CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	August 7, 2015
Reviewer(s):	Mona Patel, Pharm.D. Division of Risk Management
Acting Team Leader:	Naomi Redd, Pharm.D. Division of Risk Management
Acting Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Portrazza (necitumumab)
Therapeutic Class:	anti-epidermal growth factor receptor
Dosage and Route:	800 mg intravenous infusion
Division:	Division of Oncology Products – 2 (DOP-2)
Application Type/Number:	BLA 125547
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2014-2461 2014-2466

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Portrazza (necitumumab). The applicant, Eli Lilly and Company, submitted a Biologics License Application (BLA) 125547 for their proposed indication of combination treatment with gemcitabine and cisplatin chemotherapy for first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.

Eli Lilly submitted a risk management plan with identified risks of arterial and venous thromboembolic events, hypersensitivity/infusion-related reactions, and electrolyte abnormalities. A potential risk associated with necitumumab was identified in the risk management plan as severe skin reactions. Eli Lilly' s submission included a pharmacovigilance plan, which proposed to manage these events through routine pharmacovigilance and product labeling. Eli Lilly did not submit a REMS for this application.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Eli Lilly Clinical Modules (sections 2.5, 2.7.3 and 2.7.4, 5.3.5.1)
- Risk Management Plan submitted November 25, 2014
- Midcycle Slides, April 24, 2015
- Portrazza (necitumumab) draft label, July 27, 2015
- FDA Briefing Document for July 9, 2015 Oncology Drug Advisory Committee (ODAC) Meeting
- Eli Lilly Slides for July 9, 2015 ODAC

3 REGULATORY HISTORY

The review timeline for this application is Standard. Listed below are the pertinent regulatory history milestones for this NDA:

- November 17, 2008 – IND 102512 submitted for necitumumab
- December 2, 2014 –NDA application received
- April 24, 2015 – Midcycle meeting
- May 8, 2015 – Midcycle teleconference with the sponsor
- Oncologic Drugs Advisory Committee (ODAC) Meeting, July 9, 2015
- Late-Cycle Meeting August 24, 2015
- PDUFA (Action) date – December 2, 2015

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide and the leading cause of cancer related deaths in the Unites States (US). [1] In the US, lung cancer represents the third most common type of cancer. An estimated 221, 200 new cases (115, 610 in men and 105, 590 in women) will be diagnosed in 2015, accounting for approximately 13% of all new cancer diagnoses. According to the American Cancer Society, lung cancer mainly occurs in older people. About 2 out of 3 people diagnosed with lung cancer are 65 or older; fewer than 2% of all cases are found in people younger than 45. The average age at the time of diagnosis is about 70. Black men are about 20% more likely to develop lung cancer (including all types) than are white men. The rate is about 10% lower in black women than in white women. In contrast, black men are about 15% *less* likely to develop small cell lung cancer than are white men, and the risk is about 30% lower in black women than in white women.[2]

The two major histological subtypes of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 85% of all cases of lung cancer. NSCLC is further classified into squamous and non-squamous cell carcinoma, the latter comprised of adenocarcinoma and large cell carcinoma histology.[3]

Squamous cell carcinoma comprises 30-35% of all lung cancers and is often associated with heavy tobacco use. Squamous tumors are typically centrally located, arising from and extending into a bronchus. Larger tumors tend to present with central necrosis and cavitation. The majority of patients with squamous NSCLC present with locally advanced or metastatic disease at the time of diagnosis, which is incurable with currently available therapeutic options. The 5-year survival for this population is less than five percent.[1]

Treatment options for squamous NSCLC have remained unchanged over the last two decades. The current standard systemic first-line treatment for patients with advanced, metastatic squamous NSCLC consists of doublet therapy, using either cisplatin or carboplatin in combination with a taxane (paclitaxel, docetaxel, or albumin-bound nab-paclitaxel), gemcitabine, vinorelbine, or pemetrexed. Despite the available chemotherapy options, the prognosis for patients with squamous cell carcinoma remains very poor, with a median overall survival of 9.5 to 10.8 months from the start of first-line treatment.[4]

Necitumumab[4] Necitumumab is a recombinant human monoclonal antibody (mAb) immunoglobulin (Ig) G1 class which targets the epidermal growth factor receptor (EGFR). Based on the applicant's submission, in vitro studies demonstrate that necitumumab inhibits EGFR-dependent tumor cell proliferation and can exert cytotoxic effect in tumor cells through antibody-dependent cell-mediated cytotoxicity. The FDA revised indication for necitumumab is first-line treatment of metastatic squamous non-

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[1] FDA Briefing Document July 9, 2015 Oncologic Drugs Advisory Committee Meeting

[2] American Cancer Society. Global Cancer Facts and Figures 2014. Atlanta: American Cancer Society; 2014. Available at: http://www.cancer.org/acs/groups/content/ @research/documents/webcontent/acspc-042151.pdf. Accessed July 28, 2015.

[3] Erickson HS, Wistuba II. Pathology of Lung Cancer. In Lung Cancer: A Multidisciplinary Approach to Diagnosis and Management. Kernstine K, Reckamp K, Thomas C (eds). New York, NY: DemosMedical, Inc; 2010.

[4] Necitumumab Clinical Overview Section 2.5

small cell lung cancer in combination with gemcitabine and cisplatin.[2] The recommended dosing regimen is necitumumab 800 mg I.V. on Days 1 and 8 of each 3-week cycle in combination with gemcitabine (b) (4) (b) (4) (b) (4) until disease progression or unacceptable toxicity.

4.2 CLINICAL DEVELOPMENT PROGRAM[1, 3]

Data from 2 studies were submitted to this NDA. This included the pivotal Phase 3 study (SQUIRE) and another Phase 3 study, (INSPIRE).

4.2.1 Efficacy[1,4, 6]

At the time of this writing, the FDA clinical reviewer was still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies that support this application.

Key Efficacy Findings: Please refer to the clinical review by Dr. Lee Pai-Scherf for the full review on efficacy and safety. The following is a summary of the key findings from labeling discussions for necitumumab as of **August 5, 2015**.

Study SQUIRE was a global, multicenter, randomized, open-label, registration Phase 3 study evaluating patients with Stage IV (AJCC7) squamous NSCLC receiving first-line treatment with necitumumab plus gemcitabine and cisplatin chemotherapy (GC+N) versus gemcitabine and cisplatin chemotherapy alone (GC). The primary objective of this study was evaluation of overall survival (OS). Median OS was 11.5 months for the necitumumab + GC arm and 9.9 months for the GC arm. Secondary objectives were progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF), safety, pharmacokinetics (PK) and immunogenicity of necitumumab, and assessment of health status. The median PFS was 5.7 months for patients treated with necitumumab compared to 5.5 months for patients treated with the control treatment.

The baseline demographics and disease characteristics of the ITT (intention-to-treat) population were balanced between the two treatment arms. The median age was 62 years (range 32 to 86), 83% were males, 84% were white, 91% had ECOG PS 0 or 1, and 91% were smokers. More than half of the patients had two or more sites of metastasis, with lymph node, pleura, bone and liver as the most common sites of disease at the time of study entry. Prior treatment included surgery (~ 20%), radiation (8%) or adjuvant chemotherapy (< 5%).

A total of 1093 patients were randomized to receive either:

GC+N Arm

-Necitumumab 800 mg (intravenous [I.V.]) on Days 1 and 8 of each 3-week cycle

[5] FDA Proposed Draft Necitumumab label dated July 28, 2015

[6] Necitumumab Summary of Clinical Efficacy Section 2.7.3

-Gemcitabine 1250 mg/m^2 (I.V.) on Days 1 and 8 of each 3-week cycle (maximum of 6 cycles)

-Cisplatin 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

GC Arm

-Gemcitabine 1250 mg/m^2 (I.V.) on Days 1 and 8 of each 3-week cycle (maximum of 6 cycles)

-Cisplatin 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

Patients in both treatment arms were to receive study therapy as described above for a maximum of 6 cycles or until there was radiographic documentation of progressive disease (PD), toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

Study INSPIRE was a global, multicenter, randomized, open-label Phase 3 study of necitumumab plus pemetrexed and cisplatin (PC + N) versus pemetrexed and cisplatin (PC) alone in the first-line treatment of patients with Stage IV nonsquamous NSCLC. The primary objective was to compare OS between the treatment arms. The INSPIRE study did not meet the primary endpoint of improved OS nor did it show a statistically significant difference in PFS or overall response rate (ORR). Median OS was 11.3 months for the necitumumab arm and 11.5 months for the PC arm. Secondary objectives were evaluation PFS, ORR, TTF, safety, PK and immunogenicity of necitumumab, assessment of health status, and evaluation of the relationship between EGFR protein expression and efficacy. The median PFS was 5.6 months in each arm.

In the ITT population, the median age was 61 years (range 26 – 88), 67% were male, 93% white, 94% had ECOG PS 0 or 1, and more than 75% were smokers. Eighty nine percent had adenocarcinoma histology and 8% large cell carcinoma. Nearly a third of the patients had prior surgery, 12 % prior radiation and 3% had received prior adjuvant chemotherapy.

A total of 633 patients were randomized on a 1:1 basis to receive either:

PC+N Arm

-Necitumumab 800 mg (I.V.) on Days 1 and 8 of each 3-week cycle

-Pemetrexed 500 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

-Cisplatin 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

PC Arm

-Pemetrexed 500 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)
-Cisplatin 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

Patients in the PC Arm were permitted to undergo study treatment for a maximum of 6 cycles; patients in the PC+N Arm could receive a maximum of 6 cycles of chemotherapy in combination with necitumumab and could continue to receive further treatment with single-agent necitumumab until progressive disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. As a result, for the evaluation of AEs the treatment period (and, accordingly, the safety observation period) was longer in the PC+N Arm.

The original planned sample size for INSPIRE was 947 patients.

After enrollment of 633 patients, the Independent Data Monitoring Committee (IDMC) overseeing this trial recommended early closure of enrollment in INSPIRE. The IDMC reached this decision over a series of meetings between June 2010 and January 2011 using data on nonfatal and fatal thromboembolic events from the safety database as well as the overall number of deaths from all causes (all deaths) shown in the clinical database. Over the series of meetings, the additional data showed increasing and persistent evidence of an excess of thromboembolic and fatal thromboembolic SAEs on the investigational arm in INSPIRE, which accounted for an excess of deaths from all causes on this arm. This led the IDMC to the conclusion that the investigational treatment was disadvantageous to patients. For patients in the PC+N Arm, necitumumab treatment was discontinued in patients who had not completed 2 cycles of study treatment.

4.2.2 Safety[1, 5, 7, 8]

The safety of necitumumab is based on analysis of data from 1079 patients in Study SQUIRE and 304 patients in the INSPIRE study. The SQUIRE study was conducted between 2010-2012 with only 36/1093 patients being in the US. There were 0.9% of protocol violations (5 in each arm). The INSPIRE study was conducted between November 2009 to February 2011. The study was closed early for enrollment due to increasing and persistent evidence of an excess of thromboembolic and fatal thromboembolic SAEs on the investigator arm, which accounted for an excess of deaths on this arm.

[7] Necitumumab Summary of Clinical Safety Section 2.7.4

[8] Necitumumab Midcycle Slides April 25, 2015

The median duration of treatment for necitumumab in the SQUIRE trial was 20 weeks while the median duration of treatment on the GC arm was 17 weeks. The median number of necitumumab cycles was 6 and the median number of infusions was 12. Approximately 59% of patients completed 6 cycles of necitumumab while approximately 48% of patients received more than 6 cycles. For the gemcitabine and necitumumab arm, the median number of cycles was 5.

The safety events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0 grade as assigned by investigator.

This review highlights the necitumumab related AEs which were of concern to the review division: cardiopulmonary arrest and venous thromboembolic events. Of note, the sponsor's adverse events of interest outlines arterial and venous thromboembolic events, hypersensitivity/infusion-related reactions, and electrolyte abnormalities in their risk management plan along with a potential risk for severe skin reactions.

Cardiopulmonary Arrest: Cardiopulmonary arrest or sudden death occurred in 12 (2.2%) of 538 patients treated with necitumumab and gemcitabine and cisplatin as compared to 3 (0.5%) of 541 patients treated with chemotherapy alone in SQUIRE. All patients had comorbid conditions including coronary artery disease, hypomagnesemia, chronic obstructive pulmonary disease (COPD), hypertension, and unwitnessed death. It has been cited that progressive worsening of hypomagnesemia in 4 of these patients, 6 weeks prior to death and apparently left untreated may have attributed to cause of death. Per the study protocol, hypomagnesemia was to be treated by local standard of practice. In the SQUIRE study, hypomagnesemia occurred in 31% of the patients enrolled in the necitumumab arm. Nine percent of those were grade ≥ 3. In the INSPIRE study, hypomagnesemia was a common grade ≥ 3 AE seen in 8% of patients on the necitumumab arm vs. 2% in the PC arm. In the SQUIRE and INSPIRE study, hypomagnesemia led to treatment delays and modifications in 2.4% and 2% of patients in the necitumumab arm.

Venous Thromboembolic Events: In the SQUIRE study, thromboembolic events were noted in the necitumumab arm (9% vs. 5%). Confirmed and unconfirmed diagnosis of pulmonary embolism accounted for more than half (26/49 patients) of the venous thromboembolic events (VTEs) (5% of patients treated with N+ GC overall) and deep venous thrombosis (DVT) accounted for 20% (10/49 patients) of VTEs (2% of patients overall). In Study SQUIRE, thrombocytopenia (3.5% in the GC+N Arm vs. 1.5% in the GC Arm) had the highest treatment discontinuation. In INSPIRE, similar to SQUIRE, overall incidence of thromboembolic events (TE) and grade ≥ 3 TEs were higher in necitumumab arm compared to control (17.4% vs. 14%). The most common VTEs were confirmed or suspected pulmonary embolism and DVT. Of 13 patients who experienced an arterial thromboembolic events (ATE), 4/13 had a cardiac event (angina, myocardial infarction). Thrombocytopenia led to 2% of dose reductions.

Deaths: In Study SQUIRE, 77% of patients in the GC+N arm and 81% in the GC arm had died. The incidence of death due to an AE as the primary cause of death, per investigator was reported in 7.4% of GC+N treated patients and 7.9% of GC treated patients. Adverse events leading to death in ≥ 3 subjects were death not otherwise specified (NOS), hemoptysis/ hemorrhage, pneumonia or respiratory infection, and cardio-respiratory arrest. In Study INSPIRE, 75% of patients in the necitumumab arm and 78% in the PC arm had died. Death was attributed to disease progression in the majority of patients (61% vs. 66%).

The incidence of deaths during study and within<30 days of study drug was higher in necitumumab arm compared to PC (14% vs. 9%). Sudden death and death NOS occurred in 11 (3.6%) patients in necitumuab arm compared to 5 (1.6%) in the PC arm. Similar to the SQUIRE trial, several patients (7.6%) in necitumumab arm had uncorrected electrolyte disturbances prior to death, including hypomagnesemia and hypocalcemia that might have contributed to the event.

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS.

As per the review division, cardiopulmonary arrest and venous thromboembolic events will be managed in labeling as a boxed warning along with a postmarketing requirement for an enhanced pharmacovigilance plan to assess these risks.

4.3 ADVISORY COMMITTEE RECOMMENDATIONS

A decision was made early in the review cycle to have an Advisory Committee meeting to gain advice on whether the efficacy and safety results of SQUIRE in squamous cell NSCLC support a positive benefit: risk assessment of necitumumab in combination with gemcitabine/cisplatin in the proposed population and whether the INSPIRE trial results in the nonsquamous NSCLC population might impact the benefit: risk assessment of necitumumab for squamous NSCLC. On July 9, 2015 members of the Oncology Drugs Advisory Committee (ODAC) met to discuss the above. The review division did not take a vote for this application; however, it appeared the panel was in support of approval of necitumumab for squamous NSCLC regardless of the marginal benefit seen with this drug. The panel commented on providing well written labeling and prescriber education on magnesium supplementation for low magnesium levels given that severalof the patient deaths had uncorrected or sub-optimally corrected hypomagnesemia prior to death. Eli Lilly was in support of strengthening the labeling to address hypomagnesemia. The panel also stated the increased thromboembolic events should be addressed similarly. Eli Lilly responded to the advisory committee's comments by proposing healthcare professional education in the form of providing prominent language in product resources, a product website, clinical data presentations, and product educational programs for oncologists, nurses, and pharmacists. The sponsor also proposed patient education in the form of a patient therapy brochure and discussion guide, and a patient website. Supportive measures that the sponsor proposed at the ODAC also included a call center (LillyMedical.com) and a rash management kit.[9] In addition, Eli Lilly also proposed prophylactic anticoagulation in high risk patients with a low molecular weight heparin and a postmarketing safety study.

4.4 ASSESSMENT OF RISK: BENEFIT PROFILE

The FDA proposed indication for necitumumab will include patients for first-line treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin. Despite the available chemotherapy options, the prognosis for patients with squamous cell carcinoma remains very poor, with a median overall survival of 9.5 to 10.8 months

[9] Necitumumab Eli Lilly presentation slide CS-53, ODAC, July 9, 2015

from the start of first-line treatment.Options for squamous NSCLC have remained unchanged over the last two decades.

The prescribing population for necitumumab will be managed by prescribers who are familiar with the disease and adverse events seen with drugs used for the treatment of squamous NSCLC. These prescribers will likely include oncologists familiar with treating squamous NSCLC and the adverse events associated with necitumumab.

The anticipated duration of use is 800 mg I.V. on Days 1 and 8 of each 3-week cycle in combination with gemcitabine [redacted] (b) (4) on Days 1 and 8 of each 3-week cycle) [redacted] (b) (4) [redacted] (b) (4) until disease progression or unacceptable toxicity.

The most serious Grade 3 or 4 treatment-emergent adverse event (TEAE) of necitumumab were cardiopulmonary arrest and related hypomagnesemia and thromboembolic events. The Division determined these events were serious enough to address with a Boxed Warning.

The current standard systemic first-line treatment for patients with advanced, metastatic squamous NSCLC consists of doublet therapy, using either cisplatin or carboplatin in combination with a taxane (paclitaxel, docetaxel, or albumin-bound nab-paclitaxel), gemcitabine, vinorelbine, or pemetrexed.

Infusion and skin reactions along with electrolyte disturbances are common amongst panitumumab, cetuximab and necitumumab treatment. A Boxed Warning is used to describe the dermatologic toxicities with panitumumab therapy. With cetuximab, a Boxed Warning is used to describe serious infusion reactions and along with necitumumab, cardiopulmonary arrest with close monitoring of serum electrolytes. The electrolyte disturbances for all three treatments are addressed under the Warnings and Precautions section of the label.

Although the safety profile of necitumumab appears to be similar to other anti-EGFR mAbs currently marketed, i.e., cetuximab and panitumumab, a higher than expected incidence of thromboembolic (TE) events were observed in both trials for necitumumab. TEs emerged as an early safety signal in the INSPIRE trial and lead to premature closure of the trial. A small increase in the risk of sudden death was observed (2.2% vs. 0.5% in SQUIRE and 3.6% vs. 1.6% in INSPIRE). Several patients had uncorrected or sub-optimally corrected hypomagnesemia prior to death. It is possible that the electrolyte disturbances associated with necitumumab and platinum therapy played a role in these events.

5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

There are no proposed PMR's or PMC's at this time.

6 CONCLUSION

DRISK and DOP-2 concur that at this time a REMS for necitumumab is not necessary to ensure that the benefits outweigh the risks for the FDA proposed indication of the first-

line treatment of metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin. The risks associated with necitumumab treatment will be communicated through professional labeling and routine pharmacovigilance. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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08/07/2015

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Concur