CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761102Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761102
PDUFA Goal Date	December 22, 2018
OSE RCM #	2017-2618
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 28, 2018
Subject	Evaluation of the Need for a REMS
Established Name	Calaspargase pegol
Trade Name	Asparlas
Name of Applicant	Baxalta US, Inc.
Therapeutic class	Asparagine specific enzyme
Formulation	Injection 3,750 Units/5ml in a single dose vial
Dosing Regimen	2,500 Units per m^2 intravenously not more frequently than every 21 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Asparlas (calaspargase pegol) is necessary to ensure the benefits outweigh its risks. Baxalta US, Inc., submitted a Biologics License Application (BLA 761102) for calaspargase pegol with the proposed indication as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL). The Division of Hematology Products (DHP) is proposing the indication as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in adults up to 21 years and pediatric and young adult patients age 1 month of age and older. The risks associated with calaspargase pegol include: hypersensitivity (b) (4) The applicant did not submit a proposed REMS or risk management plan with this application.

The use of asparaginase products as a component of chemotherapy for the treatment of ALL has been approved since 1994. Because of the long-term use of this product in the oncology field, and the fact that the adverse event profile of calaspargase pegol is like the currently approved asparaginases, DRISK and the DHP agree that a REMS is not needed to ensure the benefits of calaspargase pegol outweigh its risks.

1 Introduction

This review by DRISK evaluates whether a REMS for the NME Asparlas (calaspargase pegol) is necessary to ensure the benefits outweigh its risks. Baxalta US, Inc., submitted a BLA 761102 for calaspargase pegol with the proposed indication as a component of a multi-agent chemotherapeutic regimen for the treatment of patients ALL. The indication currently in review for this product by DHP is as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in adults up to 21 years and pediatric and young adult patients age 1 month of age and older. The risks associated with calaspargase pegol include: hypersensitivity (b) (4) The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Calaspargase pegol contains an asparagine specific enzyme (L-asparagine amidohydrolase) derived from *Escherichia coli*, and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker. The SC linker is a chemically stable carbamate bond between the mPEG moiety and the lysine groups of L-asparaginase.[1] The enzyme, L-asparaginase, catalyzes the conversion of the amino acid, L-asparagine into aspartic acid and ammonia. The mechanism of action is thought to be based on selective killing of leukemic cells due to the depletion of plasma L-asparagine. The proposed indication is as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) in adults up to 21 years and pediatric and young adult patients age 1 month of age and older.[a] Calaspargase pegol is likely to be prescribed by oncologists to patients in an inpatient setting.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

This drug is not part of a class of medications with a REMS or Boxed Warning. Calaspargase pegol is an NME[b] and on Priority Review. Calaspargase pegol is currently not approved in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761102 relevant to this review:

- 12/21/2017: BLA 761102 submission received
- 06/07/2018: A Post Mid-cycle teleconference was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for calaspargase pegol

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

ALL is a heterogenous group of lymphoid neoplasms that result from proliferation and accumulation of lymphoblasts in the bone marrow, peripheral blood, and other organs.[2] This is the most commonly diagnosed cancer in children, and represents 25% of cancer diagnoses among children younger than 15 years.[2] Though ALL is most commonly diagnosed in children, most deaths from ALL occur in adults. ALL has an overall survival of approximately 80%, with certain subsets of ALL experiencing greater than 98% cure rates.[3] The risk for developing ALL is highest in children younger than 5 years of age, and then this risk declines slowly until the mid-20's and begins to rise again slowly after age 50.[4] According to the American Cancer Society, estimates for ALL in the United States for 2018 in both children and adults are approximately 5,960 new cases (3,290 males, 2,670 females) and approximately 1,470 deaths (830 males, 640 females).[4, c,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are four major components of treatment of newly diagnosed ALL, reflecting a reliance on multidrug regimens to avoid development of resistance. Different blocks of chemotherapy have varying intensity depending on the group of patients at risk, with increasingly intensive regimens corresponding to more aggressive disease categories.[3] Asparaginase is a component of treatment of pediatric and adult patients with newly diagnosed, refractory and relapsed ALL. The mechanism of action of L-asparaginase is thought to be based on selective killing of leukemic cells due to depletion of plasma asparagine. Three major L-asparaginase preparations are currently availably globally; the preparations are: native

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Eschericha coli L-asparaginase (Elspar), which is no longer available in the US; PEG-asparaginase (Oncaspar), approved in 1994, which was the first pegylated form of L-asparaginase, and Erwinia (Erwinaze) a non-pegylated form derived from *Erwinia chrysanthemi*.[5,6,7] Erwinaze was approved in 2011, and is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients who have developed hypersensitivity to *Eschericha coli*-derived asparaginase. Glucose intolerance can occur with Oncaspar and Erwinaze administration[6,7], and all these medications carry the risks of hypersensitivity reactions, including anaphylaxis, severe or hemorrhagic pancreatitis and thrombosis or hemorrhage. None of these drugs have a Boxed Warning or were approved with a REMS.

4 Benefit Assessment[1]

The primary demonstration of efficacy was based on the demonstration, achievement, and maintenance of serum asparaginase activity above the level of 0.1Units/ml. Samples from 1245 patients with B cell lineage ALL treated with calaspargase pegol in Study 1 (n = 13) and Study 2 (n = 111) were evaluated. The median age was 11.5 years (range 1 – 26); 50% (n=62) were male and 82% (n = 102) were Caucasian. Imputation of nadir serum asparaginase activity (NSAA) of calaspargase pegol showed that 99% of patients sustained NSAA above the protocol-specified level of 0.1 Units/ml during the post-induction phase. [e]

5 Risk Assessment & Safe-Use Conditions[1]

Common adverse events of calaspargase administration include hypoalbuminema, increased liver function tests, increased pancreatic enzymes, and hypoglycemia. These adverse events did not differ greatly from its comparator, pegaspargase. As with all therapeutic proteins, there is the potential risk for immunogenicity.[1, f] Anti-PEG antibodies were detected in 8.4% of evaluable patients treated with calaspargase pegol, however none of the patients developed persistent anti-calaspargase pegol binding antibodies, or tested positive for neutralizing antibodies against calaspargase pegol. The following information below are serious risks that will be communicated in Warnings and Precautions of the calaspargase label. There is no boxed warning proposed in the labeling for calaspargase at this time.

5.1 HYPERSENSITIVITY

Grade 3 and 4 hypersensitivity reactions including anaphylaxis have been reported in clinical trials with calaspargase pegol with an incidence between 7 to 21%. Hypersensitivity reactions observed with other asparaginases include angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnea, pruritus and rash. Because of the risk of serious allergic reactions (e.g.,

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

life-threatening anaphylaxis), recommendations are to administer calaspargase pegol in a clinical setting with resuscitation equipment and other agents necessary to treat anaphylaxis.

5.2 (b) (4)

Cases of pancreatitis have been reported in clinical trials with calaspargase pegol with an incidence between 12 to 16%. Hemorrhagic or necrotizing pancreatitis have been reported with other asparaginases.

5.3 (b) (4)

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia have been reported in patients receiving calaspargase pegol. Serious thrombotic events, including sagittal sinus thrombosis, have been reported in clinical trials with calaspargase pegol with an incidence between 11 to 14%.

5.4 (b) (4)

Administration of calaspargase pegol with hepatotoxic products can result in severe hepatic toxicity. Caution is required when calaspargase pegol is given in combination with hepatotoxic products. Monitor the patient for changes in liver function parameters. There may be an increased risk of hepatotoxicity in Philadelphia chromosome positive patients, for whom treatment with tyrosine kinase inhibitors (e.g., Imatinib) is combined with asparaginase therapy. There is also an increased risk of hepatic effects (such as increase in transaminases, bilirubin increase, hypofibrinogenemia) among patients >18 years of age. This should be considered when considering the use of calaspargase pegol in these patient populations.

(b) (4)

6 Expected Postmarket Use

Calaspargase pegol will likely be prescribed by oncologists and given in an in-patient setting, as the proposed indication is to be used as an adjunct to chemotherapy treatment, and due to its risk of anaphylaxis.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for calaspargase beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Despite significant advances in treatment, approximately 15% to 20% of patients with ALL will suffer relapsed disease, the most common cause of treatment failure.[3] Asparaginase is often used during the

first phase of treatment (induction period) in addition to chemotherapy to improve patient outcomes by depleting leukemic cancer cells.[3]

If approved, calaspargase pegol would provide another therapeutic asparaginase product, with a potentially longer half-life[5] than the currently approved asparaginase products. In the clinical trial, 99% of the patients achieved the primary endpoint of having a therapeutic nadir of asparaginase of 0.1 Units/ml. The adverse event profile of calaspargase pegol is like the currently approved asparaginases Oncaspar and Erwinaze. The Warnings and Precautions sections of the labels for these products include the risks of anaphylaxis, pancreatitis, and thrombotic events. The use of asparaginase products as a component of chemotherapy for the treatment of ALL has been approved since 1994. The clinical reviewer for this product states that there are no clinical issues that would prevent approval of this application.[8]

Because of the long-term use of this product in the oncology field, and the fact that the adverse event profile of calaspargase pegol is like the currently approved asparaginases, DRISK and DHP agree that a REMS is not needed to ensure the benefits of calaspargase pegol outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for calaspargase pegol to ensure the benefits outweigh the risks. The safety concerns associated with calaspargase pegol have been documented with the use of other asparaginase therapy, and healthcare providers who treat ALL with this drug combination should be familiar with the risks of these drugs and the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated if necessary.

10 Appendices

10.1 REFERENCES

[1] Calaspargase pegol FDA Draft Prescribing Information, August 15, 2018

[2] https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq (accessed July 10, 2018)

[3] Cooper S and Brown P. Treatment of Pediatric Acute Lymphoblastic Leukemia. *Pediatri Clin North Am.* 2015 Feb; 62(1): 61-73

[4] https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/key-statistics.html accessed August 17, 2018

[5] Calaspargase pegol Clinical Overview, submitted December 21, 2017

[6] Oncaspar US Prescribing Information, Baxalta US Inc., 1994

[7] Erwinaze US Prescribing Information, Jazz Pharmaceuticals, 2011

[8] Dinndorf P. BLA 761102 Clinical Review Memorandum. Submitted in DAARTS August 16, 2018

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/s/

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