: 0.89, 1.36; median OS [mOS]: 9.2 vs 9.3 months, see section 4.4), patients pre-treated with taxanes (HR 0.81; 95 % CI:0.62 to 1.07; mOS 10.8 vs 10.4 months) and those with time since start of prior therapy ≥ 9 months (HR 0.95; 95 % CI: 0.75 to 1.2; mOS: 13.7 vs 13.3 months). Efficacy results are shown in Table 13.

**Table 13: Summary of efficacy data – ITT population**

| | Cyramza plus docetaxel N = 628 | Placebo plus docetaxel N = 625 |
|---|---|---|
| Overall survival, months | | |
| Median – months (95 % CI) | 10.5 (9.5, 11.2) | 9.1 (8.4, 10.0) |
| Hazard ratio (95 % CI) | 0.857 (0.751, 0.979) | |
| Stratified log-rank p-value | 0.024 | |
| Progression free survival, months | | |
| Median (95 % CI) | 4.5 (4.2, 5.4) | 3.0 (2.8, 3.9) |
| Hazard Ratio (95 % CI) | 0.762 (0.677, 0.859) | |
| Stratified log-rank p-value | < 0.001 | |
| Objective response rate (CR + PR) | | |
| Rate – percent (95 % CI) | 22.9 (19.7, 26.4) | 13.6 (11.0, 16.5) |
| Stratified CMH p-value | < 0.001 | |

Abbreviations: CI = confidence interval, CR= complete response, PR= partial response, CMH = Cochran-Mantel-Haenszel

**Figure 7: Kaplan-Meier curves of overall survival for Cyramza plus docetaxel versus placebo plus docetaxel in REVEL**

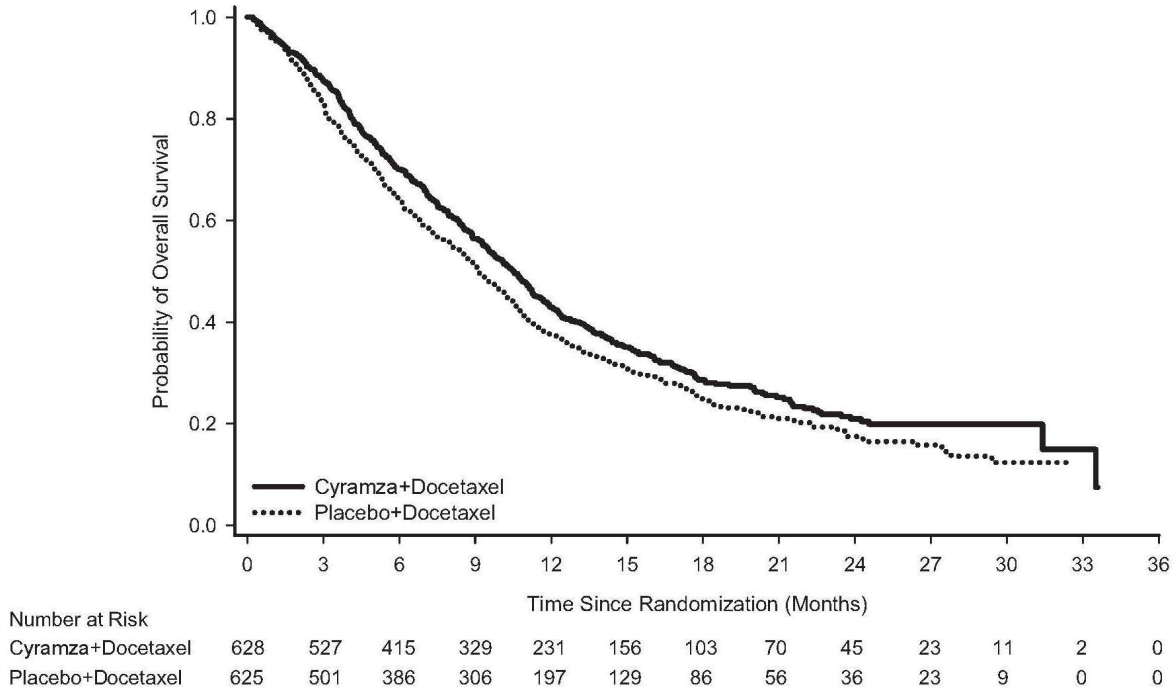
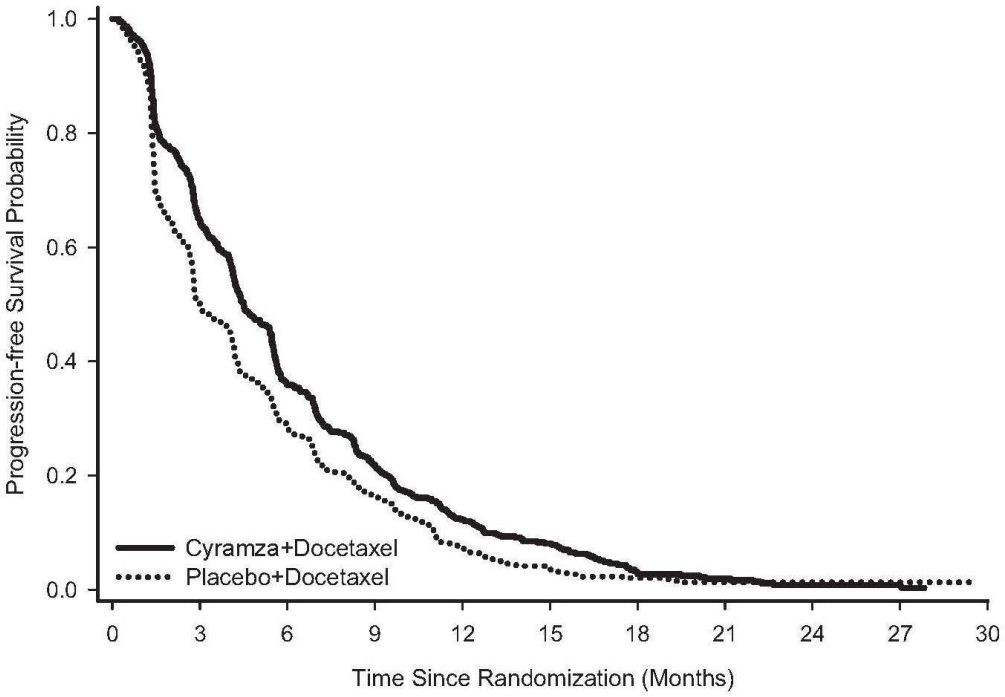


**Figure 8: Kaplan-Meier curves of progression-free survival for Cyramza plus docetaxel versus placebo plus docetaxel in REVEL**




| Number at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyramza+Docetaxel | 628 | 383 | 204 | 120 | 59 | 38 | 11 | 7 | 3 | 3 | 0 |
| Placebo+Docetaxel | 625 | 301 | 172 | 95 | 37 | 17 | 9 | 4 | 3 | 2 | 0 |

*Hepatocellular carcinoma*

*REACH-2*

REACH-2 was a global, randomised, double-blind study of Cyramza plus 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 Cyramza plus BSC or placebo plus BSC that had disease progression on or after prior sorafenib therapy.

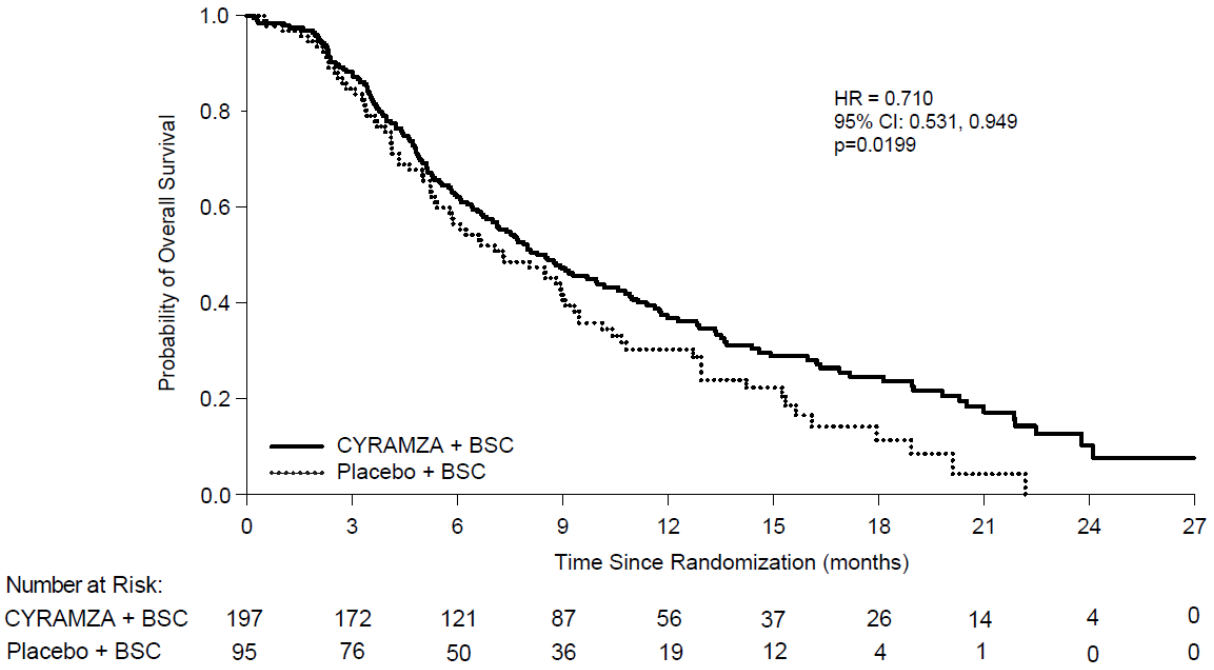
In REACH-2, baseline patient demographics and disease characteristics were generally balanced between arms, except for AFP, which was lower in the placebo arm. Patients treated with Cyramza experienced a statistically significant improvement in OS, compared to placebo (Table 14). The major efficacy outcome in REACH-2 was supported by a statistically significant improvement in progression free survival in Cyramza treated patients compared to placebo treated patients. The relative treatment effect (assessed by HR) of Cyramza compared to placebo was generally consistent across subgroups, including age, race, aetiology of disease and reason for discontinuation of sorafenib (progressive disease vs. intolerance). A relevant exposure-efficacy association was observed for ramucirumab in REACH-2 (see section 5.2). REACH-2 efficacy results are shown in Table 14 and Figure 9.

**Table 14: Summary of efficacy data in REACH-2 – Intent to treat (ITT) population**

| | Cyramza N = 197 | Placebo N = 95 |
|---|---|---|
| **Overall survival, months** | | |
| Median (95 % CI) | 8.51 (7.00, 10.58) | 7.29 (5.42, 9.07) |
| Hazard ratio (95 % CI) | 0.710 (0.531, 0.949) | |
| Stratified log-rank p-value | 0.0199 | |
| **Progression free survival, months** | | |
| Median (95 % CI) | 2.83 (2.76, 4.11) | 1.61 (1.45, 2.69) |
| Hazard ratio (95 % CI) | 0.452 (0.339, 0.603) | |
| Stratified log-rank p-value | < 0.0001 | |
| **Objective Response Rate (CR + PR)** | | |
| ORR % (95 % CI) | 4.6 (1.7, 7.5) | 1.1 (0.0, 3.1) |
| p-value | 0.1697 | |

Abbreviations: CI = confidence interval, CR = complete response, ORR = objective response rate and PR = partial response

**Figure 9: Kaplan-Meier curves of Overall Survival for Cyramza versus placebo in REACH-2**




*Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥ 2 patients*
Patients with ECOG score ≥ 2 were excluded from the pivotal studies in all indications, therefore the safety and efficacy of Cyramza in this patient population is unknown.

Immunogenicity

Patients in two phase 3 studies, RAINBOW and REGARD were tested at multiple time-points for anti-drug antibodies (ADAs). Samples were tested from 956 patients: 527 ramucirumab treated patients and 429 control treated patients. Eleven (2.2 %) of ramucirumab treated patients and two (0.5 %) of control treated patients developed ADAs. None of the patients with ADAs experienced an IRR. No patients had neutralising antibodies to ramucirumab. There is insufficient data to evaluate the effects of ADAs on the efficacy or safety of ramucirumab.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Cyramza in all subsets of the paediatric population in gastric adenocarcinoma, in adenocarcinoma of the colon and rectum, in lung carcinoma, and liver cancer (see section 4.2 for information on paediatric use).

The safety and pharmacokinetics (PK) of ramucirumab, as a single agent, were evaluated in I4T-MC-JVDA, a multicenter, open-label, phase 1 study in paediatric and young adult patients aged 1 to 21 years to determine the recommended phase 2 dose (RP2D). The study consisted of 2 parts. In Part A, ramucirumab was administered at a dose of 8 mg/kg or 12 mg/kg intravenously over 60 minutes every 2 weeks to 23 patients with recurrent or refractory non-CNS tumours. A maximum tolerated dose was not reached. The RP2D was determined to be 12 mg/kg when given every 2 weeks. In Part B, ramucirumab was administered at the RP2D to 6 patients with relapsed or refractory CNS tumours for evaluation of tolerability in this population. No tumour responses were observed in either Part A or B.

The efficacy and safety of ramucirumab in combination with cyclophosphamide and vinorelbine versus cyclophosphamide and vinorelbine alone was evaluated in J1S-MCJV01 (JV01), a randomised, multicentre, global, Phase 2 study in 30 paediatric patients and young adults aged 36 months to 29 years, with relapsed, recurrent, or refractory desmoplastic small round cell tumour (DSRCT). Randomisation (2:1) was stratified by staging at relapse (metastatic disease versus locally advanced). JV01 did not meet the pre-specified success criterion for the study, which required a 99% posterior probability of superiority (HR<1) to declare success for the intervention. At the final analysis, according to the frequentist analysis, the median PFS was 6.75 months in the experimental arm and 1.71 months in the control arm (HR 0.465 [80% CI: 0.261, 0.827]). There was one partial response and one complete response in the experimental arm. One partial response and no complete response was observed in the control arm. Due to the limited size of this study, it is not possible to conclude that the benefits of the use outweigh the risks.

The efficacy and safety of ramucirumab in combination with gemcitabine and docetaxel compared to gemcitabine and docetaxel alone was evaluated in J1S-MC-JV02 (JV02), a randomised, multicentre, global, Phase 2 study in 23 paediatric patients and young adults aged 36 months to 29 years with relapsed, recurrent, or progressive synovial sarcoma (SS). Randomization (2:1) was stratified by staging at relapse (metastatic disease versus locally advanced). The study was terminated without formal evaluation of the primary PFS endpoint since at the interim futility analysis, JV02 did not meet the pre-specified 60 % confidence in treatment superiority (PFS HR of less than 1 for SS). There was one partial response and no complete response in the experimental arm. No responses, complete or partial, were observed in the control arm.

## 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

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

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).

Paediatric population

The mean peak concentration was 165 µg/mL following 8 mg/kg (study JVDA), 231 µg/mL following 9 mg/kg (study JV02), 238 µg/mL (CV%=35) following 12 mg/kg (study JV01) and 285 µg/mL (CV%=26) following 12 mg/kg (study JVDA), respectively. The $C_{trough}$ was 41.6 (CV%=57) and 48.3 µg/mL (CV%=41) at Day 15 Cycle 1 (n=19) in study JV01 and study JVDA, respectively. Exposure to ramucirumab in paediatric and young adult patients (children > 12 months and < 21 years) with refractory solid tumours, including CNS tumours following a single dose or multiple doses of 8 mg/kg or 12 mg/kg was similar to the exposure obtained in adult patients. Further, ramucirumab exposure following 12 mg/kg dose was similar across the age range of > 12 months to < 21 years.

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 reactions 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 (E 640)
Polysorbate 80 (E 433)
Water for injections

## 6.2 Incompatibilities

Cyramza should not be administered or mixed with dextrose solutions.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

Unopened vial

3 years.

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 at 25 ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use 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 - 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

10 ml solution in a vial (Type I glass) with a chlorobutyl rubber stopper, an aluminium seal and a polypropylene cap.
50 ml solution in a vial (Type I glass) with a chlorobutyl rubber stopper, an aluminium seal and a 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 ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/ml solution of ramucirumab. Only use sodium chloride 9 mg/ml (0.9 %) solution for injection as a diluent.

<u>In case of pre-filled intravenous infusion container usage</u>

Based on the calculated volume of ramucirumab, remove the corresponding volume of sodium chloride 9 mg/ml (0.9 %) solution for injection from the pre-filled 250 ml intravenous container. Aseptically transfer the calculated volume of ramucirumab 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.

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

Aseptically transfer the calculated volume of ramucirumab 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 ramucirumab 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. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000
3528 BD Utrecht
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/957/001
EU/1/14/957/002
EU/1/14/957/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 December 2014
Date of latest renewal: 26 September 2019

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

ImClone Systems LLC
33 ImClone Drive,
Branchburg
New Jersey
NJ 08876
UNITED STATES

Eli Lilly Kinsale Limited
Dunderrow
Kinsale
County Cork
Ireland

Name and address of the manufacturers responsible for batch release

Lilly, S.A.
Avda de la Industria, 30
Alcobendas
28108 Madrid
Spain

Lilly France Fegersheim
2 rue du Colonel Lilly
67640 Fegersheim
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON - 10 ml vial**

## 1. NAME OF THE MEDICINAL PRODUCT

Cyramza 10 mg/ml concentrate for solution for infusion
ramucirumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 10 mg ramucirumab.

## 3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride, sodium chloride, glycine, polysorbate 80, water for injections. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

100 mg/10 ml
1 vial
2 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
For single use only.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000
3528 BD Utrecht
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/957/001 - 1 vial of 10 ml.
EU/1/14/957/002 - 2 vials of 10 ml.

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL – 10 ml vial**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cyramza 10 mg/ml sterile concentrate
ramucirumab
For IV use after dilution.

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/10 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 50 ml vial**

## 1. NAME OF THE MEDICINAL PRODUCT

Cyramza 10 mg/ml concentrate for solution for infusion
ramucirumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 10 mg ramucirumab.

## 3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride, sodium chloride, glycine, polysorbate 80, water for injections. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

500 mg/50 ml
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
For single use only.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000
3528 BD Utrecht
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/957/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL – 50 ml vial**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cyramza 10 mg/ml sterile concentrate
ramucirumab
For IV use after dilution.

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg/50 ml

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Cyramza 10 mg/ml concentrate for solution for infusion**
ramucirumab

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What Cyramza is and what it is used for
2. What you need to know before you are given Cyramza
3. How you are given Cyramza
4. Possible side effects
5. How to store Cyramza
6. Contents of the pack and other information


## 1. What Cyramza is and what it is used for

Cyramza is a cancer medicine that contains the active substance ramucirumab, which is a monoclonal antibody. This is a specialised protein that can recognise and attach to another protein found on blood vessels called 'VEGF receptor 2'. This receptor is needed in the development of new blood vessels. To grow, cancer needs new blood vessels to develop. By attaching to 'VEGF receptor 2' and blocking it the medicine cuts off the blood supply to the cancer cells.

Cyramza is given in combination with paclitaxel, another anti-cancer medicine, for the treatment of advanced stomach cancer (or cancer of the junction between the oesophagus and the stomach) in adults whose disease has worsened after treatment with medicines to treat cancer.

Cyramza is used for the treatment of advanced stomach cancer (or cancer of the junction between the oesophagus and the stomach) in adults whose disease has worsened after treatment with medicines to treat cancer and for whom treatment of Cyramza in combination with paclitaxel is not suitable.

Cyramza is used to treat advanced cancers of the colon or rectum (parts of the large intestine) in adults. It is given with other medicines called 'FOLFIRI chemotherapy', including '5-fluorouracil', 'folinic acid', and 'irinotecan'.

Cyramza is given in combination with erlotinib, another anti-cancer medicine, as the first therapy for the treatment of adult patients with advanced non-small cell lung cancer when the cancer cells have specific changes (mutations) in the epidermal growth factor receptor gene.

Cyramza is given in combination with docetaxel, another anti-cancer medicine, for the treatment of adult patients with advanced stage of lung cancer whose disease has worsened after treatment with medicines to treat cancer.

Cyramza is used to treat liver cancer that is advanced or cannot be taken out by surgery, in adults who have been previously treated with another anticancer medicine (sorafenib) and who have an elevated level of a particular protein in the blood (alpha fetoprotein).

## 2. What you need to know before you are given Cyramza

**You must not be given Cyramza**
- if you are allergic to ramucirumab or any of the other ingredients of this medicine (listed in section 6).
- if there is X-ray evidence that the lung cancer has a cavity or hole in it or if the lung cancer is close to major blood vessels.

**Warnings and precautions**
Talk to your doctor or nurse **before** you are given Cyramza if you:

- have any condition which increases the risk of bleeding. Also tell your doctor if you are taking any medicines which may increase the risk of bleeding or which affect blood clotting ability. In such cases, your doctor will perform regular blood tests to monitor the risk of bleeding.

- have liver cancer and have had previous bleeding from enlarged veins in your food pipe (oesophagus) or have high blood pressure in the portal vein, which carries the blood from the bowel and spleen to the liver.

- have lung cancer and have had recent bleeding in the lung (coughing up bright red blood) or you are regularly taking non-steroidal anti-inflammatory medicines, or medicines which affect blood clotting ability.

- have high blood pressure. Cyramza can increase the incidence of high blood pressure. Your doctor will make sure that if you already have high blood pressure, it is brought under control before starting Cyramza. Your doctor will monitor your blood pressure and adjust your blood pressure medicine as needed during treatment with Cyramza. Treatment with Cyramza may need to be stopped temporarily until high blood pressure is controlled with medicines, or stopped permanently if it cannot be adequately controlled.

- have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- are going to have planned surgery, if you had recent surgery or if you have poor wound healing after surgery. Cyramza may increase the risk of problems with wound healing. You should not receive Cyramza for at least 4 weeks before you undergo planned surgery and your doctor will decide when to re-start treatment. If you have a wound that heals poorly during treatment, dosing of Cyramza will be stopped until the wound is fully healed.

- have severe liver disease (‘cirrhosis’) and associated conditions, such as excessive accumulation of fluid in your abdomen (‘ascites’). Your doctor will discuss with you if the potential benefits of treatment are judged to outweigh the potential risks for you. If you have liver cancer your doctor will monitor you for signs and symptoms of confusion and/or disorientation associated with chronic liver problems and will stop treatment with Cyramza if you develop these signs and symptoms.

- have severe kidney problems. There are limited data available about the use of Cyramza in patients with severely impaired kidney function.

Talk to your doctor or nurse **immediately** if any of the following applies to you (or you are not sure) **during treatment** with Cyramza **or anytime thereafter:**

- **Blocking of the arteries by a blood clot** (‘arterial thromboembolic events’):
  Cyramza can cause blood clots in your arteries. Arterial blood clots can lead to serious conditions, including heart attack or stroke. Symptoms of a heart attack may include chest pain or heaviness in the chest. Symptoms of a stroke may include sudden numbness or weakness of the arm, leg and face, feeling confused, difficulty speaking or understanding others, sudden

difficulty in walking or loss of balance or coordination or sudden dizziness. Cyramza will be permanently stopped if you develop a blood clot in your arteries.

- **A hole in the wall of your gut** ('gastrointestinal perforation'): Cyramza may increase the risk of developing a hole in the wall of your gut. Symptoms include severe abdominal pain, being sick (vomiting), fever or chills. Cyramza will be permanently stopped if you develop a hole in the wall of your gut.

- **Severe bleeding:** Cyramza may increase the risk of severe bleeding. Symptoms may include: extreme tiredness, weakness, dizziness or changes in the colour of your stools. Cyramza will be permanently stopped if you experience severe bleeding.

- **Infusion-related reaction:** Infusion-related reactions may happen during treatment because Cyramza is given as an intravenous infusion via a drip (see section 3). Your doctor or nurse will check for side effects during your infusion. Symptoms may include: increased muscle tension, back pain, chest pain and/or tightness, chills, flushing, difficulty in breathing, wheezing, and feeling of tingling or numbness in hands or feet. In severe cases, symptoms may include breathing distress caused by narrowing of the airways, faster heartbeat, and feeling faint. Cyramza will be permanently stopped if you experience a severe infusion-related reaction.

- **A rare but serious brain condition** called 'posterior reversible encephalopathy syndrome' or 'PRES': Cyramza may increase the risk of developing this brain condition. Symptoms may include fits (seizures), headache, feeling sick (nausea), being sick (vomiting), blindness or reduced level of consciousness, with or without high blood pressure. Cyramza will be stopped if you experience this brain condition.

- **Cardiac Failure**: Cyramza, when given in combination with chemotherapy or erlotinib may increase the risk of cardiac failure. Symptoms may include weakness and tiredness, swelling, and fluid build-up in the lungs, which can cause shortness of breath. Your symptoms will be evaluated and suspension of your treatment with Cyramza may be considered.

- **Abnormal tube-like connections or passageways inside the body** ('fistula'): Cyramza may increase the risk of abnormal tube-like connections or passageways inside the body between internal organs and skin or other tissues. Cyramza will be permanently stopped if you develop a fistula.

- **Abnormal urine test** ('proteinuria'): Cyramza may increase the risk of developing or worsening of abnormal levels of protein in the urine. Treatment with Cyramza may need to be stopped temporarily until the levels of protein in the urine decrease and then treatment resumed at a lower dose, or stopped permanently if the urine protein level does not reduce sufficiently.

- **Inflammation of the mouth** ('stomatitis'): Cyramza, when given in combination with chemotherapy may increase the risk of developing inflammation of the mouth. Symptoms may include a burning sensation in the mouth, ulceration, blisters or swelling. Your doctor may prescribe treatment to help with the symptoms.

- **Fever or infection**: You may develop a temperature of 38 ºC or greater during treatment (since you might have fewer white blood cells than normal which is very common). Symptoms may include sweating or other signs of infection, such as headache, pain in the limbs or decreased appetite. Infection (sepsis) may be severe and could lead to death.

- **Elderly people with lung cancer**: Your doctor will carefully evaluate the most appropriate treatment for you.

**Children and adolescents**
Cyramza should not be given to patients under the age of 18 years because there is no information about how it works in this age group.

**Other medicines and Cyramza**
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

**Pregnancy, breast-feeding and fertility**
Before starting treatment you must tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or you are planning to have a baby. You should avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose of Cyramza. Talk to your doctor about the best contraception for you.

As Cyramza inhibits the development of new blood vessels, it may decrease the likelihood of you becoming pregnant or maintaining a pregnancy. It may also cause damage to your unborn baby. You should not use this medicine during pregnancy. If you become pregnant during treatment with Cyramza, your doctor will discuss with you if the benefit of treatment for you is greater than any possible risk to you or your unborn baby.

It is not known if the medicine passes into breast milk and could affect a breastfed baby. Therefore, you should not breast-feed your baby during treatment with Cyramza and for at least 3 months after you receive the last dose.

**Driving and using machines**
Cyramza has no or negligible influence on your ability to drive and use machines. If you experience any symptoms affecting your ability to concentrate and react, do not drive or use machines until the effect goes away.

**Cyramza contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) in each 10 ml vial, that is to say essentially ‘sodium free’.
This medicine contains approximately 85 mg sodium (main component of cooking/table salt) in each 50 ml vial. This is equivalent to approximately 4 % of the recommended maximum daily dietary intake of sodium for an adult.

**Cyramza contains polysorbate**
This medicine contains approximately 1 mg of polysorbate 80 in each 10 ml vial, and 5 mg of polysorbate 80 in each 50 ml vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 3. How you are given Cyramza

This cancer treatment will be given to you by a doctor or nurse.

**Dosage and frequency of administration**
The correct amount of Cyramza needed to treat your disease will be calculated by your doctor or hospital pharmacist depending on your body weight.

The recommended dose of Cyramza for the treatment of gastric cancer, for the treatment of advanced cancer of the colon or rectum and for the treatment of liver cancer is 8 mg per kilogram of your body weight once every 2 weeks.

The recommended dose of Cyramza for the treatment of lung cancer is 10 mg per kilogram of your body weight once every 2 weeks when given in combination with erlotinib or once every 3 weeks when given in combination with docetaxel.

The number of infusions you will receive depends on how you are responding to treatment. Your doctor will discuss this with you.

**Premedication**
You may be given another medicine to reduce the risk of an infusion-related reaction before you receive Cyramza. If you experience an infusion-related reaction during Cyramza therapy, you will be given premedication for all future infusions.

**Dose adjustments**
During each infusion, your doctor or nurse will check for side effects.

If you experience an infusion-related reaction during treatment, the time taken to give your infusion will be increased for the rest of that infusion and for all future infusions.

The amount of protein in your urine will be checked regularly during treatment. Depending on the protein level measured, Cyramza may be temporarily discontinued. Once the urine protein level has decreased to a certain level, treatment may be restarted with a lower dose.

**Route and method of administration**
Cyramza is a concentrate for solution for infusion (also called "sterile concentrate"). A hospital pharmacist, nurse or doctor will have diluted the contents of the vial with sodium chloride 9 mg/ml (0.9 %) solution before use. This medicine is given by infusion via a drip over a period of approximately 60 minutes.

**Cyramza treatment will be temporarily stopped if you:**
- develop high blood pressure, until it is controlled with anti-hypertensive medicine
- develop wound healing problems, until the wound is healed
- will undergo planned surgery, four weeks prior to surgery

**Cyramza treatment will be permanently stopped if you:**
- develop a blood clot in your arteries
- develop a hole in the wall of your gut
- experience severe bleeding
- experience a severe infusion-related reaction
- develop high blood pressure that cannot be controlled with medicine
- are passing more than a certain amount of protein with your urine or if you develop a severe kidney disease (nephrotic syndrome)
- develop abnormal tube-like connections or passageways inside the body between internal organs and skin or other tissues (fistula)
- develop confusion and/or disorientation associated with chronic liver problems
- decline in kidney function (in the setting of liver failure)

**When receiving Cyramza in combination with paclitaxel or docetaxel**
Paclitaxel and docetaxel are also given by a drip into a vein (intravenous infusion) over a period of approximately 60 minutes. If you are receiving Cyramza in combination with either paclitaxel or docetaxel on the same day, Cyramza will be given first.

The amount of paclitaxel or docetaxel needed depends on the surface area of your body. Your doctor or hospital pharmacist will calculate your body surface area by measuring your height and weight and will work out the right dose for you.

The recommended dose of paclitaxel is 80 mg for every square metre ($m^2$) of your body's surface area once every week for 3 weeks followed by 1 week without treatment.

The recommended dose of docetaxel is 75 mg for every square metre ($m^2$) of your body's surface area once every 3 weeks. If you are of East Asian origin, you may receive a reduced docetaxel starting dose of 60 mg per every $m^2$ of your body's surface area once every 3 weeks.

Prior to being given any paclitaxel infusion, you will have blood tests to check that your blood counts are high enough and that your liver is functioning well.

Read the paclitaxel or docetaxel package leaflet for further information.

**When receiving Cyramza in combination with FOLFIRI**
FOLFIRI chemotherapy is given by intravenous infusion, after the Cyramza infusion has finished. Please read the package leaflets for the other medicines that are part of your treatment, to see if they are suitable for you. If you are unsure, ask your doctor, pharmacist or nurse if there are any reasons why you can't use these medicines.

**When receiving Cyramza in combination with erlotinib**
Please read the erlotinib package leaflet for information on erlotinib and whether it is suitable for you. If you are unsure, ask your doctor, pharmacist or nurse if there are any reasons why you can't use erlotinib.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if you experience any of the following serious side effects that have been observed during Cyramza treatment (see also **What you need to know before you are given Cyramza**):

**Common side effects** (may affect up to 1 in 10 people):
- **hole in the wall of your gut:** this is a hole that develops in the stomach, gut or bowel. Symptoms include severe abdominal pain, being sick (vomiting), fever or chills.
- **severe bleeding in your gut:** symptoms may include extreme tiredness, weakness, dizziness or changes in the colour of your stools.
- **blood clots in the arteries:** arterial blood clots can lead to a heart attack or stroke. Symptoms of a heart attack may include chest pain or heaviness in the chest. Symptoms of a stroke may include sudden numbness or weakness of the arm, leg and face, feeling confused, difficulty speaking or understanding others, sudden difficulty in walking or loss of balance or coordination or sudden dizziness.

**Rare side effects** (may affect up to 1 in 1 000 people):
- **a brain condition** called posterior reversible encephalopathy syndrome: symptoms may include fits (seizures), headache, feeling sick (nausea), being sick (vomiting), blindness or reduced level of consciousness, with or without high blood pressure.

**Tell your doctor if you experience any of the following other side effects:**

**Very common side effects** (may affect more than 1 in 10 people):
- feeling tired or weak
- low white blood cell counts (may increase the risk of infection)
- infections
- diarrhoea
- hair loss
- nose bleed
- inflammation of the lining of the mouth
- high blood pressure
- reduction in red blood cells which can make the skin pale
- swelling of hands, feet and legs due to fluid retention
- low platelet count (blood cells that help the blood to clot)
- abdominal pain

- protein in the urine (abnormal urine test)
- headache
- inflammation of mucous membranes, such as digestive and respiratory tracts

**Common side effects** (may affect up to 1 in 10 people):
- fever accompanied by low white blood cell counts
- low blood levels of a protein called albumin
- infusion-related reactions
- rash
- redness, swelling, numbness/tingling, or pain and/or skin peeling in hands and/or feet (called hand-foot syndrome)
- hoarseness
- bleeding in your lungs
- low blood levels of sodium (hyponatraemia) which can cause tiredness and confusion or muscle twitching
- bleeding gums
- confusion and/or disorientation in patients with chronic liver problems
- intestinal blockage; symptoms may include constipation and abdominal pain
- underactive thyroid gland which can cause tiredness or weight gain (hypothyroidism)
- abnormal growth of blood vessels
- serious infection (sepsis)
- low blood levels of potassium (hypokalaemia) which can cause muscle weakness, twitching or abnormal heart rhythm

**Uncommon side effects** (may affect up to 1 in 100 people):
- a heart condition when the heart muscle does not pump blood as well as it should, causing shortness of breath and swelling of legs and feet

**Rare side effects** (may affect up to 1 in 1 000 people):
- abnormal blood clotting in small blood vessels

**Not known** (frequency cannot be estimated from the available data):
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Cyramza may cause changes in laboratory tests. From the side effects listed above, these are: low white blood cell counts; low platelet count in the blood; low blood levels of albumin, potassium or sodium; presence of protein in the urine.

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Cyramza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Do not freeze or shake the infusion solution. Do not administer the solution if you notice any particulate matter or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Cyramza contains**
- The active substance is ramucirumab. One ml of concentrate for solution for infusion contains 10 mg of ramucirumab.
- Each 10 ml vial contains 100 mg of ramucirumab.
- Each 50 ml vial contains 500 mg of ramucirumab.
- The other ingredients are histidine, histidine monohydrochloride, sodium chloride, glycine (E 640), polysorbate 80 (E 433) and water for injections (see section 2 “Cyramza contains sodium” and “Cyramza contains polysorbate”).

**What Cyramza looks like and contents of the pack**
The concentrate for solution for infusion (or sterile concentrate) is a clear to slightly opalescent and colourless to slightly yellow solution in a glass vial with a rubber stopper.

Cyramza is available in packs of:
- 1 vial of 10 ml
- 2 vials of 10 ml
- 1 vial of 50 ml

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
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**This leaflet was last revised in .**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

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 ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/ml solution of ramucirumab. Only use sodium chloride 9 mg/ml (0.9 %) solution for injection as a diluent.

<u>In case of pre-filled intravenous infusion container usage</u>

Based on the calculated volume of ramucirumab, remove the corresponding volume of sodium chloride 9 mg/ml (0.9 %) solution for injection from the pre-filled 250 ml intravenous container. Aseptically transfer the calculated volume of ramucirumab 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.

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

Aseptically transfer the calculated volume of ramucirumab 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.

After dilution and preparation, the medicine must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

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 ramucirumab 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.