CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s000

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	NDA
Application Number	210259
PDUFA Goal Date	February 17, 2018
OSE RCM #	2017-1196
	2017-1199
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	September 29, 2017
Subject	Evaluation of Need for a REMS
Established Name	Acalabrutinib
Trade Name	Calquence
Name of Applicant	Acerta Pharma BV
Therapeutic Class	Bruton Tyrosine Kinase Inhibitor
Formulation(s)	Capsule for oral use: 100 mg
Dosing Regimen	100 mg by mouth twice daily

Table of Contents

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 Calquence (acalabrutinib) is necessary to ensure the benefits outweigh its risks. Acerta Pharma BV submitted a New Drug Application (NDA) # 210259 for acalabrutinib with the proposed indication for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The risks associated with acalabrutinib include hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation tumor lysis syndrome. The applicant did not submit a REMS with this application but proposed routine pharmacovigilance activities to identify and characterize safety concerns for acalabrutinib.

If approved, the labeling will communicate the risks of acalabrutinib with Warning and Precautions specifically highlighting the risks of hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and tumor lysis syndrome. DRISK and the Division of Hematology Products (DHP) agree that a REMS is not needed to ensure the benefits of acalabrutinib outweigh its risks for the proposed indication: for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Calquence (acalabrutinib) is necessary to ensure the benefits outweigh its risks. Acerta Pharma BV submitted a New Drug Application (NDA) # 210259 for acalabrutinib with the proposed indication for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a REMS with this application but proposed routine pharmacovigilance activities to address the risks of hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and tumor lysis syndrome.

2 Background

2.1 PRODUCT INFORMATION

Calquence (acalabrutinib), a new molecular entity,[a] is a bruton tyrosine kinase (BTK) inhibitor proposed for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Acalabrutinib, if approved, will be the second drug in the pharmacologic class of bruton tyrosine kinase inhibitors. Acalabrutinib is proposed as a 100 mg capsule for oral administration. The recommended dose is 100 mg by mouth twice daily until disease progression or unacceptable toxicity.[b] Acalabrutinib is not currently approved in any jurisdiction.

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

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

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210259 relevant to this review:

- 11/27/2013: IND 118717 submission received for acalabrutinib
- 06/13/2017: NDA 210259 submission for the treatment of patients with MCL who received at least one prior therapy
- 07/31/2017: Breakthrough designation granted
- 09/01/2017: Midcycle telecommunication with the applicant; the FDA stated there were no safety issues that require a REMS for acalabrutinib

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Mantle Cell Lymphoma (MCL) is one of 70 different subtypes of Non-Hodgkin Lymphoma (NHL). It's estimated that MCL represents 2-10% of all non-Hodgkin lymphomas.[1] NHL represents approximately 4% of all cancer diagnoses and is the seventh most common cancer.[c] In 2017, the estimated number of new cases of NHL is 72,240 and the estimated number of deaths is 20,140.[2],[d] MCL carries a poor prognosis with the median time to treatment failure being less than 18 months and 10-year survival rate being low at 5-10%.[1]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

MCL has an aggressive clinical course and patients usually present with extensive disease, including widespread lymphadenopathy, bone marrow involvement, splenomegaly, circulating tumor cells, and bowel infiltration.[3] Treatment is non-curative and is based upon patient specific factors such as prior treatment, comorbidities and performance status, the regimens' expected toxicities and the clinicians experience.[4] Non-pharmacologic treatment of MCL consists of non-myeloablative allogenic hematopoietic cell transplantation (HCT) in certain patient populations or radiation therapy for chemotherapy refractory disease. In the relapsed or refractory setting, combination chemotherapy with or without rituximab and single agent therapy with bortezomib, lenalidomide, or ibrutinib are considered salvage therapy.

Combination chemotherapy regimens are associated with many toxicities, which are often intolerable. Examples used as salvage therapy in relapsed/refractory MCL include RICE (rituximab, ifosfamide, carboplatin and etoposide) and ESHAP (etoposide, methylprednisolone, high-dose cytarabine and

[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.*

cisplatin). Single agent therapy avoids the toxicities while providing at least a partial response with subsequent progression free survival.

Table 1:[5] Monotherapy Treatment for Relapsed/Refractory Mantle Cell Lymphoma

Product Trade Name (Generic) Year Approved	Dosing and Administration	Important Safety and Tolerability Issues	Risk Management Approaches
Revlimid (Lenalidomide) 2005 Immunomodulator	25 mg by mouth once daily on days 1 – 21 of repeated 28-day cycles	Risk of embryo-fetal exposure Fetal Risk – birth defects or embryo-fetal death Neutropenia and thrombocytopenia Venous and arterial thromboembolism	REMS Program* Labeling - Boxed Warning
Velcade (Bortezomib) 2003 Proteasome Inhibitor	1.3 mg/m^2 subcutaneously or IV twice weekly for 2 weeks followed by a 10 day rest period	Peripheral neuropathy Cardiac effects Pulmonary effects Neutropenia and thrombocytopenia Liver failure Diabetes GI effects Tumor lysis syndrome	Labeling – Warning and Precautions
Imbruvica (Ibrutinib) 2013 Bruton Tyrosine Kinase Inhibitor	420 mg by mouth daily	Hemorrhage Infections Hematologic effects Cardiovascular effects Hypertension GI toxicity Renal toxicity Secondary primary malignancies Tumor lysis syndrome Waldenstrom macroglobulinemia Hyperuricemia	Labeling – Warning and Precautions
*REMS is to mitigate embryo-fetal exposure			

4 Benefit Assessment[e]

The pivotal trial (ACE-LY-004) supporting the application for acalabrutinib consisted of a Phase 2, multicenter, open-label, single-arm study that is ongoing. Through January 5, 2016, the study enrolled 124 patients who were ≥ 18 years with histologically confirmed MCL. The patients were required to have no previous BTK inhibitor exposure, have disease that relapsed after or been refractory to ≥ 1 prior therapy for MCL and required further treatment. The primary endpoint of study ACE-LY-004 was overall response rate (ORR). The secondary endpoints were duration of response (DOR) and progression free survival (PFS) based on investigator assessment and ORR, DOR and PFS based on an independent review committee (IRC) assessment. All of the endpoints studied were assessed according to the Lugano

[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.*

classification. The primary endpoint, investigator assessment of ORR, resulted as 80.6% (95% CI: 72.6%, 87.2%). The primary and secondary endpoints are shown in Table 2 below.

Table 2[6]: Acalabrutinib (ACE-LY004) Primary and Secondary Endpoints

	Investigator Assessment N = 124	95% CI[a]	IRC Assessment N= 124	95% CI[a]
Overall response rate	80.6%	(72.6%, 87.2%)	79.8%	(71.7%, 86.5%)
Duration of response (median)	13.5 months	NE	14.8 months	NE
Progression-free survival (median)	15.2 months	NE	15.2 months	NE

[a] 95% exact binomial confidence interval

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; NE = not estimable

The clinical reviewer recommends accelerated approval of acalabrutinib for the treatment of mantle cell lymphoma in patients who have failed at least one therapy. This recommendation is based on the ORR (80.6%) showing a clinically meaningful benefit and the durable overall response (DOR) of 13.5 months.[7]

5 Risk Assessment & Safe-Use Conditions

The safety profile of acalabrutinib was derived from the pivotal Phase 2 study ACE-LY-004 and an integrated analysis of 7 pooled studies in patients with hematological malignancies treated with acalabrutinib monotherapy that support the proposed indication. These studies were analyzed in 3 analysis pools based on the underlying hematologic malignancy and dosing regimen.[8] Overall, 319/612 (52.1%) patients experienced an adverse event ≥ CTCAE (Common Terminology Criteria for Adverse Events, Version 4) Grade 3 with 122/612 (19.9%) being deemed related to acalabrutinib by the applicant.

- ISS-LY004 (N=124): This population consists of all subjects in the pivotal study treated with acalabrutinib monotherapy at 100 mg by mouth twice daily.
- ISS-100 (N=443): This population consists of subjects treated with acalabrutinib monotherapy with 100 mg by mouth twice daily as the starting dose.
- ISS-All (N=612): This population consists of all subjects treated with acalabrutinib monotherapy at any dose and frequency.

The serious adverse events (referred to as risks) determined to be associated with acalabrutinib are hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and tumor lysis

syndrome.[f] The Warnings and Precautions section of the acalabrutinib proposed label includes these risks and will be discussed below along with the deaths that occurred.

5.1 HEMORRHAGE

Overall, hemorrhage of all grades was reported in 316/612 patients (51.6%). Major hemorrhage occurred in 1/124 (0.8%) patients in the ISS-LY004 population, 10/443 (2.3%) in the ISS-100 population and 17/612 (2.8%) in the ISS-All population. One death (CTCAE Grade 5 adverse event) occurred in ISS-100 which was an intracranial hematoma. The proposed label advises healthcare providers to monitor for bleeding and manage appropriately.

5.2 INFECTIONS

Infections ≥ CTCAE Grade 3 occurred in 17/124 (13.7%) in ISS-LY004, 67/443 (15.1%) in ISS-100 and 109/612 (17.8%) in ISS-All. The most frequently reported infection, CTCAE Grade 3 or higher, was pneumonia. The proposed label advises healthcare providers to monitor patients for signs and symptoms of infection and treat as medically appropriate

5.3 CYTOPENIAS

Cytopenias including anemia, thrombocytopenia, and neutropenia occurred in patients receiving acalabrutinib. Anemia ≥ CTCAE Grade 3 occurred in 11/124 (8.9%) in ISS-LY004, 33/443 (7.4%) in ISS-100 and 45/612 (7.4%) in ISS-All. Thrombocytopenia ≥ CTCAE Grade 3 occurred in 6/124 (4.8%) in ISS-LY004, 21/443 (4.7%) in ISS-100 and 29/612 (4.7%) in ISS-All. Neutropenia ≥ CTCAE Grade 3 occurred in 16/124 (12.9%) in ISS-LY004, 60/443 (13.5%) in ISS-100 and 82/612 (13.4%) in ISS-All. The proposed label advises healthcare providers to monitor complete blood counts monthly during treatment.

5.4 SECOND PRIMARY MALIGNANCIES

Second primary malignancies of CTCAE Grade 3 or higher occurred in 4/124 patients (3.2%) in ISS-LY004, 17/443 patients (3.8%) in ISS-100 and 25/612 patients (4.1%) in ISS-All. The most frequently reported malignancy type were skin malignances (basal cell carcinoma, squamous cell carcinoma and squamous cell carcinoma of the skin). The proposed label recommends healthcare providers advise patients to use sun protection.

5.5 ATRIAL FIBRILLATION

Atrial fibrillation, all CTCAE Grades, was reported in the ISS-All population in 82/612 (13.4%) patients with 18/612 patients (2.9%) ≥ CTCAE Grade 3. One patient discontinued study treatment due to the atrial fibrillation adverse event. There were no cases of atrial fibrillation reported in the ISS-LY004

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

population. The proposed label advises healthcare providers to monitor for atrial fibrillation and manage as appropriate.

5.6 TUMOR LYSIS SYNDROME

Tumor lysis syndrome occurred in 3/124 patients (2.4%) in ISS-LY004, and 4/612 patients (0.7%) in ISS-All. All of the events in IS-LY004 were ≥ CTCAE Grade 3. The proposed label advises healthcare providers to assess baseline risk and take precaution and to monitor and treat for tumor lysis syndrome.

5.7 DEATHS

Overall, 79/612 (12.9%) patients died during treatment and 36/612 (5.9%) died within 30 days of discontinuing acalabrutinib. On treatment, disease progression was the most common cause of death amongst all analysis groups (ISS-LY004, 25/30; ISS-100, 33/56; ISS-All 47/79). Fatal adverse events (CTCAE Grade 5) occurred in 25/612 (4.1%) of patients in the ISS-All population. The most frequently reported fatal adverse event was pneumonia (6/25, 24%). Of the fatal adverse events, 2/124 (1.6%) occurred in the ISS-LY004 population and the applicant attributed the deaths to aortic stenosis and non-small cell lung cancer.

6 Expected Postmarket Use

Acalabrutinib will be primarily prescribed in the outpatient setting by hematologists and oncologists who should be familiar with the management of adverse reactions associated with bruton tyrosine kinase inhibitors. The draft prescribing information currently addresses the associated serious risks and management of hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and tumor lysis syndrome.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of acalabrutinib on the basis of the efficacy and safety information currently available. Mantle cell lymphoma is a serious disease that represents approximately 2-10% of all non-Hodgkin lymphomas. Based on this data, an estimated 1,400 to 7,200 new cases of MCL and up to 2,000 deaths will occur in 2017. The standard treatment of relapsed/refractory MCL with combination chemotherapy is associated with significant toxicities. Treatment with acalabrutinib provides a monotherapy option with a durable overall response and less toxicity.

The serious risks associated with acalabrutinib are hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation and tumor lysis syndrome. The hematologists and oncologists prescribing acalabrutinib should be familiar with managing these risks as they are well known in this specialty. The labeling will be used to communicate these risks. DRISK recommends that, should acalabrutinib be

approved, a REMS is not necessary to ensure its benefits outweigh its risks for the treatment of mantle cell lymphoma.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable for the treatment of mantle cell lymphoma and therefore, a REMS is not necessary for acalabrutinib to ensure the benefits outweigh the risks. 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; this recommendation can be reevaluated.

10 Appendices

10.1 References

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/s/

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