CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210656Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210656
Review #1

Drug Name/Dosage Form	Daurismo(glasdegib) Tablets
Strength	25 and 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Pfizer
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	27-Apr-18	All
Amendment (SD 0003)	24-May-18	Biopharm, DP
Amendment (SD 0005)	16-Jun-18	Biopharm
Amendment (SD 0009)	06-Jul-18	DP
Amendment (SD 0010)	23-Jul-18	DP
Amendment (SD 0020)	14-Aug-18	DS, DP, Biopharm
Amendment (SD 0023)	21-Aug-18	Biopharm
Amendment (SD 0022)	07-Sept-18	DS
Amendment (SD 0033)	12-Sept-18	Biopharm, DP
Amendment (SD 0052)	31-Aug-18	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Monica Cooper	Suong Tran
Drug Product	Amit Mitra	Anamitro Banerjee
Process	Hang Guo	Rapti Madurawe
Microbiology	n/a	n/a
Facility	Hang Guo	Derek Smith
Biopharmaceutics	Gerlie Gieser	Banu Zolnik
PAT	Chunsheng Cai	Bogdan Kurtyka
Regulatory Business Process Manager	Rabiya Laiq	n/a

Emerging Technology Team (ETT) Lead	Rapti Madurawe	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Amit Mitra	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105453	Glasdegib development

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 210656 for DAURISMO (glasdegib) tablets 25 and 100 mg. As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance and a 24-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 210656 was submitted for Glasdegib Immediate Release Tablets 25 and 100 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Glasdegib is a once daily, orally bioavailable, small-molecule, hedgehog pathway inhibitor Glasdegib is (b) (4) an NME which was originally investigated under IND 105453 and was granted orphan designation for both indications (AML and MDS) in 2017.

Glasdegib maleate is a small chiral molecule that is considered as a BCS class 4 compound by the applicant. It has two stereogenic centers and is manufactured (b) (4) The drug product is presented as 25 and 100 mg, immediate-release tablets containing glasdegib maleate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, (b) (4) and magnesium stearate. The 25 mg tablets are presented as round, yellow film-coated tablets debossed with "Pfizer" on one side and "GLS" over "25" on the other side. The 100 mg tablets are presented as round, pale orange film-coated tablets debossed with "Pfizer" on one side and "GLS" over "100" on the other side.

The recommended dosing regimen for Daurismo (glasdegib) Tablets is 100 mg orally daily until disease progression or unacceptable toxicity.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 210656 and grants a (b) (4)-month re-test period for the drug substance and a **24**-month expiration period for the drug product when stored at USP controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	100 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Glasdegib is a chiral (specific rotation: -32.5° at 25 °C), non-hygroscopic, white to pale colored solid moderately soluble in water at low pH, but sparingly soluble at high pH. Glasdegib is sparingly in most organic solvents, except for DMSO, DMF, and DMA. The applicant reports a melting point of ~207°C and two pK_a values of 1.7 and 6.1 for the conjugate acid. The applicant indicates (b) (4)

The applicant has provided spectroscopic evidence for the structure of glasdegib. This includes (b) (4) the proposed structure including the stereochemistry

The drug substance is manufactured (b) (4)

(b) (4)

(b) (4)

The applicant provided a list of impurities (related substances, residual solvents, and elemental impurities). The applicant did not provide any spectroscopic evidence for the specified impurities.

The drug substance is packaged (b) (4) The applicant provided specifications for the container closure. The applicant confirms (b) (4)

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A. The applicant provided a list of the analytical methods and a summary of the validation data. The applicant provided batch analysis data for 20 lots, 11 of which are manufactured using the commercial route (b) (4) The batches appear to be fairly consistent with no OOS data reported.

The applicant proposed a (b) (4) **month retest period** for the drug substance when stored at (b) (4) The applicant provided up to 12 months of long term and 6 months accelerated data for three pilot scale registration batches ((b) (4) kg scale; under long term (b) (4) storage conditions along with statistical analysis. Data for supporting batches were also included in the NDA. No OOS result or obvious trends are noticeable in the data provided. The data provided is adequate to support the proposed (b) (4) month retest period.

NDA 210656 is recommended for approval from a drug substance perspective.

Drug Product

The drug product is an immediate release film-coated tablet (FCT) provided as 25 mg and 100 mg strengths (expressed as free base). The drug product composition includes glasdegib maleate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, (b) (4) magnesium stearate, Opadry II yellow and/or Opadry

II beige. All the components of the coating agents are compendial grade. No novel excipients are used. (b) (4) safety evaluation for adventitious agents are provided. The 25 mg tablets are presented as round, yellow film-coated tablets debossed with "Pfizer" on one side and "GLS" over "25" on the other side. The 100 mg tablets are presented as round, pale orange film-coated tablets debossed with "Pfizer" on one side and "GLS" over "100" on the other side.

The drug product specifications included appearance, identification, assay, content uniformity, individual, unspecified and total degradants and dissolution. The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The applicant provided a screening of (b) (4) elemental impurities in the Section 3.2.P.5.5. The acceptance limits for the specified impurities are high. The non-clinical reviewer, informally consulted regarding their qualification status. Microbial limits testing (tested for registration batches) in not included in the proposed specifications. The applicant justifies this based on ICH Q6A. The applicant provided a detailed description of the analytical methods and validation data for all the methods.

The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 24 month expiry for the drug product, the applicant provided 12 months of long-term (25 °C/60%RH) stability data and 6 months data for lots placed under accelerated (40°C/75%RH) for three lots of 25 mg (45 and 90 count, which brackets the proposed commercial 60 count) and three lots of 100 mg, which includes 30 count configurations (15 to 90 counts used in the study) in 60 ml HDPE bottles. The drug product lots were manufactured with different lots of drug substance (refer to 3.2.P.5.4 for this information).

The stability studies were executed in accordance with the ICH 1A and Q1B. No significant changes were observed in description, assay, or degradation products under any storage condition (b) (4) all results remained within the proposed acceptance criteria.

The available stability data shows consistency over time and support the proposed expiry. Based on the 12 months of stability data included in this application Pfizer, Inc. proposed and the FDA accepts the expiration dating period of **24 months** for the 25 and 100 mg drug products when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to

86°F).

The application is recommended for approval from a drug product and process perspective.

Drug Product Process and Facility – Emerging Technology Summary

(b) (4)

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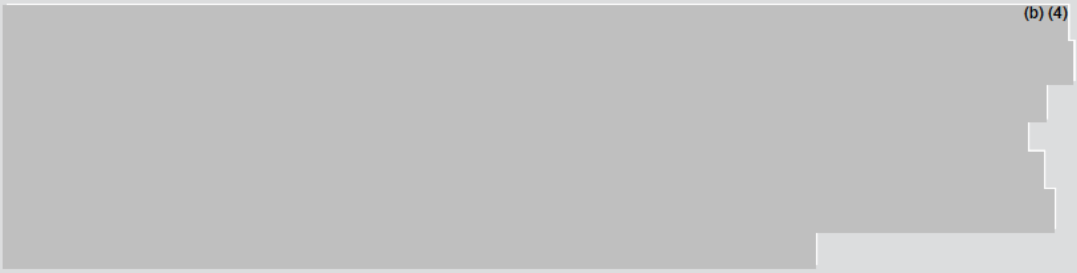


The final risk assessment table with risk mitigation and residual risks for lifecycle follow up are given below.

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability; (2) bridging to the To-Be-Marketed Drug Product; and (3) the biowaiver request (b) (4)

Dissolution Specification and Method: The dissolution method includes a USP Apparatus 2 (Paddle) with peak vessels at 75 rpm in 900 mL of 0.05M Potassium Phosphate (pH 6 (b) (4)). The proposed dissolution acceptance criterion for the 25 and 100 mg tablets is Q (b) (4)% in 30 minutes. The proposed dissolution method and acceptance criteria were deemed acceptable for batch release and stability testing for the 25 and 100 mg drug products.

Bridging to the To-Be-Marketed Drug Product: The Applicant established the bridge between the different formulations by way of a bioequivalence (BE) study. Based on the comparative *in vitro* dissolution profile data, (1) the debossing introduced to the proposed commercial glasdegib maleate film-coated tablet after conducting the pivotal BE study is not anticipated to impact the *in vivo* performance of the proposed commercial drug product, and (2) the proposed (b) (4) (b) (4) does not impact *in vitro* dissolution profile of the glasdegib maleate tablet. The bridging approach was deemed acceptable.

Biowaiver Request (b) (4): The request to waive the requirement of an

in vivo bioavailability/bioequivalence study for the 25 mg tablet is supported by compositional proportionality and similar dissolution profiles in multi-pH media as compared to the bio-batch/bio-strength (100 mg) that was evaluated in the pivotal BE study. The biowaiver request is granted.

This application is recommended for approval from a biopharmaceutics perspective.

Facilities

There were 5 facilities included in this application:

(b) (4)

All facilities listed in NDA 210656 were deemed acceptable for the responsibility listed in the application; however, the reviewer noted the following life cycle management considerations:

(b) (4)

Additional details of lifecycle considerations are highlighted in the appended facilities/process review.

This application is recommended for approval from a compliance perspective.

Environmental Assessment

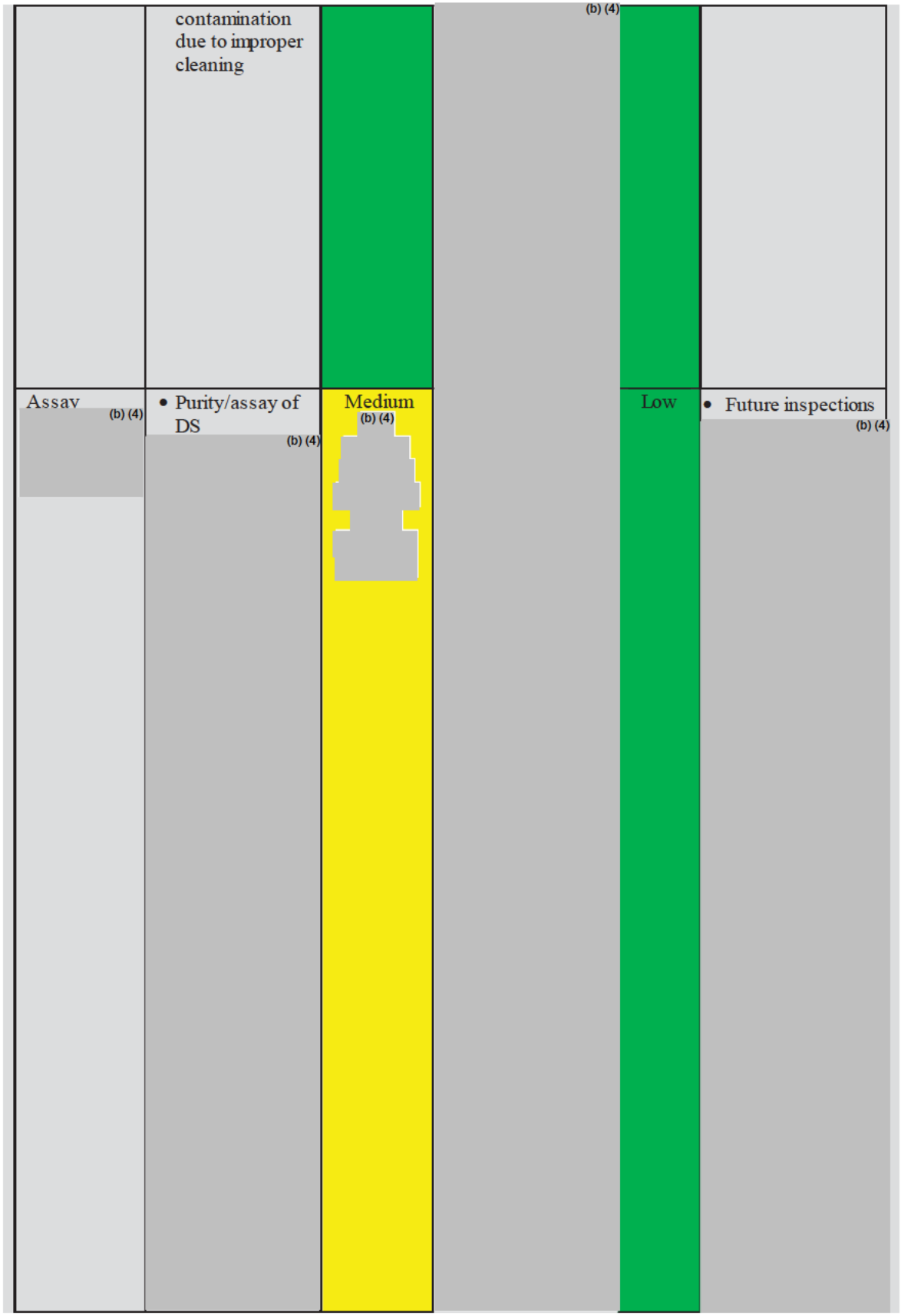
The approval of this application will increase the use of duvelisib; however, the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb ((b) (4) ppb). The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

DP Attribute /CQA	Factors that can impact the CQA	Initial Risk	Risk Mitigation Approach	Final Risk	Lifecycle Considerations / Comments (Items in blue ink are to be discussed at the NDA post-action meeting)
Appearance (tablets are debossed)	(b) (4)	Low	(b) (4)	Low	Future inspections of DS and/or DP sites - (b) (4)
Identification	• Incorrect DS (b) (4) • Cross	Low	• Standard CGMP procedures (b) (4) (b) (4)	Low	None



					(b) (4)
Impurities	• Impurities in the drug substance • (b) (4)	Low	• DS is stable, not heat sensitive and impurities are controlled ((b) (4)%) (b) (4)	Low	None

	(b) (4)		(b) (4)		
Dissolution	• DS is BCS IV (pH-dependent and low solubility) • DS particle size (b) (4) • Tablet hardness • Film coating	High	• Use of a clinically relevant dissolution specification (based mainly on pivotal BE lot) Dissolution data and in vivo BE data support the DS specification (b) (4)	Low	(b) (4)

			(b) (4)		(b) (4)
Uniformity of Dosage Units (b) (4)	(b) (4)	Medium		Low	• Refer to "Assay" comments •

			(b) (4)		
Microbial limits	(b) (4)	Low		Lo w	• None

Note to OLDP: Notify OPF (b) (4)

Sherita McLamore

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Rapti Madurawe

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LABELING

{For NDA only}

R Regional Information (NDA 210-656)

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: DAURISIMO Established Name: glasdegib tablets	Satisfactory
Dosage form, route of administration	tablets, oral	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 100, 25 mg	Satisfactory

Reviewer's Assessment: The highlight is satisfactory with respect to proprietary and established name, dosage form and strengths. The PI is yet to be finalized.

(b) "Full Prescribing Information" Section

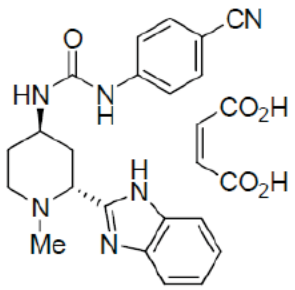
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Satisfactory
Strengths: in metric system	25 and 100 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	100 mg tablet: round, pale orange film-coated tablet debossed with "Pfizer" on one side and "GLS 100" on the other 25 mg tablet: round, yellow film-coated tablet debossed with "Pfizer" on one side and "GLS 25" on the other	Satisfactory

Reviewer's Assessment: This section may be modified according to PLR, if needed.

#11: Description (21CFR 201.57(c)(12))

DAURISMO (glasdegib) is a potent small molecule inhibitor of Smoothened (SMO) for oral use. It is formulated with the maleate salt of glasdegib. The molecular formula for glasdegib maleate is $C_{25}H_{26}N_6O_5$. The molecular weight for glasdegib maleate is 490.51 Daltons. The chemical name of glasdegib maleate is 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate. The molecular structure is shown below:



Glasdegib maleate is a white to pale colored powder with pKa values of 1.7 and 6.1. The aqueous solubility of gladegib maleate is 1.7 mg/ml.

DAURISMO supplied as a film-coated tablet containing either 100 mg gladegib (equivalent to 131.1 mg glasdegib maleate) or 25 mg ~~of~~ glasdegib (equivalent to 32.8 mg glasdegib maleate) together with microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate as inactive ingredients in the tablets. The film-coating consists of Opadry II® Beige (33G170003) and Opadry II® Yellow (33G120011) containing: hypromellose, titanium dioxide, lactose monohydrate, macrogol, triacetin, iron oxide yellow, and iron oxide red.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: DAURISIMO Established name: glasdegib tablets	Satisfactory
Dosage form and route of administration	Tablets, Oral	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	"DAURISMO (glasdegib) tablet is supplied as a film-coated tablet for oral use containing either 100 mg glasdegib (equivalent to 131.1 mg glasdegib maleate) or 25 mg of glasdegib (equivalent to 32.8 mg glasdegib maleate) together with microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate as inactive ingredients in the ---"	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under "Description" section	Satisfactory for oral dosage form
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	inhibitor of Smoothened (SMO)	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Other important chemical or physical properties (such as pKa, solubility, or pH)	Glasdegib maleate is a white to pale colored powder with pKa values of 1.7 and 6.1. The aqueous solubility of glasdegib maleate is 1.7 mg/ml.	Satisfactory

Reviewer's Assessment: Edits (highlighted in yellow and strikeouts) of the "Description Section" was included in the PI.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

DAURISMO film-coated tablets			
Package Configuration	Capsule/Tablet Strength (mg)	NDC	Print(description)
30 count bottle	100 mg	0069-0299-30	100 mg strength: 11 mm round, pale orange film-coated tablet debossed with "Pfizer" on one side and "GLS 100" on the other
60 count bottle	25 mg	0069-0298-60	25 mg strength: 7 mm round, yellow film-coated tablet debossed with "Pfizer" on one side and "GLS 25" on the other

Handling and Disposal:

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

Reviewer's Assessment: It was decided in the labeling meeting that no special handling of this oncology drug is needed.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	25 and 100 mg tablets	Satisfactory
Available units (e.g., bottles of 100 tablets)	25 mg (60 counts); 100 mg (30 counts)	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	25 mg tablet: 7 mm round, yellow film-coated tablet debossed with "Pfizer" on one side and "GLS 25" on the other; 100 mg tablet: 100 mg strength: 11 mm round, pale orange film-coated tablet debossed with "Pfizer" on one side and "GLS 100" on the other	Satisfactory
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Pfizer Labs, Division of Pfizer Inc., NY, NY 10017	Satisfactory

Immediate Container Label

25 mg tablets

100 mg tablets

Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength, prescription only, lot #, bar code, and expiration date. DMEPA may have additional comments. The applicant was requested to revise the salt equivalency statement to comply with FDA salt policy as follows: Revise the bottle label for 100 mg strength from: (b) (4) to (b) (4) based on the FDA guidance on "Naming of Drug Products Containing Salt Drug Substance". Make similar changes to the bottle label for 25 mg strength. In an amendment, dated 31-AUG-2018, the applicant made the requested change. The change is acceptable. The revised 25 and 100 mg labels are provided below.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Daurismo Established name: glasdegib tablets	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Correct strength was included (25 mg or 100 mg)	Satisfactory
Net contents (21 CFR 201.51(a))	25 mg (60 tablets); 100 mg (30 tablets)	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Revised container label

25 mg

(b) (4)

100 mg

(b) (4)

Reviewer's Assessment: The revised labels are satisfactory

Carton Labeling: None included.

Reviewer's Assessment: The labels are satisfactory.

List of Deficiencies: **None**

Primary Labeling Reviewer Name and Date:

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Amit Mitra

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Anamitro Banerjee

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BIOPHARMACEUTICS

Product Background:

NDA: 210656; NME; Priority Review Requested; Orphan Drug Designation

Drug Product Name / Strength: Glasdegib maleate immediate release film-coated tablets / 25 mg and 100 mg (as free base)

Route of Administration/Dosage:

(b) (4)

Applicant Name: Pfizer

Review Recommendation:

From the Biopharmaceutics perspective, NDA 210656 for glasdegib maleate tablets is recommended for **APPROVAL.**

Review Summary:

Dissolution method and acceptance criterion

The dissolution method and acceptance criterion (as tabulated below) are approved for the routine QC of both 25 mg and 100 mg strengths of glasdegib maleate film-coated tablets at batch release and during stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddle), with peak vessels	75 rpm	0.05M Potassium Phosphate, pH 6.8 (deaerated) 37 ± 0.5°C	900 mL	NLT (b) (4)% (Q) of the label claim dissolved in 30 min

During the internal discussion within the OPQ review team, (b) (4)

(b) (4)

[redacted]

Biowaiver Request for the 25 mg strength

The biowaiver request for the 25 mg strength of the proposed drug product is granted based on evidence of compositional proportionality, and similar dissolution profiles in multi-pH media (including the proposed QC dissolution method), as compared to the bio-batch/bio-strength (100 mg) that was evaluated in the pivotal BE study.

Bridging To the To-Be-Marketed Drug Product

The final proposed to-be-marketed drug product is adequately bridged to the drug product that was evaluated in pivotal clinical efficacy and safety trials, based on the comparative *in vitro* and *in vivo* data provided.

Comparable *in vivo* bioavailability or bioequivalence to the glasdegib [redacted] (b) (4) uncoated tablets (100 mg) that were evaluated in pivotal Phase 1b/2 clinical safety and efficacy trials was established for the early [redacted] (b) (4) glasdegib maleate [redacted] (b) (4)) film-coated tablets (100 mg) and the glasdegib maleate (commercial [redacted] (b) (4)) film-coated tablets (100 mg).

Based on the comparative *in vitro* dissolution profile data, (1) the debossing introduced to the proposed commercial glasdegib maleate film-coated tablet after conducting the pivotal BE study is not anticipated to impact the *in vivo* performance of the proposed commercial drug product, and (2) the proposed [redacted] (b) (4) does not impact *in vitro* dissolution profile of the glasdegib maleate tablet.

List Submissions reviewed:

SDN-1, 4/27/2018 (Original NDA)
SDN-3, 5/24/2018 (30-Day Stability Update)
SDN-5, 6/19/2018 (Response to Quality Information Request)
SDN-11, 7/23/2018 (Response to Quality Information Request)
SDN-21, 8/14/2018 (Response to Quality Information Request including Dissolution of Process Validation Batches)
SDN-23, 8/21/2018 (Response to Biopharmaceutics Information Request)
SDN-33, 9/12/2018 (Response to Quality Information Request)

Concise Description of Outstanding Issues Remaining:

None

BCS Designation

The Applicant considers glasdegib maleate as a BCS-4 (low solubility/low permeability) drug substance.

Reviewer's Assessment:

Solubility: *Low*
The solubility of glasdegib maleate is pH dependent and low (per BCS criteria). (b) (4) For details, refer to the pH-solubility profile of glasdegib maleate in 2.3.S.1 General Information.

Permeability: *Low to Moderate*
In Study B1371022, the absolute bioavailability of a single oral dose of 100 mg glasdegib maleate tablets (Lot # 17-000225) in fasted healthy subjects was 77.12%.

Dissolution: (b) (4)
At least (b) (4)% drug dissolution is achieved from the glasdegib maleate film-coated tablets (b) (4) in 900 mL of pH (b) (4) 6.8 media [using USP Apparatus 2 (paddle) rotating at 75 rpm, and peak vessels]; see Figure 3.2.P.2.2-16.

Dissolution Method and Acceptance Criterion

Reviewer's Assessment:

DISSOLUTION METHOD *- ADEQUATE*

The parameters of Dissolution Method TM100004596 (TM-8149A) are shown in Table 1 below.

Table 1. Parameters of the Proposed Dissolution Method

Apparatus:	USP Apparatus 2 (Paddles), Peak Vessels
Medium:	0.05M Potassium Phosphate, pH 6.8 (de-aerated)
Volume:	900 mL
Temperature:	37.0°C ± 0.5°C
Agitation Rate:	75 RPM
Sampling:	Aliquot withdrawn at appropriate time point (b) (4) (b) (4)

Justification for Chosen Method Parameters

(b) (4)

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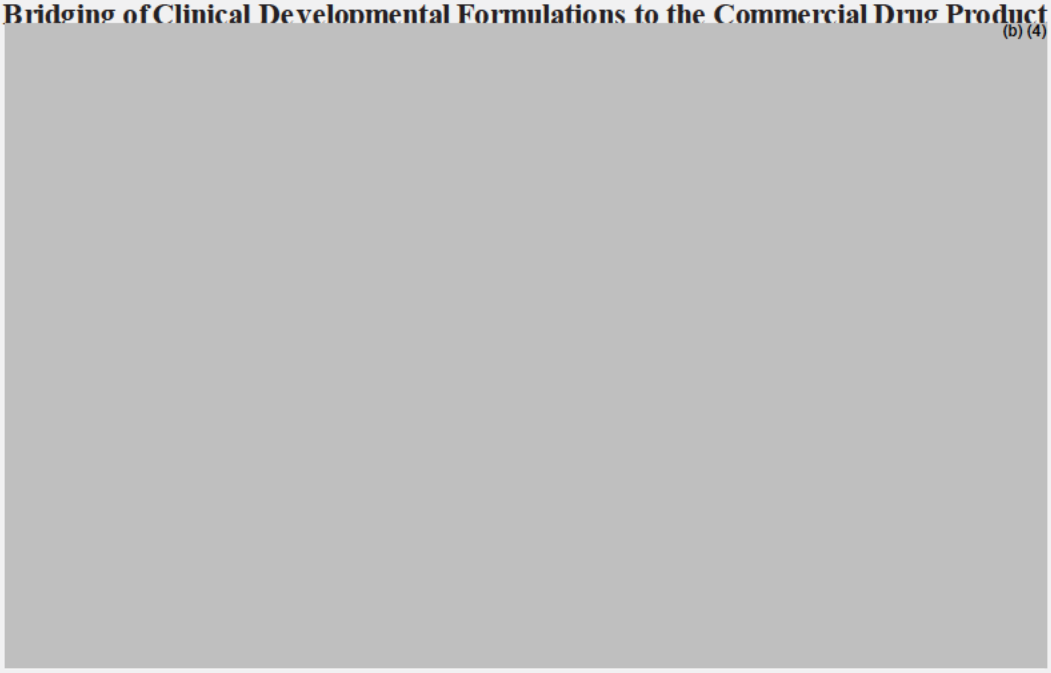
Bridging of Formulations

The Applicant's strategy for bridging various clinical development drug products to the proposed commercial drug product is summarized in the Figure 8.

Per the Applicant, the physical/chemical stability of the (b) (4) salt form used to manufacture the glasdegib tablets evaluated in the pivotal Phase 1b/2 safety and efficacy trial (Study B1371003) was not deemed acceptable for commercial use. Thus, the final proposed to-be-marketed (FTBM) drug product uses a salt form (i.e., maleate) different from that used to manufacture the pivotal clinical trial (PCT) lots. Additionally, whereas the PCT lots are uncoated tablets (b) (4) the FTBM tablets are film-coated tablets (b) (4) For a complete summary of the differences/similarities in the quality attributes of these two products, the lot ID numbers, and clinical trial use, refer to Table 3.

Figure 8
Bridging of Clinical Developmental Formulations to the Commercial Drug Product



Source: Figure 3.2.P.2.2-15

Table 3. Comparison of the Glasdegib Clinical and Commercial Tablet Formulations

(b) (4)

[redacted]

Source: Table 1 of the Applicant's Response to the Early Biopharmaceutics IR (SDN-5, 6/19/2018). Per the Applicant, the glasdegib maleate (b) (4) tablets were not used in any clinical trial.

Reviewer's Assessment: *ADEQUATE*

Bridging the Final To-Be-Marketed Drug Product to the Clinical Trial Lots:
As shown in Figure 8, bioequivalence data were provided by the Applicant to bridge the 100 mg strengths of the pivotal clinical trial lot and the proposed commercial drug product (as represented by at least two of the primary registration stability batches). Additionally, comparative *in vitro* dissolution profile data were provided to bridge the lower strength (25 mg) to the bio-strength (100 mg) of the proposed drug product.

The formulation and manufacturing process for glasdegib tablets evolved during clinical development. For example, as shown in Table 3, the pivotal clinical trial lots were manufactured (b) (4) The decision to conduct Pivotal BE Study 1371026 to generate *in vivo* PK data that would bridge the 100 mg strengths of the pre-market Phase 1/2 clinical trial product and the Commercial (b) (4) product is justified (b) (4)

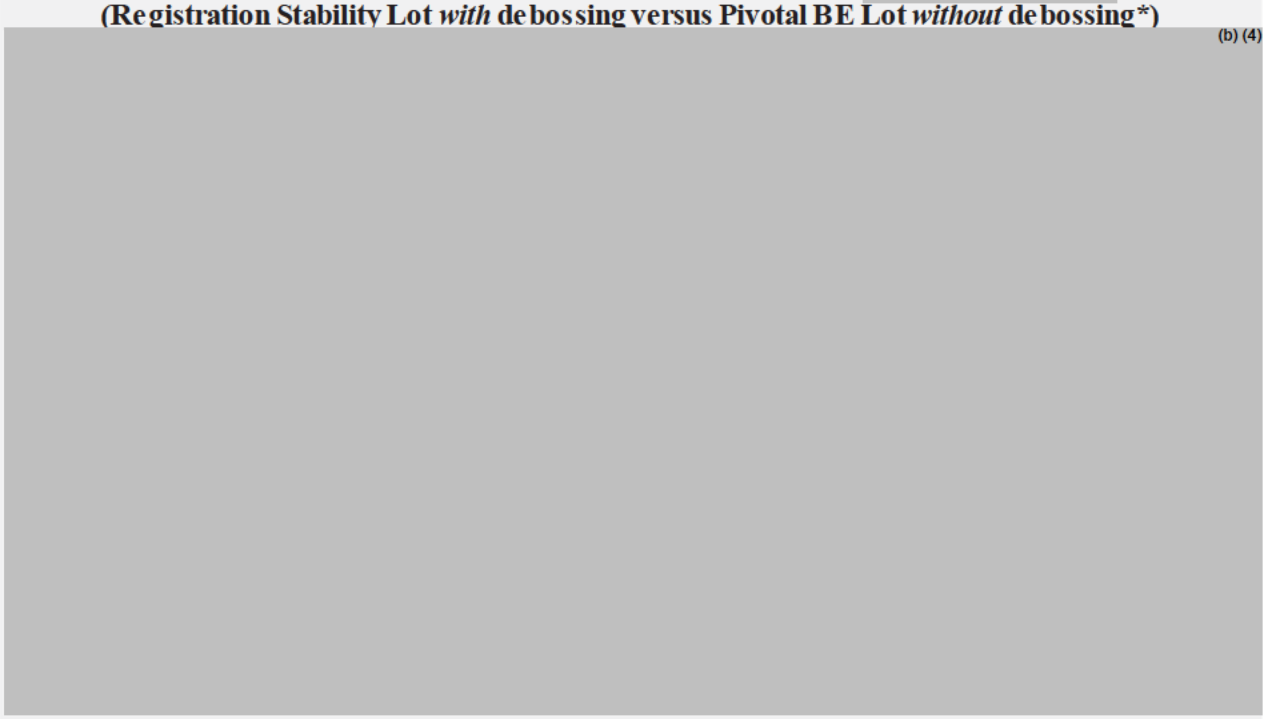
The bridge between the final proposed to-be-marketed (FTBM) and the pivotal clinical trial (PMCT) tablets is established based on the following lines of evidence:

(1) Per the Applicant (and as confirmed by the Clinical Pharmacology Reviewer, Dr. Sriram Subramanian), the 100 mg strengths of the pivotal clinical trial (glasdegib (b) (4) (b) (4)) tablets and the proposed commercial (glasdegib maleate/ (b) (4) (b) (4)) tablets are bioequivalent in terms of glasdegib AUC_{inf} and C_{max} (in fasted healthy subjects; Pivotal BE Study B1371026).

(2) The *in vitro* dissolution profiles of the 100 mg Commercial/ (b) (4) tablets with and without debossing were comparable, as demonstrated by the similar profiles of Registration Stability Lot 17-000223 (with tablet debossing) and Pivotal BE Lot 17-000224 (without debossing) in Figure 9. Thus, the debossing introduced to the proposed commercial tablet after conducting the pivotal BE study did not impact dissolution. Note that all registration stability lots of the proposed commercial tablets were not debossed, except for one lot of each strength (i.e., the ones shown in Figure 7B above).

Figure 9
Comparative *In Vitro* Dissolution Profiles of 100 mg Commercial (b) (4) Tablets (Registration Stability Lot *with* debossing versus Pivotal BE Lot *without* debossing*)

(b) (4)



*Both Registration Stability Lot 17-000223 and Pivotal BE Lot 17-000224 were manufactured using the same formulation and process. However, Lot 17-000223 is debossed (like the final proposed commercial tablet) whereas 17-000224 is not debossed.

(b) (4)

Figure 10.
Comparative *In Vitro* Dissolution Profiles of Process Validation Batches and Pivotal BE Batch of Proposed Commercial Glasdegib Maleate Tablets

Biowaiver Request

Reviewer's Assessment: *ADEQUATE*

A biowaiver request was submitted for the lower (25 mg) strength of the final proposed to-be-marketed immediate release drug product because only the higher strength (100 mg) was tested for BE to the pivotal clinical trial lot. The following data and information support the biowaiver request for the 25 mg strength of the final to-be-marketed drug product: (1) proportional similarity (b) (4) to the 100 mg (bio-strength), (2) similar dissolution profiles in multi-pH media of 25 mg strength vs. the bio-strength (100 mg) (Figure 11), (3) similar profiles (showing (b) (4) % dissolution within 30 min) when tested using the proposed QC dissolution method (see Table 3.2.P.5.6-11 and -12 of Justification of Specifications), as well as (4) dose proportional and linear pharmacokinetics across the 5 mg to 600 mg dose range [see Section 2.7.2 of the NDA].

Of note, the Applicant indicated that the Commercial/ (b) (4) glasdegib maleate immediate release film-coated tablets in Table 3.2.P.5.4-2, i.e., including the registration stability lots of the 25 mg strength, are intended to be introduced into the Phase 3 clinical trials.

Figure 11. Comparative *In Vitro* Dissolution Profiles of 25 mg and 100 mg Tablets (Registration Stability Lots with debossing on tablet*)

R Regional Information

Comparability Protocols

Reviewer's Assessment: *ADEQUATE*

A Comparability Protocol was submitted (b) (4)

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:

Gerlie Gieser, Ph.D. (9/13/2018)

Secondary Reviewer Name and Date:

Banu Zolnik, Ph.D. (9/19/2018)

Gerlie Gieser

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