

Medicinal product no longer authorised

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Portrazza 800 mg concentrate for solution for infusion

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 50 mL vial contains 800 mg of necitumumab.

Each mL of concentrate for solution for infusion contains 16 mg of necitumumab.

The concentrate must be diluted before use (see section 6.6).

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

### Excipient with known effect

Each 50 mL vial contains approximately 76 mg sodium.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent and colourless to slightly yellow liquid, with pH 6.0.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Portrazza in combination with gemcitabine and cisplatin chemotherapy is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition.

### **4.2 Posology and method of administration**

Necitumumab therapy must be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Appropriate medical resources for the treatment of severe infusion reactions should be available during necitumumab infusions. Availability of resuscitation equipment must be ensured.

### Posology

Portrazza is administered in addition to gemcitabine and cisplatin-based chemotherapy for up to 6 cycles of treatment followed by Portrazza as a single agent in patients whose disease has not progressed, until disease progression or unacceptable toxicity.

The recommended dose of Portrazza is 800 mg (flat dose) administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle. If a decreased infusion rate is indicated, the infusion duration should not exceed 2 hours.

Patients should be monitored during infusion for signs of infusion-related reactions (see section 4.4).

#### Premedication

In patients who have experienced a previous Grade 1-2 hypersensitivity or infusion-related reaction to Portrazza, premedication with a corticosteroid and an antipyretic in addition to an antihistamine is recommended.

Prior to each necitumumab infusion, premedication for possible skin reactions must be considered (see section 4.4).

#### Posology adjustments

Recommendations for the management of infusion-related and skin reactions are provided in tables 1 and 2.

#### *Hypersensitivity/Infusion-related reactions*

**Table 1 – Management recommendations for hypersensitivity/infusion-related reactions**

<b>Toxicity grade<sup>a</sup></b>	<b>Management recommendations (any occurrence)</b>
Grade 1	<ul style="list-style-type: none"><li>• Decrease infusion rate by 50 % for the duration of infusion.<sup>b</sup></li><li>• Monitor patient for worsening of condition.</li><li>• For subsequent infusions, please see premedication section.</li></ul>
Grade 2	<ul style="list-style-type: none"><li>• Stop the infusion; when the reaction has resolved to Grade <math>\leq 1</math>, resume infusion at a 50 % decreased infusion rate.<sup>b</sup></li><li>• Monitor patient for worsening of condition.</li><li>• For subsequent infusions, please see premedication section.</li></ul>
Grade 3-4	<ul style="list-style-type: none"><li>• Immediately and permanently discontinue treatment with necitumumab.</li></ul>

<sup>a</sup> Grade per NCI-CTCAE, Version 3.0

<sup>b</sup> Once the infusion rate has been reduced for a Grade 1 or 2 hypersensitivity/infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

## Skin reactions

**Table 2 – Management recommendations for skin reactions**

<b>Toxicity grade<sup>a</sup></b>	<b>Management recommendations (any occurrence)</b>
Grades 1 and 2	<ul style="list-style-type: none"><li>• No dose adjustment necessary</li></ul>
Grade 3	<ul style="list-style-type: none"><li>• Temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade <math>\leq 2</math>. Permanently discontinue if symptoms do not resolve to Grade <math>\leq 2</math> after holding for 2 consecutive cycles (6 weeks)</li><li>• Following improvement to Grade <math>\leq 2</math>, resume at reduced dose of 400 mg. If symptoms worsen at 400 mg, permanently discontinue.</li><li>• If symptoms do not worsen at 400 mg for at least 1 treatment cycle, the dose may be increased to 600 mg. If symptoms worsen at 600 mg, temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade <math>\leq 2</math>. Following improvement to Grade <math>\leq 2</math>, resume at reduced dose of 400 mg.</li><li>• If symptoms do not worsen at 600 mg for another treatment cycle, the dose may be further increased to 800 mg.</li><li>• Permanently discontinue if patients experience Grade 3 skin induration/fibrosis.</li></ul>
Grade 4	<ul style="list-style-type: none"><li>• Immediately and permanently discontinue treatment with necitumumab.</li></ul>

<sup>a</sup> Grade per NCI-CTCAE, Version 3.0

## Special populations

### Paediatric population

There is no relevant use of necitumumab in the paediatric population in the non-small cell lung cancer indication.

### Elderly

No dose reductions other than those recommended for all patients are necessary (see sections 4.4 and 5.1).

### Renal impairment

No dose adjustments are required in patients with mild or moderate renal impairment (see section 5.2). There are no data regarding necitumumab administration in patients with severe renal impairment. No dose reductions are recommended.

### Hepatic impairment

There are no data regarding necitumumab administration in patients with moderate or severe hepatic impairment (see section 5.2). No dose reductions are recommended.

## Method of administration

Portrazza is for intravenous use only. It is administered as an intravenous infusion over approximately 60 minutes via an infusion pump. Portrazza must not be administered as an intravenous bolus or push. In case of previous hypersensitivity or infusion-related reaction, recommendations for management of hypersensitivity/infusion-related reactions should be followed, as for Table 1.

Only sodium chloride 9 mg/mL (0.9 %) solution for injection should be used as a diluent. Portrazza infusions should not be administered or mixed with glucose solutions. For instructions on dilution of the medicinal product before administration, see section 6.6.

### 4.3 Contraindications

Patients with a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

### 4.4 Special warnings and precautions for use

#### Thromboembolic events

Venous thromboembolic events (VTE) and arterial thromboembolic events (ATE), including fatal cases, were observed with necitumumab in combination with gemcitabine and cisplatin (see also section 4.8).

Administration of necitumumab should be carefully considered in those patients with a history of thromboembolic events (such as pulmonary embolism, deep vein thrombosis, myocardial infarction, stroke) or preexisting risk factors for thromboembolic events (such as advanced age, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with acquired or inherited thrombophilic disorders). The relative risk of VTE or ATE was approximately three-fold higher in patients with a reported history of VTE or ATE.

Necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient.

Thromboprophylaxis should be considered after careful assessment of a patient's risk factors (including the increased risk of serious bleeding in patients with tumour cavitation or tumour involvement of large central blood vessels).

Patients and physicians should be aware of signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

Discontinuation of necitumumab in patients who experience a VTE or ATE should be considered after a thorough benefit risk assessment for the individual patient.

In a clinical trial in advanced non-squamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm (see also section 4.8). The addition of necitumumab did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced non-squamous NSCLC.

#### Cardiorespiratory disorders

An increased frequency of cardiorespiratory arrest or sudden death was observed with necitumumab. Cardiorespiratory arrest or sudden death was reported in 2.8% (15/538) of patients treated with necitumumab in combination with gemcitabine and cisplatin compared to 0.6% (3/541) of patients treated with chemotherapy alone. Twelve of the fifteen patients died within 30 days of the last dose of necitumumab and had comorbid conditions including history of coronary artery disease (n=3), hypomagnesemia (n=4), chronic obstructive pulmonary disease (n=7), and hypertension (n=5). Eleven of the 12 patients had an unwitnessed death. Patients with significant coronary artery disease, myocardial infarction within 6 months, uncontrolled hypertension, and uncontrolled congestive heart failure were not enrolled in the pivotal study. The incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.

#### Hypersensitivity/infusion-related reactions

Hypersensitivity/infusion-related reactions (IRRs) were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Monitor patients during and following the infusion for signs of hypersensitivity and infusion-related reactions with

resuscitation equipment and appropriate medical resources readily available. In patients who have experienced a previous Grade 1 or 2 hypersensitivity or infusion related reaction to Portrazza, premedication with a corticosteroid and an antipyretic in addition to an antihistamine is recommended. For management and dose adjustments, see section 4.2.

#### Skin reactions

Skin reactions were reported with necitumumab (see section 4.8). The onset of events occurred mainly during the first cycle of treatment. For management and dose adjustments, see section 4.2. Pre-emptive skin treatment including skin moisturiser, sun screen, topical steroid cream (1 % hydrocortisone) and an oral antibiotic (e.g. doxycycline) may be useful in the management of dermatologic reactions as clinically appropriate. Patients may be advised to apply moisturiser, sunscreen and topical steroid cream to face, hands, feet, neck, back and chest.

#### Electrolyte abnormalities

Progressively decreasing serum magnesium levels occur frequently (81.3%) and may lead to severe Hypomagnesaemia (18.7%) (see also section 4.8). Hypomagnesaemia may reoccur at the same grade or worse after a dose delay. Patients should be carefully monitored for serum electrolytes, including serum magnesium, potassium, and calcium, prior to each necitumumab administration and after completion of necitumumab treatment, until within normal limits. Prompt electrolyte repletion is recommended, as appropriate.

#### Infections

In a phase 2 clinical trial investigating necitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone as the first-line therapy in patients with Stage IV metastatic squamous NSCLC, an increased rate of infections was observed early after start of treatment, which led to subsequent infectious complications such as pneumonia and/or sepsis. A similar observation was made in a clinical trial investigating necitumumab in combination with pemetrexed and cisplatin versus pemetrexed and cisplatin alone as the first-line therapy in patients with advanced non-squamous NSCLC.

Special attention should be given to patients with clinical evidence of concomitant infectious conditions including early signs of active infections. Treatment of any infection should be initiated according to local standards.

#### Elderly

No overall differences in efficacy between arms were observed in patients above 70 years of age. Cardiovascular comorbidities, performance status and the likely tolerability to chemotherapy with add-on necitumumab should therefore be thoroughly evaluated prior to the initiation of treatment in patients above 70 years of age.

#### Women of childbearing potential/contraception in females

Based on its mechanism of action and animal models where EGFR expression is disrupted, necitumumab may cause foetal harm or developmental anomalies. Women of childbearing potential should be advised to avoid becoming pregnant while on necitumumab. Effective contraception has to be used during necitumumab treatment and up to 3 months after last administration of necitumumab treatment. Contraceptive measures or abstinence are recommended (see section 4.6).

#### Sodium restricted diet

This medicinal product contains 76 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

No drug-drug interactions were observed between Portrazza and gemcitabine/cisplatin. The pharmacokinetics of gemcitabine/cisplatin were not affected when co-administered with necitumumab

and the pharmacokinetics of necitumumab were not affected when co-administered with gemcitabine/cisplatin.

No other formal interaction studies with necitumumab have been performed in humans.

#### **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 necitumumab and should be informed of the potential hazard to the pregnancy and foetus. Women of childbearing potential have to use effective contraception during necitumumab treatment and up to 3 months after last administration of necitumumab treatment. Contraceptive measures or abstinence are recommended.

##### Pregnancy

There are no data from the use of necitumumab in pregnant women. Animal reproduction studies have not been conducted with necitumumab. Based on animal models, epidermal growth factor receptor (EGFR) is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Portrazza should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus.

##### Breast-feeding

It is unknown whether necitumumab is excreted in human milk. Excretion in milk and oral absorption is expected to be low. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Portrazza and for at least 4 months after the last dose.

##### Fertility

There are no data on the effect of necitumumab on human fertility. Animal studies to assess fertility directly have not been conducted (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Portrazza has no known influence on the ability to drive and use machines. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

The most common serious adverse reactions (Grade  $\geq 3$ ) observed in necitumumab-treated patients are skin reactions (6.3 %) and venous thromboembolic events (4.3 %).

The most common adverse reactions were skin reactions, venous thromboembolic events and laboratory abnormalities (hypomagnesaemia and albumin-corrected hypocalcaemia).

##### Tabulated list of adverse reactions

Adverse drug reactions (ADRs) which were reported in patients with squamous non-small cell lung cancer are listed below in MedDRA body system organ class, frequency and grade of severity. The following convention has been used for classification of frequency:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

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

The following table provides the frequency and severity of ADRs based on results from SQUIRE, a global, multicenter, two-arm, randomized Phase 3 study in adult patients with squamous NSCLC randomised to treatment with necitumumab in combination with gemcitabine/cisplatin or gemcitabine/cisplatin.

**Table 3. ADRs reported in  $\geq 1\%$  of necitumumab treated patients in SQUIRE**

System organ class	Frequency	ADR <sup>a</sup>	Portrazza + GC <sup>b</sup> (N=538)		GC (N=541)	
			Any grade (%)	Grade $\geq 3$ (%)	Any grade (%)	Grade $\geq 3$ (%)
Infections and infestations	Common	Urinary tract infection	4.1	0.2	1.7	0.2
Nervous system disorders	Common	Headache	8.6	0	5.7	0.4
	Common	Dysgeusia	5.9	0.2	3.3	0
Eye disorders	Common	Conjunctivitis	5.6	0	2.2	0
Vascular disorders	Common	Venous thromboembolic events	8.2	4.3	5.4	2.6
	Common	Arterial thromboembolic events	4.3	3.0	3.9	2.0
	Common	Phlebitis	1.7	0	0.4	0
Respiratory, thoracic and mediastinal disorders	Common	Haemoptysis	8.2	0.9	5.0	0.9
	Common	Epistaxis	7.1	0	3.1	0.2
	Common	Oropharyngeal pain	1.1	0	0.7	0
Gastrointestinal disorders	Very common	Vomiting	28.8	2.8	25.0	0.9
	Very common	Stomatitis	10.4	1.1	6.3	0.6
	Common	Dysphagia	2.2	0.6	2.2	0.2
	Common	Mouth ulceration	1.5	0	0.4	0
Skin and subcutaneous tissue disorders	Very common	Skin reactions	77.9	6.3	11.8	0.6
	Common	Hypersensitivity reactions/infusion-related reactions	1.5	0.4	2.0	0



Musculoskeletal and connective tissue disorders	Common	Muscle spasms	1.7	0	0.6	0
Renal and urinary disorders	Common	Dysuria	2.4	0	0.9	0
General disorders and administration site conditions	Very common	Pyrexia	12.3	1.1	11.1	0.4
Investigations	Very common	Hypomagnesaemia <sup>c</sup>	81.3	18.7	70.2	7.2
	Very common	Albumin-corrected hypocalcaemia <sup>c</sup>	33.0	4.2	22.9	2.3
	Very common	Hypophosphataemia <sup>c</sup>	28.9	6.3	22.7	5.7
	Very common	Hypokalaemia <sup>c</sup>	23.6	4.4	17.6	3.2
	Very common	Weight decreased	12.1	0.6	6.3	0.6

Abbreviations: GC = gemcitabine and cisplatin alone; Portrazza+GC = necitumumab plus gemcitabine and cisplatin; MedDRA = Medical Dictionary for Regulatory Activities.

a MedDRA preferred term (Version 16).

b The table reflects the frequency of ADRs during the chemotherapy phase of study treatment in which Portrazza+GC was directly compared with GC.

c Based on laboratory assessments. Only patients with baseline and at least one post-baseline result are included.

#### Description of selected adverse reactions

##### Thromboembolic events

Venous thromboembolic events (VTEs) were reported in approximately 8 % of patients and mainly present as pulmonary embolism and deep vein thrombosis. Severe VTEs were reported in approximately 4 % of patients. The incidence of fatal VTEs was similar between arms (0.2%). Arterial thromboembolic events (ATEs) were reported in approximately 4 % of patients and mainly present as stroke and myocardial infarction. Severe ATEs were reported in 3 % of patients. The incidence of fatal ATEs was 0.6% in the experimental arm versus 0.2% in the control arm (see also section 4.4).

In a clinical trial in advanced non-squamous NSCLC, venous thromboembolic events (VTEs) were reported in approximately 11 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 8 % in the pemetrexed and cisplatin alone arm) and mainly presented as pulmonary embolism and deep vein thrombosis. Severe VTEs were reported in approximately 6 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 4 % in the pemetrexed and cisplatin alone arm).

Arterial thromboembolic events (ATEs) were reported in approximately 4 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 6 % in the pemetrexed and cisplatin alone arm) and mainly present as stroke and myocardial infarction. Severe ATEs were reported in approximately 3 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 4 % in the pemetrexed and cisplatin alone arm).

### Skin reactions

Skin reactions were reported in approximately 78 % of patients and mainly presented as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia and palmar-plantar erythrodysesthesia syndrome. Severe skin reactions were reported in approximately 6 % of patients while 1.7 % of patients discontinued due to skin reactions. The majority of skin reactions developed during the first cycle of treatment and resolved within 17 weeks after onset (see also section 4.4).

### Infusion-related reactions

Infusion-related reactions were reported in 1.5 % of patients and mainly present as chills, fever or dyspnoea. Severe infusion-related reactions were reported in 0.4 % of patients. The majority of infusion-related reactions developed after the first or second administration of necitumumab.

### Toxicity in the elderly or in patients with ECOG PS 2

Clinically relevant toxicities with respect to the elderly and those patients with Eastern Cooperative Oncology Group (ECOG) performance status score 2 (ECOG PS2) were similar to the overall population in patients receiving necitumumab plus chemotherapy consisting of gemcitabine and cisplatin.

### Eyelash trichomegaly

Isolated cases of Grade 1 trichomegaly have been reported in patients treated with necitumumab.

### 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](#).

## **4.9 Overdose**

There has been limited experience with necitumumab overdose in human clinical trials. The highest dose of necitumumab studied clinically in a human dose-escalation Phase 1 study is 1,000 mg once a week or once every other week. Adverse events observed included headache, vomiting and nausea and were consistent with the safety profile at the recommended dose. There is no known antidote for necitumumab overdose.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC22

#### Mechanism of action

Necitumumab is a recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor 1 (EGFR) and blocks the ligand binding site, blocking activation by all known ligands and inhibiting relevant biological consequences *in vitro*. Activation of EGFR has been correlated with malignant progression, induction of angiogenesis and inhibition of apoptosis or cell death. In addition, necitumumab induces EGFR internalization and degradation *in vitro*. *In vivo* studies in cell line-derived xenograft models of human cancer, including non-small cell lung carcinoma, demonstrate that necitumumab has antitumor activity both in monotherapy and in combination with gemcitabine and cisplatin.

#### Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity.

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

### Clinical efficacy

SQUIRE, a global, multicenter, two-arm, randomized study of Portrazza, was conducted in 1,093 patients with stage IV (American Joint Committee on Cancer Version 7) squamous NSCLC, including patients with ECOG PS2, who had received no prior anticancer therapy for metastatic disease. Patients were randomised to receive first-line Portrazza at 800 mg plus chemotherapy consisting of gemcitabine at 1,250 mg/m<sup>2</sup> and cisplatin at 75 mg/m<sup>2</sup> (Portrazza+GC Arm), or gemcitabine-cisplatin chemotherapy alone (GC Arm). Portrazza and gemcitabine were administered on days 1 and 8 of each 3-week treatment cycle, and cisplatin was administered on day 1 of each 3-week treatment cycle. There was no premedication for Portrazza mandated by the study. Pre-emptive treatment for skin reaction was not permitted prior to the beginning of the second treatment cycle. Patients received a maximum of six cycles of chemotherapy in each arm; patients in the Portrazza+GC arm who had no progression continued to receive single-agent Portrazza until disease progression, unacceptable toxicity, or withdrawal of consent. The major efficacy outcome measure was overall survival (OS) and the supportive efficacy outcome measure was progression-free survival (PFS). Patients underwent radiographic assessment of disease status every six weeks, until radiographic documentation of progressive disease (PD).

Demographics and baseline characteristics were balanced between arms. Median age was 62 (32-86), 83 % of patients were men; 83.5 % were Caucasian; and 91 % were smokers. The ECOG PS was 0 for 31.5 %, 1 for 59.7 %, and 2 for 9 % of patients; over 50 % had metastatic disease at more than 2 sites. In the Portrazza+GC arm, 51 % of patients continued with single-agent Portrazza after completing chemotherapy. Use of post-study systemic therapy was similar in the 2 arms (47.3 % in the Portrazza+GC arm and 44.7 % in the GC arm).

Efficacy results are shown in Table 4.

**Table 4. Summary of efficacy data (ITT population)**

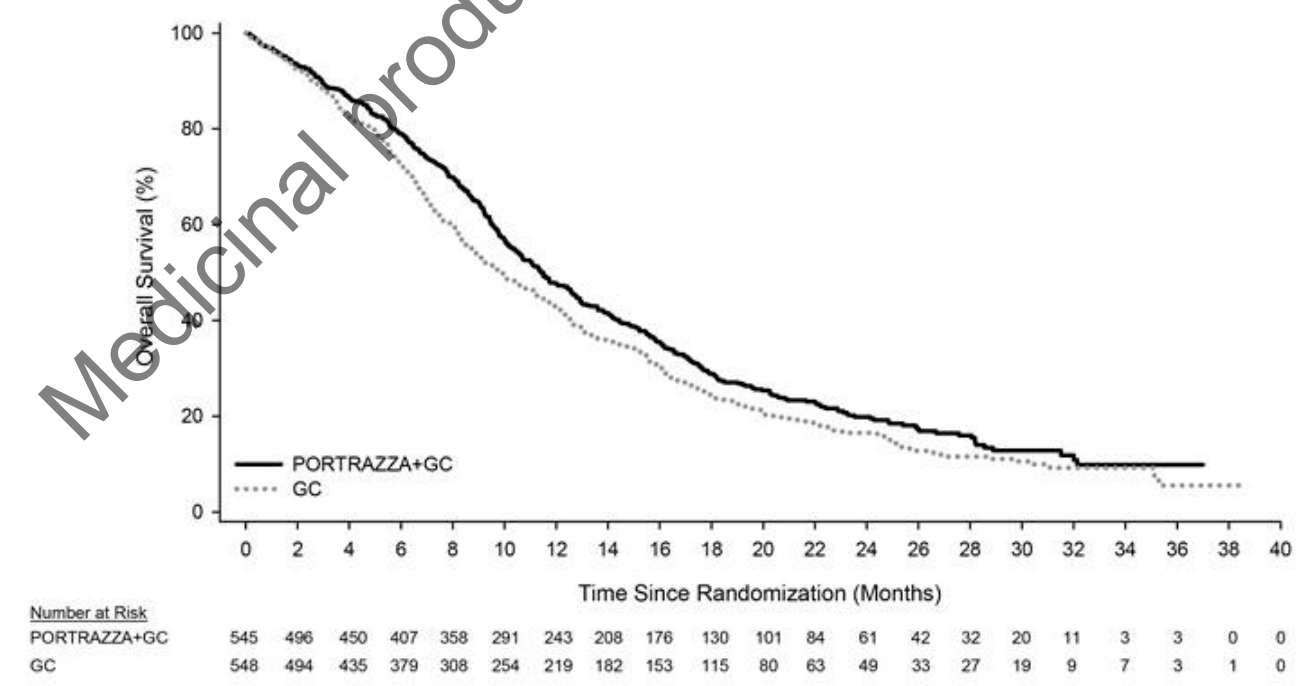
	<b>Portrazza+GC Arm</b> <b>N=545</b>	<b>GC Arm</b> <b>N=548</b>
Overall survival		
Number of events (n)	418	442
Median – months (95 % CI) <sup>a</sup>	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Hazard ratio (95 % CI) <sup>b, c</sup>	0.84 (0.74, 0.96)	
Two-sided log-rank p-value <sup>c</sup>	0.012	
1-year Overall survival rate (%)	47.7	42.8
Progression free survival		
Number of events (n)	431	417
Median – months (95 % CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Hazard ratio (95 % CI) <sup>b, c</sup>	0.85 (0.74, 0.98)	
Two-sided log-rank p-value <sup>c</sup>	0.020	

a Abbreviations: CI = confidence interval

b Hazard ratio is expressed as treatment/control and estimated from Cox model

c Stratified by the randomization strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia])

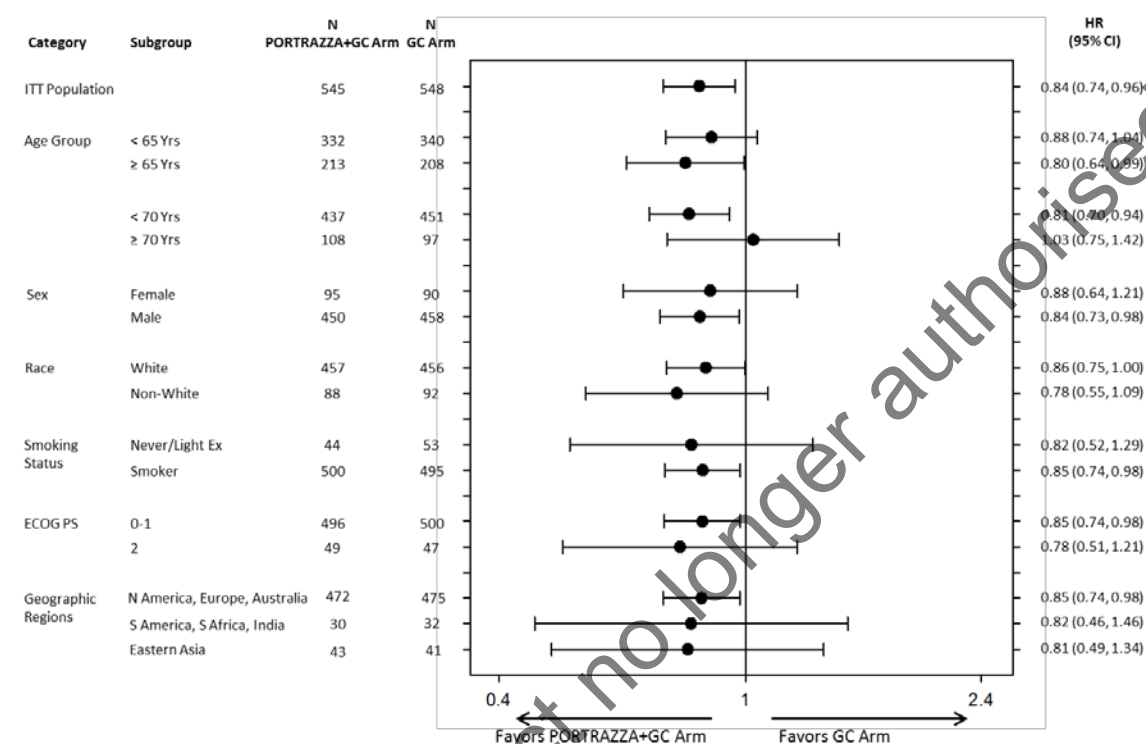
**Figure 1. Kaplan Meier plot of overall survival (ITT population)**



Abbreviations: C = cisplatin; G = gemcitabine.

An improvement was observed in subgroups for OS and PFS including the pre-specified stratification factors [ECOG PS score (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia)]; in patients age 70 and over, the hazard ratio for overall survival was 1.03 (0.75, 1.42) (see Figure 2).

**Figure 2. Forest plot for subgroup analysis of overall survival (ITT population)**



Abbreviations: C = cisplatin; G = gemcitabine; ITT = intent-to-treat.

A pre-planned exploratory analysis performed after the primary analysis, determined clinical efficacy outcome according to the level of tumour EGFR protein expression.

Of the ITT population, 982 patients (89.8%) were evaluable for an EGFR protein expression analysis by immunohistochemistry (IHC) using Dako PharmDx Kit. A tumour was considered to be EGFR-expressing if at least one stained cell could be identified. The large majority of patients (95.2% of evaluable patients, n = 935) had tumor samples expressing EGFR protein; 4.8% (n = 47) were not detectable for EGFR protein expression. There were no relevant differences in the distribution of demographics, disease characteristics, or the use of post-study systemic therapy between the subset of patients with detectable EGFR protein expression and the ITT population.

In patients with detectable EGFR protein expression (indicated patient population), overall survival was statistically significantly improved in the Portrazza+GC Arm as compared to the GC Arm with an estimated reduction in risk of death of 21% (hazard ratio [HR] = 0.79 [0.69, 0.92]; p = 0.002) and a median OS of 11.7 months in the Portrazza+GC Arm and 10.0 months in the GC Arm.

A statistically significant improvement in progression-free survival was also observed (HR = 0.84 [0.72, 0.97]; p = 0.018), with a median PFS of 5.7 months in the Portrazza+GC Arm and 5.5 months in the GC Arm.

In patients with detectable EGFR protein expression, there was no trend observed for increased efficacy with increasing levels of EGFR expression.

In patients with no detectable EGFR protein expression, no improvement in overall survival (hazard ratio [HR] = 1.52 [0.74, 3.12]) or progression free survival (hazard ratio [HR] = 1.33 [0.65, 2.70]) was observed.

In a phase 2 clinical trial investigating necitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone (106 versus 55 patients, 2:1 randomisation) as the first-line therapy in patients with Stage IV metastatic squamous NSCLC, a higher rate of death, including death due to infection, was observed for the necitumumab plus paclitaxel/carboplatin arm during the first 4 months (see also section 4.4), with a later trend towards improved survival after 4 months. The overall survival hazard ratio [HR] was 0.83 [0.55, 1.52].

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Portrazza in all subsets of the paediatric population in non-small cell lung cancer (see section 4.2 for information on paediatric use).

### **5.2 Pharmacokinetic properties**

Following the dose regimen of 800 mg necitumumab on day 1 and day 8 of a 21 day schedule, the geometric mean of necitumumab  $C_{min}$  was 98.5 µg/mL (Coefficient of Variation 80 %) in serum from patients with squamous NSCLC after five cycles of treatment in combination with gemcitabine and cisplatin.

#### Absorption

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

#### Distribution

Distribution of Portrazza follow a biphasic decline. Based on population pharmacokinetic approach (PopPK), the mean volume of distribution at steady state ( $V_{ss}$ ) for necitumumab was 6.97 L (CV 31 %).

#### Elimination

Necitumumab exhibits concentration-dependent clearance. Mean total systemic clearance ( $CL_{tot}$ ) at steady state following 800 mg on Day 1 and Day 8 of a 21-day cycle was 0.014 l/hr (CV 39 %). This corresponds to a half-life of approximately 14 days. The predicted time to reach steady state was approximately 70 days.

#### Special populations

Population pharmacokinetic analysis suggested age, gender, and race had no effect on the pharmacokinetics of necitumumab, while  $CL$  and volume of distribution had a less than proportional positive correlation with body weight. Although modeling results suggest that the disposition of necitumumab was statistically dependent on body weight, simulations indicated that weight-based dosing would not significantly decrease PK variability. No dose adjustment is necessary for these sub-populations.

#### Elderly

Based on the results of the population pharmacokinetic analysis, there was no impact of age on necitumumab exposure.

#### Renal impairment

No formal studies have been conducted to evaluate the effect of renal impairment on the PK of necitumumab. Based on the results of the population pharmacokinetic analysis, there was no impact of renal function as assessed by creatinine clearance [ $CrCl$ ] on the pharmacokinetics of necitumumab.

### Hepatic impairment

No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of necitumumab. Based on the results of the population pharmacokinetic analysis, hepatic status (as assessed by alanine aminotransferase, aspartate transaminase and total bilirubin) had no significant effect on the pharmacokinetics of necitumumab.

## **5.3 Preclinical safety data**

Dose dependent reversible skin toxicity was observed in the 26-week monkey study. The skin effects were consistent with the known class effects of EGFR inhibitors.

Specific animal studies to test necitumumab for carcinogenic potential or potential to impair fertility have not been performed. The risk of fertility impairment is unknown. However, no adverse effects on male or female reproductive organs were observed in monkeys treated for 26 weeks with necitumumab.

Human IgG1 is known to cross the placenta; therefore, necitumumab has the potential to be transmitted from the mother to the developing foetus. No animal studies have been specifically conducted to evaluate the effect of necitumumab on reproduction and foetal development; however, based on its mechanism of action and animal models where EGFR expression is disrupted, necitumumab may cause foetal harm or developmental anomalies.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium citrate dihydrate (E331)  
Citric acid anhydrous (E330)  
Sodium chloride  
Glycine (E640)  
Mannitol (E421)  
Polysorbate 80 (E433)  
Water for injections

### **6.2 Incompatibilities**

Portrazza infusions should not be administered or mixed with glucose 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  
2 years

#### After dilution

When prepared as directed, infusion solutions of Portrazza contain no antimicrobial preservatives.

It is recommended that the prepared dosing solution be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared necitumumab dosing solution must be stored at 2°C to 8°C for a duration not to exceed 24 hours, or may be held at 9°C to 25°C for up to 4 hours. Store protected from light. Brief exposure to ambient light is acceptable while preparation and administration is taking place.

#### **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

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**

50 mL solution in a vial (Type I glass) with a chlorobutyl elastomer stopper, an aluminium seal and a polypropylene cap.

Pack of 1 vial.

#### **6.6 Special precautions for disposal and other handling**

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 contents of the vials for particulate matter and discolouration. The concentrate for solution for infusion must be clear to slightly opalescent and colourless to slightly yellow prior to dilution. If particulate matter or discolouration is identified, discard the vial.

Vials contain 800 mg as a 16 mg/mL solution of necitumumab; one 50 mL vial contains the complete dose. Only use sodium chloride 9 mg/mL (0.9 %) solution for injection as a diluent.

##### To administer using pre-filled intravenous infusion containers

Aseptically remove 50 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection from the prefilled 250 mL container and transfer 50 mL of necitumumab medicinal product into the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix. **DO NOT FREEZE OR SHAKE** the infusion solution. **DO NOT** dilute with other solutions or co-infuse with other electrolytes or medicines.

##### To administer using empty intravenous infusion containers

Aseptically transfer 50 mL of necitumumab medicinal product into an empty intravenous container and add 200 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection to the container to bring the total volume to 250 mL. Gently invert the container to mix. **DO NOT FREEZE OR SHAKE** the infusion solution. **DO NOT** dilute with other solutions or co-infuse with other electrolytes or medicines.

Administer via an infusion pump. A separate infusion line must be used and the line must be flushed with sodium chloride 9 mg/mL (0.9 %) solution for injection at the end of the infusion.

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 necitumumab left in a vial, as the product contains no antimicrobial preservatives.

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.  
Papendorpseweg 83  
3528 BJ Utrecht  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1084/001

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

Date of first authorisation: 15 February 2016

**10. DATE OF REVISION OF THE TEXT**

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

Medicinal product no longer authorised

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S)  
AND MANUFACTURER(S) 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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) of the biological active substance(s)

ImClone Systems LLC  
33 ImClone Drive  
Branchburg  
New Jersey  
NJ 08876  
United States

Name and address of the manufacturer(s) responsible for batch release

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

**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**

The requirements for submission of periodic safety update reports 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. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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.
- **Additional risk minimisation measures**

Prior to launch of Portrazza (necitumumab) in each Member State the MAH must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Portrazza (necitumumab) is marketed, all physicians (i.e. oncologists) are notified about the key conditions for the safe use of necitumumab. The materials will address the risks concerning arterial / venous thromboembolic events and cardiorespiratory disorders.

**Key elements of the physician educational material:**

- Importance of assessing the risks before starting treatment with necitumumab
- Description of thromboembolic events including incidence rates from clinical trials
- Advice that patients and physicians should be aware of signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms of thromboembolism such as shortness of breath, chest pain, arm or leg swelling.
- The need to carefully consider use of necitumumab in patients with a history of thromboembolic events or pre-existing risk factors for thromboembolic events
- Information on relative risk of VTE or ATE in patients with a history of VTE or ATE
- Advice that necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient
- The need to consider thromboprophylaxis after careful assessment of a patient's risk factors
- Discontinuation of necitumumab in patients who experience a VTE or ATE should be considered after a thorough benefit risk assessment for the individual patient.
- Description of cardiorespiratory disorders including incidence rates from clinical trials
- Information that the incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.
- Instruction for healthcare professionals to read the materials in conjunction with the SmPC.

**The physician educational material package** should also contain:

- The Summary of Product Characteristics
- Patient Information Leaflet

Medicinal product no longer authorised

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

Medicinal product no longer authorised

#### **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Portrazza 800 mg concentrate for solution for infusion  
necitumumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial of 50 mL contains 800 mg necitumumab (16 mg/mL).

**3. LIST OF EXCIPIENTS**

Excipients: sodium citrate dihydrate, citric acid anhydrous, sodium chloride, glycine, mannitol, polysorbate 80 and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion

800 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.  
Papendorpseweg 83  
3528 BJ Utrecht  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1084/001

**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:



<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>VIAL LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Portrazza 800 mg sterile concentrate  
necitumumab  
For IV use after dilution.

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

Read the package leaflet before use.

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

800 mg/50 mL

<b>6. OTHER</b>
-----------------

Medicinal product no longer authorised

## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Portrazza 800 mg concentrate for solution for infusion necitumumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

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

Portrazza contains the active substance necitumumab, which belongs to a group of substances called monoclonal antibodies.

Necitumumab recognises and binds specifically to a protein on the surface of some cancer cells. The protein is known as epidermal growth factor receptor (EGFR). Other body proteins (called growth factors) can attach to the EGFR and stimulate the cancer cell to grow and divide. Necitumumab hinders other proteins from binding to the EGFR and thus prevents the cancer cell from growth and division.

Portrazza is used in combination with other anti-cancer medicines for the treatment of adults with certain type of lung cancer at an advanced stage (squamous non-small cell lung cancer), whose cancer cells have the EGFR protein on their surface. The anti-cancer medicines it is combined with are gemcitabine and cisplatin.

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

##### **You must not be given Portrazza**

- if you have ever had a severe allergic reaction to necitumumab or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

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

- **Blood clots in the arteries or the veins**  
Portrazza can cause blood clots in your arteries or your veins. Symptoms may include swelling, pain and tenderness of the limb, difficulty breathing, chest pain, or an abnormal heartbeat and

discomfort. Your doctor will discuss with you whether you need any preventive measures. See also section 4 for the symptoms of blood clots.

– **Cardiorespiratory disorders**

Cases of cardiorespiratory disorders and unexplained death were observed in patients treated with Portrazza in combination with gemcitabine and cisplatin and in patients treated with gemcitabine and cisplatin alone. The causes of these deaths and their relationship to treatment were not always known. Portrazza may increase this risk. Your doctor will discuss this with you.

– **Infusion-related reaction**

Infusion-related reactions may occur during treatment with Portrazza. Such reactions may be allergic. Your doctor will discuss with you whether you need any preventive measures or early treatment. Your doctor or nurse will check for side effects during your infusion. If you have a severe infusion-related reaction, your doctor may recommend adjusting the dose of Portrazza, or stop your treatment with Portrazza. See section 4 for more details about infusion-related reactions which may occur during or after the infusion.

– **Skin reactions**

Portrazza may cause side effects involving the skin. Your doctor will discuss with you whether you need any preventive measures or early treatment. If you have a severe skin reaction, your doctor may recommend adjusting the dose of Portrazza, or stop your treatment with Portrazza. See section 4 for more details about skin reactions.

– **Blood levels of magnesium, calcium, potassium and phosphate**

During treatment, your doctor will check your blood periodically for levels of several substances such as magnesium, calcium, potassium and phosphate. If these levels are too low, your doctor may prescribe appropriate supplements.

– **Infections**

If you have signs of infection before start of treatment please tell your doctor.

**Children and adolescents**

Portrazza 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 Portrazza**

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 and breast-feeding**

Before starting treatment you must tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

Avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose of Portrazza as this medicine may potentially cause harm to your unborn child. Talk to your doctor about the best contraception for you.

Do not breast-feed your baby during treatment with Portrazza and for at least 4 months after you receive the last dose, as this medicine may harm the growth and development of your baby.

**Driving and using machines**

If you experience any symptoms affecting your ability to concentrate and react, do not drive or use machines until the effect goes away.

### **Portrazza contains sodium**

This medicine contains 76 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

### **3. How you are given Portrazza**

A doctor experienced in the use of anti-cancer medicines will supervise your Portrazza therapy.

#### **Premedication**

You may be given medicines to reduce the risk of an infusion-related reaction or a skin reaction before you receive Portrazza.

#### **Dose and administration**

The recommended dose of Portrazza is 800 mg on days 1 and 8 of each 3-week cycle. Portrazza is given in combination with the medicines gemcitabine and cisplatin for up to 6 cycles and then it is given on its own. The number of infusions that you receive will depend on how and for how long you respond to treatment with Portrazza. Your doctor will discuss this with you.

This medicine is given as an intravenous (into a vein) infusion via a drip. The drip lasts about 60 minutes.

Detailed instructions for your doctor or your nurse on how to prepare Portrazza infusion are included at the end of this package leaflet (see 'Handling instructions').

#### **Dose adjustments**

During each infusion, your doctor or nurse will check for side effects. If you have an infusion-related reaction during treatment, your drip will be slowed down and future doses will also be given more slowly. The infusion duration should not exceed 2 hours. See also section 2 under "Warnings and precautions".

### **4. Possible side effects**

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

The important side effects of Portrazza are skin reactions and blood clots in the veins.

**Seek medical help immediately if you experience any of the following:**

#### **Blood clots in the veins**

Venous blood clots are likely to occur in approximately 8 out of 100 patients. In approximately 4 out of 100 patients these side effects are likely to be severe. They can lead to a blockage of a blood vessel in the leg. Symptoms may include swelling, pain and tenderness of the limb. Blood clots can also lead to a blockage in the blood vessels of the lung. Symptoms may include difficulty breathing, chest pain, or an abnormal heartbeat and discomfort.

#### **Skin reactions**

Skin reactions may occur in approximately 80 out of 100 patients who take Portrazza and are usually mild to moderate. In approximately 5 out of 100 patients these skin reactions are likely to be severe. Symptoms of severe skin reactions may include acne-like skin conditions and skin rash. The skin rash commonly resembles acne and often involves the face, upper chest and back, but can affect any area of the body. Most of these side effects usually disappear over time after the end of Portrazza therapy.

### Other side effects include:

**Very common** (may affect more than 1 in 10 people):

- itching; dry skin; scaling; nail disorders (skin reactions)
- vomiting
- fever or high temperature (pyrexia)
- decreased weight
- mouth ulcers and cold sores (stomatitis)

**Common** (may affect up to 1 in 10 people)

- headache
- coughing up blood (haemoptysis)
- nosebleed (epistaxis)
- strange tastes; metallic taste (dysgeusia)
- eye inflammation (conjunctivitis)
- blood clots in the arteries
- urinary tract infection (bladder and/or kidneys)
- pain when passing urine (dysuria)
- difficulty in swallowing (dysphagia)
- muscle spasms
- inflammation of veins in the legs (phlebitis)
- allergic reactions
- pain in your mouth and throat (oropharyngeal pain)

Portrazza may also cause changes in the results of blood tests. These include low blood levels of magnesium, calcium, potassium or phosphate.

### 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 Portrazza

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.

Infusion solution: 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 to 8 °C, or up to 4 hours at 9 °C to 25 °C. Do not freeze or shake the infusion solution. Do not administer the solution if you notice any particulate matter or discoloration.

This medicine is for single use only.

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 Portrazza contains

- The active substance is necitumumab. Each millilitre of the concentrate for solution for infusion contains 16 mg of necitumumab.  
Each 50 mL vial contains 800 mg of necitumumab.
- The other ingredients are sodium citrate dihydrate (E331), citric acid anhydrous (E330), sodium chloride (*see section 2 "Portrazza contains sodium"*), glycine (E640), mannitol (E421), polysorbate 80 (E433) and water for injections.

### What Portrazza looks like and contents of the pack

Portrazza 800 mg concentrate for solution for infusion (sterile concentrate) is a clear to slightly opalescent and colourless to slightly yellow liquid in a glass vial with a rubber stopper.

It is available in packs of:

- 1 vial of 50 mL

### Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

### Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tél/Tel: + 32-(0)2 548 84 84

#### Lietuva

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тел. + 359 2 491 41 40

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**România**

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**Suomi/Finland**

Oy Eli Lilly Finland Ab  
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**Sverige**

Eli Lilly Sweden AB  
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**United Kingdom**

Eli Lilly and Company Limited  
Tel: + 44-(0) 1256 315000

**This leaflet was last revised in <{month YYYY}>.**

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

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Handling instructions  
Portrazza 800 mg  
concentrate for solution for infusion  
necitumumab

The following information is intended for healthcare professionals only:

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

Each vial is intended for single use only. Inspect the contents of the vials for particulate matter and discolouration. The concentrate for solution for infusion must be clear to slightly opalescent and colourless to slightly yellow prior to dilution. If particulate matter or discolouration is identified, discard the vial.

Vials contain 800 mg as a 16 mg/mL solution of necitumumab; one 50 mL vial contains the complete dose. Only use sodium chloride 9 mg/mL (0.9%) solution for injection as a diluent.



To administer using pre-filled intravenous infusion containers

Aseptically remove 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection from the prefilled 250 mL container and transfer 50 mL of necitumumab medicine into the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicines.

To administer using empty intravenous infusion containers

Aseptically transfer 50 mL of necitumumab medicine into an empty intravenous container and add 200 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection to the container to bring the total volume to 250 mL. Gently invert the container to mix. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicines.

Administer via an infusion pump. A separate infusion line must be used and the line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection at the end of the infusion.

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

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

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