CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213400Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 213-400 is recommended for approval from OPQ. The applicant cross references all CMC information to their own NDA 211723, which has been approved. There is no new information included in this NDA. All manufacturing and labeling sites are adequate and there are no pending review issues nor any recommended PMR/PMC actions from OPQ. A shelf life of 24 months is granted when the tablets are stored below 30°C (86°F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Epizyme, Inc. submitted NDA 213-400 for Tazverik (tazemetostat) tablets, 200 mg, indicated for the treatment of patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies. Tazemetostat is a new molecular entity that has low solubility, but high permeability. The drug product is supplied as red, round, biconvex, film-coated 200 mg tablets, debossed on one side with the dosage strength and the letters EZM. The proposed dose is 800 mg twice daily. The tablets are packaged in bottles of 240 tablets with a desiccant (a one-month supply). The recommended storage is below 30°C (86°F) and the applicant is requesting a 24-month shelf life. Tablets are to be administered whole with or without food. No provisions in the package insert allow for extemporaneous solutions that enable dosing to pediatric patients or patients who have trouble swallowing.

The drug product is a (b) (4) (b) (4) (b) (4) The manufacturing process has remained consistent through development and into the proposed commercial process, changing only sites and batch size. Bridging to early formulations and dosage strengths was not necessary.

Drug substance and drug product specified impurities are limited based on qualification studies. The nonclinical reviewer verified these proposed limits are qualified and acceptable.

No biowaiver request was submitted or required for the proposed Tazemetostat Tablets, 200 mg. The Applicant performed clinical (safety and efficacy) studies (Studies E7438-G000-101, EZH-202, EZH-203 and

EZH-501 for safety, and Study #EZH-202 for efficacy) to support the 505(b)(1) submission with the intended commercial formulation under NDA 211-723.

The primary issue cutting across the review disciplines was that the applicant proposed a (b) (4) (b) (4)

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies
Duration of Treatment	Treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	1,600 mg/day (800 mg BID)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance is the mono-hydrobromide salt of tazemetostat, a small synthetic molecule. It has been well characterized using state-of the-art methods regarding its physicochemical characteristics and structure. Polymorph (b) (4)

[redacted]

[redacted] Methods to control the quality of the drug substance are adequate.

Stability data support an expiry of [redacted] months for the tazemetostat drug substance [redacted] There are no approvability issues or deficiencies with respect to the drug substance portion of this application. The data is adequate to support the use of tazemetostat drug substance in the manufacture of tazemetostat drug product.

Drug Product: Adequate

The drug product is supplied as red, round, biconvex, film coated 200 mg tablets. The tablets are debossed on one side with "200 EZM". 240 tablet counts are packaged in HDPE bottles with desiccant and stored at < 30 °C. The applicant provided satisfactory drug product information including adequate stability data for TAZVERIK (tazemetostat). Tazemetostat is a selective, S-adenosylmethionine-competitive inhibitor of enhancer of zeste homolog 2, a histone methyltransferase. The drug product is formulated as immediate release tablet containing tazemetostat hydrobromide and common pharmaceutical excipients: lactose monohydrate, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate. The tablets are film-coated with [redacted] red. The drug substance, tazemetostat hydrobromide is a [redacted] for use in the drug product. Based on polymorphism study of tazemetostat during stability, [redacted] support the proposed storage conditions of "do not store above 30°C". Based on the 12 months available data at long term and 6 months at accelerated storage conditions, 24 months expiration date may be granted.

Labeling: Adequate

Minor labeling changes were suggested to the clinical division and communicated through the clinical PM to align the container labels to the version approved under NDA 211-723. At the time of this executive

summary, labeling negotiation is on-going and there are no major CMC related concerns.

Manufacturing: Adequate

Refer to the executive summary regarding the impact of (b) (4) (b) (4)

Biopharmaceutics: Adequate

The Applicant first investigated the solubility of tazemetostat HBr in various aqueous media and reported (b) (4) the pH range of (b) (4). As 0.1N HCl represents the in vivo pH condition of the stomach, it is the most commonly used and preferred dissolution medium for IR products. The Applicant's selection of 0.1N HCl as the dissolution medium is appropriate (b) (4) (b) (4) (b) (4) For selection of the volume and apparatus for dissolution testing, the Applicant performed dissolution of the test product (b) (4) (b) (4) applicant selected USP Apparatus 2 with 900 mL for testing discriminating ability of the method. (b) (4)

(b) (4)

(b) (4) the Applicant's selection of 900 mL as the dissolution medium volume is acceptable (b) (4)

(b) (4)

The Applicant's proposed dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 30 minutes' is based on the dissolution data from the clinical batches. Also, the data from the discriminating ability studies indicate that the proposed dissolution method with dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 30 minutes' is likely to identify deviation in the product's quality. Based on the provided information/data, the proposed dissolution acceptance criterion is deemed 'adequate' for quality control testing of the proposed product.

Microbiology (if applicable): Adequate

The drug product is a solid oral dosage form. (b) (4)

(b) (4)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay at Release and Stability	Strong drug substance stability	Low	NA	Acceptable	
Physical Stability (solid state)	(b) (4)	Medium	(b) (4)	Acceptable	
Content Uniformity		Low		Acceptable	

	(b) (4)		(b) (4)		
Microbial Limits		Low		Acceptable	
Dissolution		Medium		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date: Olen Stephens 2/11/20

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/s/

OLEN M STEPHENS
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NDA is recommended for approval from CMC. No pending deficiencies.

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/s/

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