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

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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 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.*

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