



Lilly Files for European Approval of ALIMTA(R) (pemetrexed for injection) for First-Line Treatment of Non-Small Cell Lung Cancer

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Eli Lilly and Company (NYSE: LLY) today announced that it has submitted an application with the European Medicines Agency (EMA) for centralised review of ALIMTA(R) (pemetrexed for injection), in combination with cisplatin, for the first-line treatment of advanced non-small cell lung cancer (NSCLC).

ALIMTA is currently indicated in more than 85 countries as a second-line, single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy, and is also indicated, in combination with cisplatin, for the treatment of patients with malignant pleural mesothelioma (MPM) whose disease is unresectable or who are otherwise not candidates for curative surgery.

The EMA submission is based on a study which evaluated ALIMTA plus cisplatin versus GEMZAR(R) (gemcitabine HCl for injection) plus cisplatin. The study met its primary endpoint of non-inferiority relative to overall survival in a first-line NSCLC setting.

"As non-small cell lung cancer is the leading cause of cancer death worldwide, it is important that doctors have a range of treatments for this devastating illness," said Richard Gaynor, M.D., vice president of cancer research and global oncology platform leader for Lilly. "In this clinical study, ALIMTA plus cisplatin demonstrated similar efficacy to GEMZAR plus cisplatin, a widely used regimen for first-line NSCLC, while providing a more favorable toxicity profile and greater convenience. We look forward to the outcome of the EMA review."

In September 2004, the EMA approved ALIMTA as a single agent, second-line treatment for patients suffering from advanced NSCLC, as well as in combination with cisplatin for the treatment of patients with MPM.

In the U.S., ALIMTA was approved by the FDA as a second-line therapy for locally advanced or metastatic NSCLC in August 2004, as well as in combination with cisplatin as a first-line treatment for MPM in February 2004.

Notes to Editor:

About Non-Small Cell Lung Cancer (NSCLC)

NSCLC is the most common type of lung cancer and represents 75 to 80 per cent of all lung cancers.(i) NSCLC has five-tier staging, starting at 0 and rising to the severity of stage IV.(ii) NSCLC can spread through the lymphatic system, penetrating the chest lining, ribs and the nerves and blood vessels that lead to the arm. The liver, bones and brain are potential targets if the cancerous cells enter the blood stream.

According to the World Health Organization (WHO) Cancer Report, lung cancer is the world's most common cancer and the leading cause of cancer death for both men and women. More than one million people die from lung cancer each year.(iii)

About Lilly Oncology, a Division of Eli Lilly and Company

For more than four decades, Lilly Oncology has been collaborating with cancer researchers to deliver innovative treatment choices and valuable programs to patients and their physicians. Inspired by courageous patients living with cancer, Lilly Oncology is providing treatments that are considered global standards of care and developing a broad portfolio of novel targeted therapies to accelerate the pace and progress of cancer care. To learn more about Lilly's commitment to cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific

organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs.

P-LLY

ALIMTA(R) (pemetrexed for injection), Lilly

GEMZAR(R) (gemcitabine HCl for injection), Lilly

This press release contains forward-looking statements about the potential of ALIMTA for the treatment of non-small cell lung cancer and reflects Lilly's current beliefs. However, as with any pharmaceutical products under development, there are substantial risks and uncertainties in the process of development, commercialization, and regulatory review. There is no guarantee that the product will receive additional regulatory approvals. There is also no guarantee that the product will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

ALIMTA ABBREVIATED PRESCRIBING INFORMATION

Uses

ALIMTA is indicated in combination with cisplatin for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma. ALIMTA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after prior chemotherapy.

Dosage and Administration

The drug is to be administered intravenously, under the supervision of a physician qualified in the use of cytotoxic anti-cancer therapy.

Malignant pleural mesothelioma: Pemetrexed in combination with cisplatin has been investigated using a three-week (21-day) cycle. Pemetrexed is used at 500 mg/m(squared) of body surface area (BSA), given by ten-minute infusion, on day 1 of each 21-day cycle. Cisplatin is used at 75 mg/m(squared) BSA, given by two-hour infusion, approximately 30 minutes after completion of the pemetrexed infusion on day 1 of each cycle. Adequate anti-emetic treatment and hydration for cisplatin treatment must be given.

Non-small cell lung cancer: The recommended dose of pemetrexed is 500 mg/m(squared) BSA, given by ten-minute infusion, on day 1 of each 21-day cycle.

Pre-medication: Supplement with 1000 micrograms intramuscular vitamin B12 and oral folic acid (350 to 1000 micrograms) to reduce toxicity (for full details see Summary of Product Characteristics [SPC]). To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration - this should be equivalent to 4mg of dexamethasone administered orally twice a day.

Monitoring: Monitor prior to each dose for complete blood cell count, including a differential white cell count and platelet count. Absolute neutrophil count should be $> \text{or} = 1,500 \text{ cells/mm}^3$ and platelets $> \text{or} = 100,000 \text{ cells/mm}^3$. Prior to each dose, collect blood chemistry tests to evaluate renal and hepatic function. Dose adjustments to pemetrexed and/or cisplatin at the start of a subsequent cycle should be based on nadir haematological counts or maximum non-haematological toxicity. If necessary, delay or withhold treatment in the presence of haematological toxicity, neurotoxicity, and/or impaired hepatic/renal function. (For full information on dose modification see SPC.)

Children and adolescents: Not recommended for use in patients under 18 years of age.

Renal impairment: Patients with creatinine clearance $> \text{or} = 45 \text{ ml/min}$ require no dose adjustment other than those recommended for all patients. Use in patients with creatinine clearance below 45 ml/min is not recommended. See also Warnings and Special Precautions.

Hepatic impairment: Patients with hepatic impairment, such as bilirubin >1.5 -times the upper limit of normal and/or transaminase >3.0 -times the upper limit of normal (hepatic metastases absent) or >5.0 -times the upper limit of normal (hepatic metastases present), have not been specifically studied.

Contra-indications

Hypersensitivity to pemetrexed or to any of the excipients. Concomitant yellow fever vaccine. Breast-feeding.

Warnings and Special Precautions

Myelosuppression is usually the dose-limiting toxicity. Patients must be instructed to take folic acid and vitamin B12 as a prophylactic measure. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions. Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in combination with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors including dehydration or pre-existing hypertension or diabetes. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to administration. Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been uncommonly reported when pemetrexed is given in combination with other cytotoxic agents; most of these patients had pre-existing cardiovascular risk. Concomitant use of live attenuated vaccines is not recommended.

Interactions

Concomitant administration of nephrotoxic drugs and substances that are also tubularly secreted could potentially result in delayed clearance of pemetrexed. If necessary, creatinine clearance should be closely monitored. Patients must avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration. In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of NSAIDs (such as ibuprofen >1600 mg/day) and aspirin at higher dosage (≥ 1.3 g daily) may decrease pemetrexed elimination and increase the occurrence of adverse events. Patients with mild to moderate renal insufficiency (creatinine clearance from 49 to 79 ml/min) should avoid taking NSAIDs (e.g., ibuprofen) or aspirin at higher dosage, for 2 days before, on the day of, and 2 days following pemetrexed administration.

There is a possible interaction between oral anticoagulants and pemetrexed; therefore, increase the frequency of International Normalised Ratio monitoring (INR) if treating with oral anticoagulants.

Pregnancy and Lactation

Avoid in pregnancy and do not use in breast-feeding women.

Pemetrexed can be genotoxic; sexually mature males are advised not to father a child during treatment and up to 6 months thereafter. Owing to the possibility of irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment. Women of childbearing potential must use effective contraception during treatment.

Driving, etc

It has been reported that pemetrexed can cause somnolence. Patients should be cautioned against driving or operating machinery.

Undesirable Effects

Haematological: Very common: Anaemia, leucopenia, thrombocytopenia, neutropenia. Common: Febrile neutropenia and infection without neutropenia. Uncommon: Pancytopenia.

Gastro-intestinal: Very common: Nausea, vomiting, stomatitis/pharyngitis, anorexia, diarrhoea, constipation. Common: Dyspepsia, abdominal pain. Rare: Colitis.

General: Very common: Fatigue. Common: Fever, conjunctivitis.

Metabolism and nutrition: Common: Dehydration.

Nervous system: Very common: Neuropathy - sensory. Common: Neuropathy - motor, dysgeusia.

Renal and urinary: Very common: Creatinine elevation, creatinine clearance decreased. Common: Renal failure.

Hepatobiliary: Common: SGPT (ALT) elevation and SGOT (AST) elevation, increased GGT. Rare: Cases of hepatitis, potentially serious, have been reported during trials.

Skin and subcutaneous tissue: Very common: Rash/desquamation, alopecia. Common: Urticaria, allergic reaction/hypersensitivity, erythema multiforme, pruritus.

Cardiovascular and cerebrovascular: Uncommon: Myocardial infarction, angina pectoris, cerebrovascular accident, arrhythmias, transient ischaemic attack. (Usually when given in combination with other cytotoxic agents and with pre-existing cardiovascular risk.) Common: Chest pain.

For full details of these and other side-effects, please see the Summary of Product Characteristics, which is available at <http://www.emea.europa.eu/humandocs/PDFs/EPAR/alimta/H-564-PI-en.pdf>

GEMZAR ABBREVIATED PRESCRIBING INFORMATION

Uses

GEMZAR is indicated for the treatment of adults with:

Non-Small Cell Lung Cancer (NSCLC)

Combination use: In combination with cisplatin as a first-line treatment of patients with locally advanced (inoperable Stage IIIA or IIIB) or metastatic (Stage IV) NSCLC.

Single-agent use: The palliative treatment of patients with locally advanced or metastatic NSCLC.

Pancreatic Cancer

The treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas, including those with 5-FU refractory pancreatic cancer.

Bladder Cancer

The treatment of advanced bladder cancer (muscle invasive Stage IV tumours with or without metastases) in combination with cisplatin therapy.

Breast Cancer

In combination with paclitaxel for patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contra- indicated.

Dosage and Administration

The drug is only administered intravenously and not more than once per week.

Non-Small Cell Lung Cancer - Combination Use

Gemcitabine in combination with cisplatin has been investigated using two dosing regimens (three week schedule or four week schedule).

The three week schedule used gemcitabine 1,250mg/m(squared), given by 30 minute intravenous infusion, on days 1 and 8 of each 21 day cycle.

The four week schedule used gemcitabine 1,000mg/m(squared), given by 30 minute intravenous infusion, on days 1, 8, and 15 of each 28 day cycle.

Cisplatin has been used at doses between 75-100mg/m(squared) once every 3 or 4 weeks.

Non-Small Cell Lung Cancer - Single-Agent Use

The recommended dose of gemcitabine is 1,000mg/m(squared), given by 30 minute intravenous infusion. This dose should be repeated once weekly for three weeks, followed by a one week rest period. This four week cycle is then repeated.

Pancreatic Cancer

The recommended dose of gemcitabine is 1,000mg/m(squared), given by 30 minute intravenous infusion. This dose should be repeated once weekly for up to 7 weeks, followed by a week of rest. Subsequent cycles consist of once weekly injections for 3 consecutive weeks out of every 4 weeks.

Bladder Cancer - Combination Use

The recommended dose for gemcitabine is 1,000mg/m(squared), given by 30 minute infusion. The dose should be given on days 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70mg/m(squared) on day 1 following gemcitabine or day 2 of each 28 day cycle. This four week cycle is then repeated.

Breast Cancer - Combination Use

The recommended regime is paclitaxel (175mg/m(squared)) on day 1 over 3 hours as an IV infusion, followed by gemcitabine (1,250mg/m(squared)) as a 30- 60 minute infusion on days 1 and 8 of each 21 day cycle. Patients should have an absolute granulocyte count of at least 1,500 ($\times 10^6/l$) prior to initiation of the combination.

Gemcitabine can be administered on an outpatient basis.

Dosage reduction is based upon the amount of toxicity experienced by the patient. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts and, if necessary, the dose may be either reduced or withheld in the presence of haematological toxicity (see Summary of Product Characteristics [SPC]). For cisplatin dosage adjustment in combination therapy, see the manufacturer's prescribing information.

The elderly: Gemcitabine has been well tolerated by patients over the age of 65 years, and there is no evidence to suggest that dose adjustments are necessary.

Patients with hepatic and renal impairment: Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function. Clinical studies have not provided sufficient information to allow clear dose recommendation for this patient population.

Periodic checks of liver and kidney functions, including transaminases and serum creatinine, should be performed in patients receiving gemcitabine.

Radical radiotherapy: Gemcitabine should not be used concurrently with radical radiotherapy.

Children: Limited Phase I and II trials in children did not provide sufficient data to establish the efficacy and safety of use of gemcitabine in children.

Contra-indications, Warnings, etc

Contra-indications

Known hypersensitivity to gemcitabine.

Warnings

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

Myelosuppression is short-lived and usually does not result in dose reductions and rarely in discontinuation.

There have been very rare cases of haemolytic uraemic syndrome and/or thrombotic thrombocytopenic purpura (signs of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH). If this occurs, discontinue gemcitabine immediately. Renal failure may not be reversible, even with discontinuation, and dialysis may be required.

Gemcitabine use in patients with concurrent liver metastases or pre- existing history of hepatitis, alcoholism, or liver cirrhosis may exacerbate underlying hepatic insufficiency. Caution in patients with impaired hepatic function.

Concurrent radiotherapy (given together or <7 days apart): Gemcitabine has radiosensitising activity and significant toxicity may occur, particularly with large volumes of radiotherapy. It is feasible to administer gemcitabine at lower doses than

1,000mg/meter squared with concurrent radiotherapy with predictable toxicity (see SPC).

Sequential radiotherapy (given >7 days apart): Enhanced toxicity has not occurred when gemcitabine was started after the resolution of acute radiation effects or at least one week after radiation. Enhanced toxicity from radiation therapy following gemcitabine exposure has not occurred.

Precautions

Usage in pregnancy or lactation: Avoid in pregnant or breast-feeding women, since safety has not been established. Experimental animal studies have shown reproductive toxicity.

Patients should be cautioned against driving or operating machinery until they are sure they do not become somnolent.

Adverse Reactions

Haematological: Very common: Anaemia, leucopenia, neutropenia, and thrombocytopenia. Common: Febrile neutropenia. Very rare: Thrombocythaemia.

Hepatobiliary: Very common: Elevation of liver transaminases (AST, ALT) and alkaline phosphatase. Common: Increased bilirubin. Very rare: Serious hepatotoxicity, including liver failure and death, in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Rare: Increased gamma-glutamyl transferase (GGT).

Gastro-intestinal: Very common: Nausea or vomiting, which require therapy in about 20% of patients and is rarely dose-limiting. Common: Diarrhoea, oral toxicity (mainly soreness and erythema), and constipation.

Renal: Very common: Proteinuria and haematuria, rarely clinically significant. Rare: Haemolytic uraemic syndrome and renal failure of unknown aetiology. GEMZAR should be withdrawn if there is any sign of micro-angiopathic haemolytic anaemia.

Skin and allergic: Very common: Rash, pruritus, and alopecia. Rare: Vesiculation and ulceration. Very rare: Desquamation, bullous skin eruptions, and anaphylaxis.

Respiratory: Very common: Dyspnoea. Bronchospasm occurs uncommonly and is usually mild and transient, but parenteral therapy may be required. In the rare event of pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS) gemcitabine should be stopped and supportive care initiated.

Cardiac: Very rare: Myocardial infarct, congestive heart failure, and arrhythmia.

Other: Very common: Influenza-like symptoms (fever, headache, back pain, chills, myalgia, asthenia, and anorexia), cough, rhinitis, malaise, sweating, insomnia, oedema or peripheral oedema, and somnolence. Common: Somnolence, fever, and asthenia. Very rare: Peripheral vasculitis and gangrene.

Combination use in breast cancer: When gemcitabine is used with paclitaxel the frequency of Grade 3 and 4 haematological toxicities increases, particularly neutropenia, although not associated with an increased incidence of infections. Fatigue and febrile neutropenia also occur more frequently with this combination.

Administration site conditions: Rare: Injection site reactions (mainly mild).

For full details of these and other side-effects, please see the Summary of Product Characteristics, approved in your country.

(i) Lilly Oncology, "Understanding Cancer: About Lung Cancer," Eli Lilly and Company, www.lillyoncology.com/patients_caregivers/lung_cancer.jsp?reqNavId=4.2.7, (January 19, 2007).

(ii) American Cancer Society, "How Is Non-Small Cell Lung Cancer Staged?," October 25, 2006, American Cancer Society, www.cancer.org/docroot/CRI/content/CRI_2_4_3x_How_Is_Non-Small_Cell_Lung_Cancer_Staged.asp?nav=cri, (January 19, 2007).

(iii) World Health Organization, Gender in Lung Cancer and Smoking Research, Department of Gender, Women and Health, 2003

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