CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212099Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212099
Review #1

Drug Name/Dosage Form	NUBEQA (Darolutamide) Tablets
Strength	300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bayer HealthCare Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Rolling NDA	12/12/2018	All
Original NDA	02/26/2019	All
Quality Amendment 0004	03/25/2019	Process
Quality Amendment 0012	05/28/2019	Process
Quality Amendment 0014	05/30/2019	DP/Biopharm
Quality Amendment 0016	06/12/2019	Biopharm
Quality Amendment 0008	06/28/2019	Process/Facility

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rajan Pragani	Suong T. Tran
Drug Product	Anamitro Banerjee	Thomas Oliver
Process	Lixia Cai	Steve Rhieu
Facility	Lixia Cai	Steve Rhieu
Microbiology	N/A	
Biopharmaceutics	Kaushal Dave	Banu S. Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	N/A	
ORA Lead	N/A	

Environmental	James Laurenson	Michael Furness

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)	Adequate	6/18/2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1)
	Type III			Adequate	6/18/2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
	Type V			N/A	6/18/2019	Type V DMF not reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114769	Initial IND was submitted to DOP1 on 7/13/2012.

2. CONSULTS
N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
OBP	N/A			
CBER	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The product quality review team that consists of the following disciplines: API, drug product, manufacturing process/facility and biopharmaceutics, recommends Approval of this NDA. Complete CMC information has been submitted to NDA 212099 and found to be adequate upon completion of the review. No PAI (pre-approval inspection) was conducted for the NDA as all API and drug product facilities are found adequate upon review of the inspection history.

II. Summary of Quality Assessments

A. Product Overview

Darolutamide is a non-steroidal androgen receptor (AR) antagonist with high binding affinity and selectivity to the AR. Darolutamide competitively prevents androgen binding to the AR and inhibits AR nuclear translocation and interaction with DNA. The darolutamide drug substance is a 1:1 mixture of two diastereomers, which are both similarly pharmacologically active. The major metabolite of darolutamide is keto-darolutamide, which has similar high binding affinity for the AR and exhibits comparable activity in *in vitro* assays. Darolutamide is indicated for the treatment of patients with nonmetastatic castration-resistant prostate cancer (nmCRPC). Darolutamide is a film-coated, immediate-release 300 mg tablet for oral application. Darolutamide is given in doses of 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg. Darolutamide received fast track designation, and was submitted as a rolling NDA.

Proposed Indication(s) including Intended Patient Population	NUBEQA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.
Duration of Treatment	Until (b) (4) unacceptable toxicity occurs
Maximum Daily Dose	NUBEQA 600 mg, (two 300 mg tablets) administered orally twice daily. Swallow tablets whole. Take NUBEQA with food.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The darolutamide drug substance is roughly a 1:1 mixture of diastereomers (S,S)-darolutamide and (S,R)-darolutamide, and the content of each diastereomer is controlled in the specification by (b) (4). The mixture was developed (b) (4) (b) (4)

(b) (4) Particle size and polymorphic form (b) (4) are both controlled in the drug substance specification. The only major impurity of concern, (b) (4), is specified in the drug substance specification with a qualified limit. (b) (4) is potentially found in much higher amounts in the drug product and is (b) (4) the drug substance. (b) (4) and (b) (4) are included with acceptable limits (per ICH Q3D and ICH M7, respectively) for quality control in the drug substance specification. Based on the stability data provided for the registration batches, a proposed retest date of (b) (4) months ((b) (4)) is acceptable for the drug substance. The drug substance information in the NDA has been reviewed and found **adequate**.

Drug Product

The proposed tablet has a high drug load ((b) (4)%), and contains common excipients for sold oral dosage form. The core tablet is film coated with (b) (4) white, and it remains the same as the ones used in Phase 3 clinical studies. All the excipients are USP/NF compendial grade and their amounts are within the IID limits. The only excipient (b) (4) was certified as safe for human use. The drug product specifications include: appearance (color, form, shape, and markings), assay, identity (two nonspecific methods: HPLC and UV), uniformity of dosage, dissolution, degradation products, and microbial purity. The applicant is monitoring only one specified impurity, (b) (4) The applicant conducted a risk analysis for elemental impurities as per ICH Q3D and concluded that control of elemental impurities in the drug product is not needed. The batch analysis data of the registration batches show minimal impurities (total impurities < (b) (4)%) for all the batches. The drug product is packaged in 120 mL HDPE white opaque wide-necked bottles closed with (b) (4) white outer and colorless (b) (4) inner caps. Each bottle contains 120 film coated tablets – a 3-month supply. The applicant conducted stability studies under ICH conditions and provided adequate stability data to support its proposed 36 months expiration dating period, which is found acceptable. The NDA is recommended for **APPROVAL** from the drug product perspective.

Process

(b) (4) No overage has been used or proposed in the exhibit batch or commercial batch record. DoE studies had been conducted during development to evaluate critical process parameters. In-process controls strategy has been studied and demonstrated to be appropriate. are in-process to assure manufacturing consistency. The DP manufacturing process information is deemed **acceptable**.

APPEARS THIS WAY ON ORIGINAL

Facility

All drug substance and drug product manufacturing and testing facilities are found to be **acceptable** based on previous history. No facility proposed in this application is requested for PAI in the current review.

Biopharmaceutics

The Biopharmaceutics review is focused on the evaluation of the 1) proposed in vitro dissolution method and acceptance criterion, and (2) formulation bridging. Darolutamide has poor aqueous solubility in the physiological pH range. The Applicant performed multiple studies to select suitable dissolution testing conditions and provided sufficient information/data justifying the selection of the proposed dissolution method. The Applicant investigated the discriminating ability of the proposed method towards drug substance particle size distribution (PSD), (b) (4), and film coating. The study results show that the proposed dissolution method is discriminating towards the drug substance PSD. The Applicant also investigated the effect of drug substance PSD on in vivo pharmacokinetics of darolutamide. The study results show that particle size distribution is not affecting the drug's pharmacokinetics in vivo. The proposed dissolution method and acceptance criteria are **acceptable** for quality control testing of the proposed product.

During the development, the Applicant changed the dosage form from a 100 mg powder in-capsule, used in early Phase 1 / 2 studies, to a 300 mg tablet for subsequent clinical studies and commercial use. Bridging of this change has been demonstrated by relative BE study, which is evaluated by Clinical pharmacology review team. During the development, the color of the non-functional film-coating of Darolutamide Film-Coated Tablets was changed from blue, which was used in the clinical studies, to white (proposed commercial product) (b) (4). The Applicant provided comparative dissolution data with the pre-change and post-change products in multi-pH conditions to support the proposed change, and it showed that there is no significant difference between the pre-change (blue coting) and post-change (white coating) tablets in terms of their dissolution.

Environmental Assessment

The applicant submitted an environmental assessment (EA) for darolutamide. FDA concludes that the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment, per 21 CFR 25.15(a). FDA concludes that the proposed action does not significantly affect the environment, and thus a finding of no significant impact (FONSI) is recommended. Refer to James Laurenson's review dated July 6, 2019 in Panorama.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs	L	The assay does not change on stability. No trends
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	BCS II/IV	L	Developmental studies show no changes to polymorphic form.
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	High drug load (b) (4)%)	L	Uniformity of dosage tested at release
Microbial limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Tested at release	L	Tested at release
Dissolution – BCS Class II & IV	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Method is discriminating for DS PSD (particle size distribution)	L	Bioavailability study showed that PSD is not affecting the drug's PK in vivo

E. Signature

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
9-July-2019

Xiao Chen

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BIOPHARMACEUTICS

Application No: NDA 212099
Drug Product Name/Strengths: Darolutamide (Nubeqa®) Tablets; 300 mg
Route of Administration: Oral
Indication: Non-metastatic castration resistant prostate cancer (nmCRPC)
Applicant Name: Bayer HealthCare Pharmaceuticals Inc.
Date of Submission: 12/12/2018 (Original)

Biopharmaceutics Review Team:
Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Banu Zolnik, PhD

RECOMMENDATION: ADEQUATE

REVIEW SUMMARY

Submission

The proposed drug product, Darolutamide (Nubeqa®) Tablets; 300 mg, submitted under NDA 212099 [a 505(b)(1) submission] is an immediate release oral dosage form developed by Bayer HealthCare Pharmaceuticals, Inc. (Bayer) for the treatment of non-metastatic castration resistant prostate cancer. Darolutamide is a non-steroidal androgen receptor (AR) antagonist with high binding affinity and selectivity to the AR. The proposed product is an immediate release tablet with a non-functional film coating, developed with a single strength of 300 mg given in doses of 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

Review Objective

The Biopharmaceutics review is focused on the evaluation of the 1) proposed in vitro dissolution method and acceptance criterion, and (2) formulation bridging.

Dissolution Method

Darolutamide has poor aqueous solubility in the physiological pH range. Therefore, the Applicant proposed a dissolution method which uses 0.01 M hydrochloric acid (HCl) containing 1.0% sodium lauryl sulphate (SLS) as the dissolution medium. The Applicant performed multiple studies to select suitable dissolution testing conditions and provided sufficient information/data justifying the selection of the proposed dissolution method (1000 mL of 0.01 M HCl containing 1.0% SLS using USP Apparatus 2 at 75 rpm). The Applicant investigated the discriminating ability of the proposed method towards drug substance particle size distribution (PSD), (b) (4), and film coating. The study results show that the proposed dissolution method is discriminating towards the drug substance PSD. The Applicant also investigated the effect of drug substance PSD on in vivo pharmacokinetics of darolutamide. The study results show that particle size distribution is not affecting

the drug's pharmacokinetics in vivo. Nonetheless, the sensitivity of the proposed dissolution method towards drug substance PSD supports the method's suitability as a quality control tool. The Applicant demonstrated the robustness of the proposed dissolution method. The proposed dissolution method is acceptable for quality control testing of the proposed product.

Dissolution Acceptance Criterion

The Applicant's proposed dissolution acceptance criterion of 'Not less than (NLT) (b) (4)% (Q) at 60 minutes' is appropriately selected and supported by the provided information/data.

The approved dissolution method and acceptance criterion for the quality control of the finished immediate release drug product at batch release and during stability testing are summarized below:

FDA Approved Dissolution Method and Acceptance Criterion for Darolutamide Tablets

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	75 rpm
Volume	1000 mL
Medium	0.01 M HCl containing 1.0% SLS
Temperature	37.0 ± 0.5 C
Acceptance Criterion	(b) (4)% (Q) at 60 minutes

Formulation Bridging

During the development, the Applicant changed the dosage form from a 100 mg powder in-capsule, used in early Phase 1 / 2 studies, to a 300 mg tablet for subsequent clinical studies and commercial use. The Applicant provided relative bioavailability study data to support this change; the data will be reviewed by the Office of Clinical Pharmacology. In all subsequent clinical studies, the Applicant used a film-coated tablet. Further during the development, the color of the non-functional film-coating of Darolutamide Film-Coated Tablets was changed from blue, which was used in the clinical studies, to white (proposed commercial product) (b) (4). The Applicant provided comparative dissolution data with the pre-change and post-change products in multi-pH conditions to support the proposed change. Based, on the provided information/data, there is no significant difference between the pre-change (blue coting) and post-change (white coating) tablets in terms of their dissolution. From a biopharmaceutics perspective, the change in the color of the non-functional film-coating of the tablets from blue to while is considered appropriately bridged and therefore acceptable.

Recommendation

From a Biopharmaceutics perspective, Darolutamide (Nubeqa®) Tablets; 300 mg, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	12/12/2018	Original NDA Submission
0003	05/30/2019	Quality/Response to Information Request
0003	06/12/2019	Quality/Response to Information Request

BACKGROUND

The Applicant performed several clinical studies to evaluate the pharmacokinetics, safety and efficacy of the proposed product. The pivotal phase 3 clinical study 17712 (ARAMIS) was a randomized, double-blind, placebo-controlled study with the primary objective of demonstrating superiority of darolutamide over placebo in metastasis-free survival (MFS) in patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC), and the secondary objectives of demonstrating the benefit of darolutamide compared with placebo for overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal event (SSE), and to characterize the safety and tolerability of darolutamide.

DRUG PRODUCT

The proposed product is manufactured by (b) (4). The composition of the proposed product is described in Table 1.

Table 1. Composition of the proposed product

Composition	Reference to Standard	Function	Amount [mg]
Drug substance			
Darolutamide (b) (4)	specification	drug substance	300.0
Excipients			
Calcium hydrogen phosphate	Ph. Eur., USP, JP	(b) (4)	
Croscarmellose sodium	Ph. Eur., NF, JP		
Lactose monohydrate	Ph. Eur., NF, JP		
Magnesium stearate	Ph. Eur., NF, JP		
Povidone K 30	Ph. Eur., USP, JP		
(b) (4)			
Weight (uncoated tablet)			
Film-coating			
(b) (4)	specification Ph. Eur., USP, JP		
Weight (film-coating)			
Weight (coated tablet)			**618.0**
a (b) (4)			
b			

c Relevant provisions of the European Food Law apply as stated in section P.4.1.

BCS Designation

In the current submission, the Applicant provided solubility and permeability information for darolutamide and claimed it to be a BCS Class 2 drug. However, the BCS designation for darolutamide was neither requested nor reviewed under the current application.

Solubility and Permeability of Darolutamide

The provided information for darolutamide indicate that its solubility in aqueous buffer solutions at physiological pH range (pH 1-6.8) is in the range of 14-23 µg/mL (Table 2). The data suggest that its solubility increases in intestinal fluid simulating solutions such as Fasted-State Simulated Intestinal Fluid (FaSSIF; 30 µg/mL) and Fed-State Simulated Intestinal Fluid (FeSSIF; 108 µg/mL). The data suggest that the total dose of darolutamide (600 mg) does not dissolve in 250 mL of aqueous buffer at physiological pH. Therefore, darolutamide is considered a low-solubility drug substance.

The Applicant investigated the in vitro permeability of darolutamide at a concentration range of 5 to 6000 µM (1.99 to 2390 µg/mL) using a Caco-2 cell assay[1]. The maximum test concentration of 6000 µM represents the concentration of a 600 mg dose of darolutamide dissolved in 250 mL. The solubility in the assay media was limited to 60 µM and therefore a suspension was applied at higher test concentrations. The study results indicated low permeability of darolutamide at a concentration of 5 µM, but high permeability at test concentrations between 30 and 6000 µM (12.0 to 2390 µg/mL). The Applicant stated that the increase in permeability is likely caused by a saturation of active efflux transport. The Applicant mentioned that at clinically relevant intestinal concentrations, assumed to be equal to the solubility in FeSSIF medium of 270 µM (108 µg/mL), darolutamide is expected to show high permeation. The in vitro permeability study results were corroborated by the in vivo pharmacokinetics study data with an oral solution of darolutamide where the Applicant reported 100% bioavailability (Study # 17831). Based on the provided information/data, the Applicant claimed the proposed drug to be a BCS 2 compound. It is important to note that BCS designation is neither requested by the Applicant nor needed.

Table 2. Physicochemical properties of darolutamide

Appearance:	White to greyish- or yellowish-white powder
Measure of the strength of an acid on a logarithmic scale (Pk)-value(s):	pKa: 11.75 ± 0.06
Melting Point	180 °C
Chirality / Stereochemistry	1:1 mixture of diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide
Solubilities:	
Water, phosphate buffer (pH 6.8)	0.014 mg/mL at 37 °C
0.1 M hydrochloric acid (pH 1.0)	0.023 mg/mL at 37 °C
Fasted-state simulated intestinal fluid (FaSSIF) (pH 6.5):	0.030 mg/mL at 37 °C
Fed-state simulated intestinal fluid (FeSSIF) (pH 5.0):	0.108 mg/mL at 37 °C
Ethanol 99.5%	6 mg/mL at 25 °C

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Dissolution Method

The FDA provided 'General Biopharmaceutics Comments' regarding the method development and acceptance criterion to the Sponsor/Applicant during the IND (#114769) stage. In the current submission, the Applicant provided information/data justifying the selection of the proposed dissolution method for quality control testing of the proposed product in the Module 3.2.P.5.3– Validation of Analytical Procedures[2]. The Applicant's proposed dissolution method and acceptance criterion are as following:

Table 3: Dissolution method and acceptance criterion proposed by the Applicant

Applicant's proposed Dissolution Method and Acceptance Criterion for Darolutamide (Nubeqa®) Tablets; 300 mg	
Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	75 rpm
Volume	1000 mL
Medium	0.01 M HCl containing 1.0% SLS
Temperature	37.0 ± 0.5°C
Acceptance Criterion	(b) (4) % (Q) at 60 minutes

For selection of the proposed dissolution testing conditions, the Applicant performed the following studies.

Selection of the Dissolution Medium

(b) (4)

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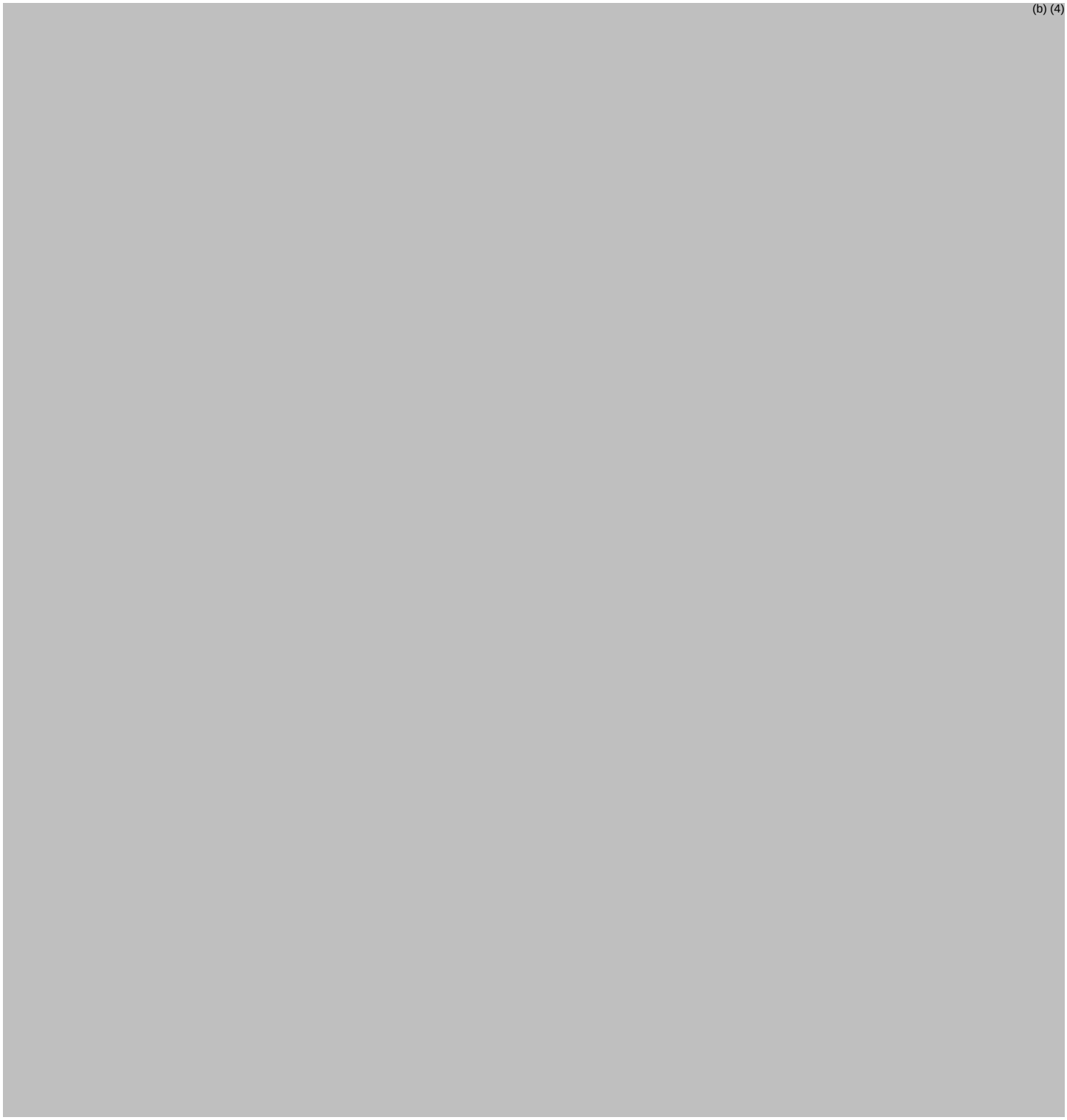
[2] Application 212099 - Sequence 0001 - Method Development - Dissolution - P.5.3.21#017764208

(b) (4)



Discriminating Ability of the Proposed Dissolution Method

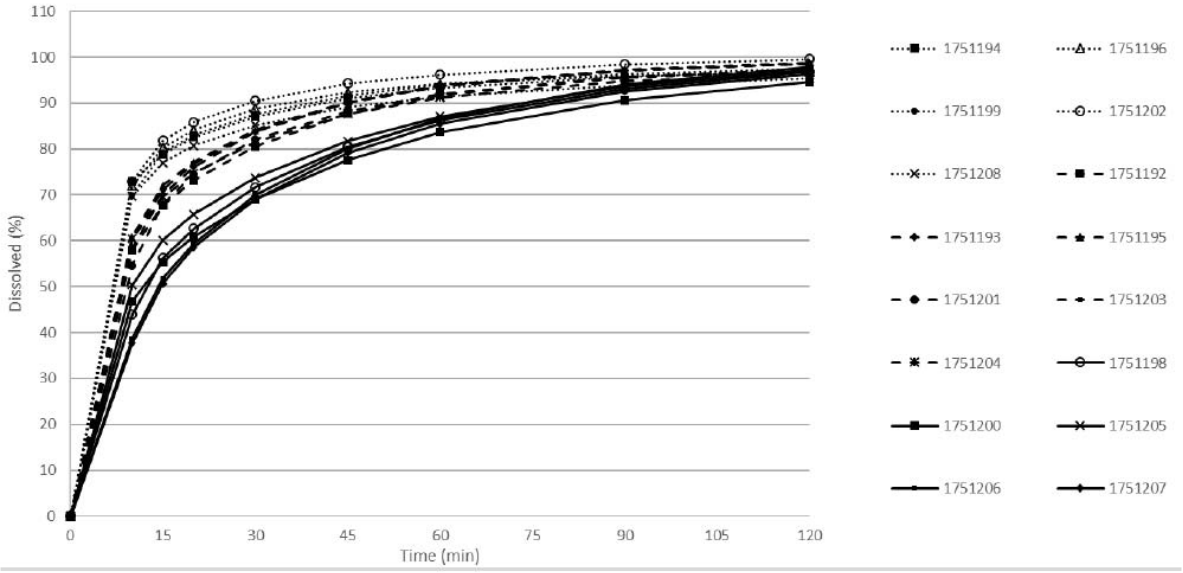
As the provided solubility data suggest, darolutamide is a low solubility drug substance. Therefore, particle size can be a critical material attribute affecting dissolution. The Applicant investigated the discriminating ability of the proposed method towards the drug substance particle size. In addition, the

Applicant also investigated the discriminating ability of the proposed method towards (b) (4) and tablet coating.

Impact of Particle Size Distribution (PSD) of the Drug Substance on Dissolution

The Applicant prepared laboratory scale batches of Darolutamide Tablets using various sized drug substance particles. The median drug substance particle size grades (d50) included in the study were (b) (4) µm. The proposed specification for drug substance particle size is as following: d50 = NMT (b) (4) µm, and d90 = NMT (b) (4) µm. The provided data (Figure 4) show that the dissolution profile of Darolutamide Tablets, 300 mg, is correlated with the particle size of the drug substance. Batches having smallest drug substance grade ((b) (4) µm) resulted in fastest dissolution and the largest grade ((b) (4) µm) resulted in slowest dissolution.

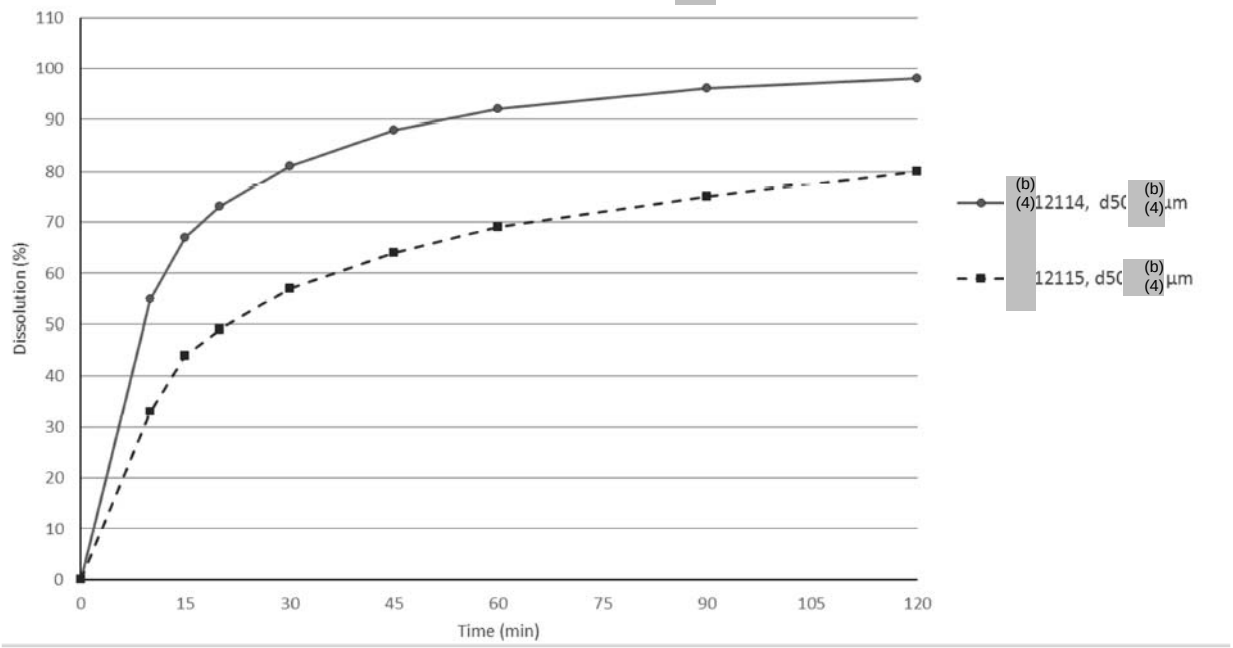
Figure 4. Dissolution profiles of Darolutamide Tablets, 300 mg, batches representing different drug substance d50 grades



PSD d50 grades: (b) (4) µm (···) (b) (4) µm (---) and (b) (4) µm (—).
Dissolution conditions: 1000 mL of 0.01 M HCl with 1.0% of added SLS, 75 rpm rotation speed

Furthermore, the Applicant prepared two Darolutamide Tablet batches consisting of drug substances with two different d50s and compared their dissolution profiles. The d50 was (b) (4) µm in Tablet A (batch no. (b) (4) 12114) and (b) (4) µm in Tablet B (batch no. (b) (4) 12115). The in vitro dissolution data (Figure 5) for the two batches reflect the dissolution behavior that was described earlier (Figure 4) for the batches with d50 values in the range of (b) (4) µm.

Figure 5. Dissolution profiles of darolutamide drug products Tablet A (batch no. (b) (4) 12114) and Tablet B (batch no. (b) (4) 12115)

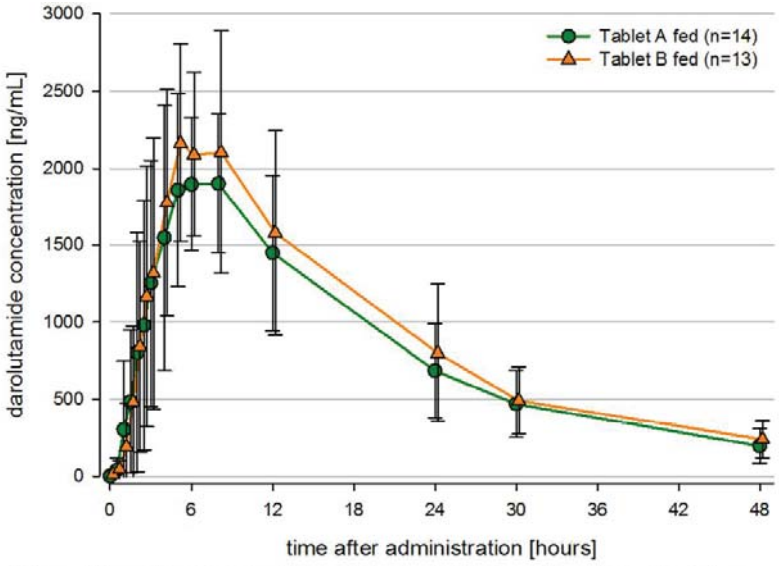


Impact of Particle Size Distribution (PSD) of the Drug Substance on Bioavailability

Considering the low solubility of darolutamide, its particle size can be critical for its timely absorption from the gastrointestinal tract. The Applicant investigated the in vivo effect of the drug substance particle size distribution in a phase 1 clinical trial (Study # 17830).

The Applicant reported that in the Phase 1 clinical study, the mean concentration-time profile of darolutamide from Tablet A containing finer material (d50 = (b) (4) µm) was similar to that from Tablet B containing coarse drug substance material (d50 = (b) (4) µm) under fed conditions (Figure 6). There was no indication that the absorption rate was different between the two tablet batches.

Figure 6. Mean concentration-time profile of darolutamide in two groups of 15 subjects each, one group receiving Tablet A (d50: (b) (4) µm) and the other Tablet B (d50: (b) (4) µm) under fed conditions (Study 17830)

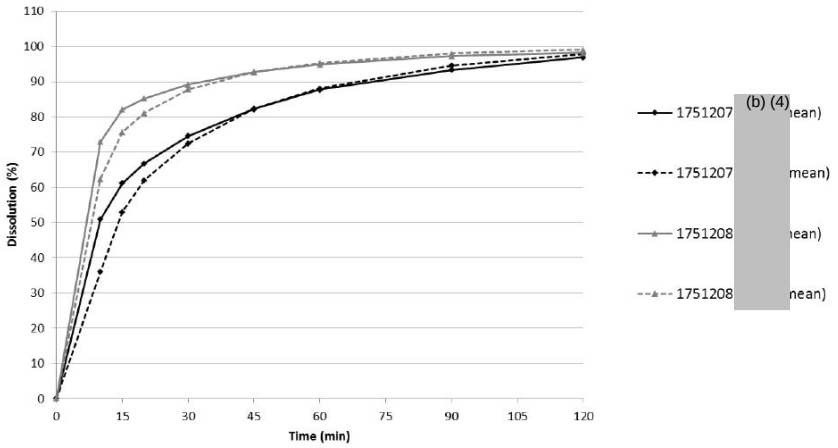


Abbreviations: d50 = median diameter of the particle size distribution; StD = standard deviation
Arithmetic mean (± StD), Dosing was following a standardized high-fat, high-calorie breakfast.

Impact of (b) (4) *on Dissolution*

The Applicant prepared two uncoated laboratory scale study batches with significantly different (b) (4) The Applicant studied this parameter using drug substance with two different particle size ranges, i.e. d50 of (b) (4) µm (tablets 1751208) and d50 of (b) (4) µm (tablets 175207). The dissolution study results (Figure 7) for these batches indicate that the (b) (4) has no significant effect on the dissolution profile of the proposed product, irrespective of the drug substance PSD.

Figure 7. The effect of (b) (4) on dissolution of Darolutamide Tablet, 300 mg



High and low batches: drug substance d50 (b) (4) µm (tablets 1751208) and (b) (4) µm (tablets 175207) (b) (4)
Dissolution conditions: 1000 mL of 0.01 M HCl with 1.0% of added SLS, 75 rpm rotation speed

Impact of Tablet Coating on Dissolution

The Applicant compared the dissolution profile of the uncoated core tablets to the dissolution profile of the coated tablets from the same manufacturing batch. The study results show that the dissolution profile of the coated and the uncoated tablets are were overlapping (Data not shown).

Reviewer's Assessment

The provided in vitro dissolution data indicate that the proposed dissolution method is discriminating towards the drug substance particle size (Figure 4 and 5); however, particle size distribution is not affecting the drug's pharmacokinetics in vivo (Figure 6). Nonetheless, the sensitivity of the proposed dissolution method towards drug substance PSD supports the method's suitability for quality control testing. The provided dissolution data indicate that the proposed dissolution method is not discriminating towards the (b) (4) (Figure 7) or tablet coating.

Based on the above study results, the Applicant selected the proposed dissolution method (USP 2 (paddle), 75 rpm, 1000 mL, 0.01 HCl containing 1.0% SLS, 37.0 ± 0.5°C) as the quality control method for the proposed drug product and further studied the robustness of the method.

Robustness of the Proposed Dissolution Method

The Applicant studied the following parameters to investigate the robustness of the proposed dissolution method:

1. Proof of Solubility (Sink Conditions)
2. Effect of Filter on Dissolution
3. Adsorption of Drug Substance in Filters
4. Filter Capacity through a Profile Run
5. Filtering of Undissolved Drug Substance Particles
6. Effect of Rotation Speed on Dissolution
7. Effect of Sampling Volume on Dissolution
8. Effect of the Composition of Dissolution Medium on Dissolution

To verify that the proposed dissolution medium has the capability to maintain sink condition during dissolution testing, the Applicant prepared three samples with drug concentration exceeding three times of the target concentration of darolutamide and investigated the drug recovery by HPLC analysis[3]. The study results reported drug recovery of 1014.9 µg/mL, indicating that the proposed dissolution medium can maintain sink condition ($C_{Darolutamide}$ > 900 µg/mL) during dissolution testing.

The Applicant evaluated the effect of the filter used in the dissolution method by studying the adsorption of darolutamide drug substance on filters, the filtering capacity during a profile run and filtering of undissolved drug substance particles. Based on this study, the Applicant reported that the

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mean recovery of the filtered samples was within 98–102% for all tested types of filters, and no adsorption of drug substance, or filtering of undissolved drug substance particles, was observed with any of the studied filters.

The Applicant further studied the dissolution of Darolutamide Tablets by changing the rotation speed of USP Apparatus 2 (proposed dissolution condition) by 4% (72 and 78 rpm). The results of the study (Table 5 and Table 6) indicate that the proposed method is not sensitive to decrease of the rotation speed to 72 rpm (f2 = 92.85 when compared with 75 rpm study results) and only slightly sensitive to increase up to 78 rpm (f2 = 66.94 when compared with 75 rpm study results).

Table 5. Comparison and relative standard deviations of 75 rpm and 72 rpm rotation speed results

Time [min]	Acceptance criterion	Experiment I (n=6), 75 rpm Average [%]	RSD [%]	Experiment II (n=6), 72 rpm Average [%]	RSD [%]	Δ Average [%] I - II
10	Δ Average dissolved amount < 10% [a]	39.96	18.8	40.10	17.8	0.14
15		58.18	8.8	59.35	7.2	1.17
20		66.77	6.0	67.79	4.6	1.02
30	Δ Average dissolved amount < 5% [b]	76.13	3.9	77.23	2.7	1.10
45		84.47	2.3	85.48	1.1	1.01
60		89.38	1.3	90.53	0.5	1.15
90		94.35	0.6	95.20	0.2	0.85
120		96.43	0.5	97.08	0.1	0.65

a sampling time points where the RSD of at least one run is more than 5%
b sampling time points where the RSD of both runs is not more than 5%, or where more than or equal to 85% of darolutamide is dissolved
RSD = Relative standard deviation

Table 6. Comparison and relative standard deviations of 75 rpm and 78 rpm rotation speed results

Time [min]	Acceptance criterion	Experiment I (n=6), 75 rpm Average [%]	RSD [%]	Experiment II (n=6), 78 rpm Average [%]	RSD [%]	Δ Average [%] I - II
10	Δ Average dissolved amount < 10% [a]	39.96	18.8	45.64	7.8	5.68
15		58.18	8.8	63.51	3.9	5.33
20		66.77	6.0	71.08	2.6	4.31
30	Δ Average dissolved amount < 5% [b]	76.13	3.9	79.77	1.6	3.64
45		84.47	2.3	87.21	1.0	2.74
60		89.38	1.3	91.35	0.7	1.97
90		94.35	0.6	95.24	0.5	0.89
120		96.43	0.5	96.65	0.7	0.22

a sampling time points where the RSD of at least one run is more than 5%
b sampling time points where the RSD of both runs is not more than 5%, or where more than or equal to 85% of darolutamide is dissolved
RSD = Relative standard deviation

The Applicant studied the potential effect of the small variation in the sampling volume by withdrawing different sample amounts. A comparison of dissolution profiles of the same sample/batch obtained using nominal 5 mL sampling volume and modified sampling volumes of 3 mL and 7 mL (performed on 6 tablets each) was carried out. The drug release calculations were performed by taking the volume of sample withdrawal (3 mL, 5 mL or 7 mL) into the account to have a meaningful comparison between

the studied groups. The evaluation of the absolute difference in the mean values was performed for each time point. Based on the study results[4], the Applicant reported that the proposed method is not sensitive towards the volume of sampling.

The Applicant also studied the effects of, 1) a small change in the concentration of SLS in the dissolution medium (from 1% to 0.98% and 1.02%), and 2) change in the grade of the SLS from NF (from (b) (4)) to Ph. Eur. (From (b) (4)). The study results[5] show that there was no significant change in dissolution upon changing the SLS concentration from 1% to 0.98% (f2 = 61.43) or 1.02% (f2 = 71.62). Similarly, the change in the SLS grade was found to have no significant effect on the dissolution[5] (f2 = 94.51).

Further, the Applicant studied the change in the pH of the dissolution medium by measuring the pH before and after the dissolution testing. The Applicant reported that the pH of the proposed dissolution medium (0.01 M HCl containing 1.0% SLS) to be 2.39 before the dissolution testing and 2.37 after the dissolution testing[6]. The study results suggest that the proposed dissolution medium has good buffer capacity and its pH does not change significantly during/after dissolution of the proposed product.

Based on the above study results, the Applicant concluded that the proposed dissolution testing method is robust and provide consistent results under below summarized study conditions:

[4] Application 212099 - Sequence 0001 - Method Development - Dissolution - P.5.3.21#017764208; Page 23 of 43
[5] Application 212099 - Sequence 0001 - Method Development - Dissolution - P.5.3.21#017764208; Page 24 of 43
[6] Application 212099 - Sequence 0001 - Method Development - Dissolution - P.5.3.21#017764208; Page 26 of 43

Table 7: Summary of robustness studies in the dissolution assay validation

Parameter	Allowed condition/settings
Rotation speed	72–78 rpm
Sampling volume	3–7 mL
Concentration of sodium lauryl sulfate in *Dissolution medium*	0.98–1.02%
Quality of sodium lauryl sulfate	If appropriate quality grade (reagent grade or higher) is used, provider of sodium lauryl sulfate may be varied.
Filters suitable for sampling, including dissolution profile, so that filter does not need to be changed between sampling time points and subsequent filtering through smaller particle size filter is not needed.	10 µm UHMW Polyethylene filters: - 10 µm UHMW Polyethylene tip filters - 10 µm UHMW Polyethylene cannula filters, Sotax - 10 Micron UHMW Polyethylene Full Flow Filter, (b) (4) Other filters materials must be proven suitable before use.

Reviewer's Assessment

The Applicant has adequately studied the robustness of the proposed method. This Reviewer deems the proposed method to be adequate for quality control testing of the proposed product.

Dissolution Acceptance Criterion

The Applicant's proposed dissolution acceptance criterion for batch release and stability testing is 'NLT (b) (4)% (Q) at 60 minutes. The full profile dissolution data for the pivotal clinical batches (Batch # 5121 and 1656119) and the primary stability batches Batch # 1748671, 1761948 and 1765123) are as following:

Figure 8. Dissolution profiles of three clinical development Darolutamide Tablets, 300 mg, batches

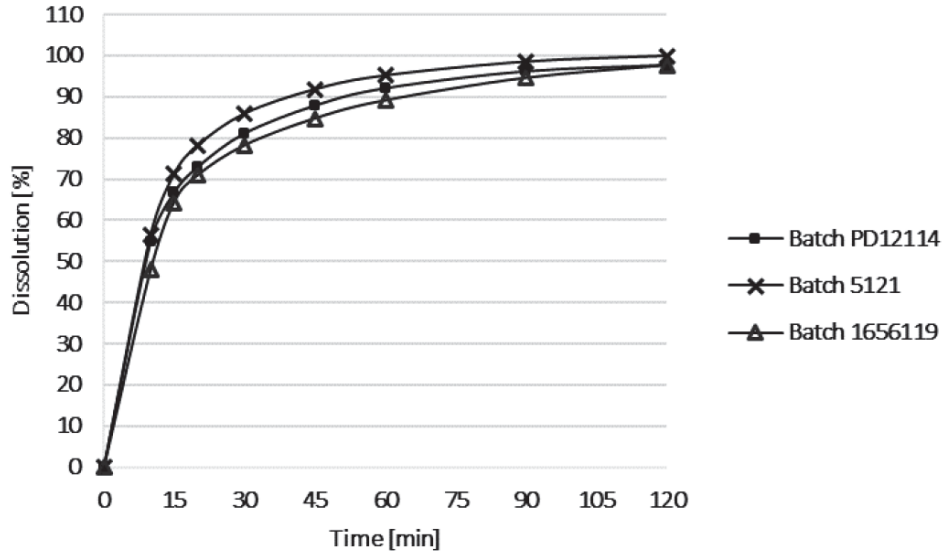


Table 8: Dissolution profiles of Darolutamide Tablets, 300 mg, in 0.01M HCl, with 1.0% SLS, Batch No. 5121

Time [min]	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	AVG [%]	±CI (95%)	SD [%]	RSD [%]	Min. [%]	Max. [%]
10												(b) (4)	57	±3.5	6.3	11.1		(b) (4)
15													71	±2.6	4.6	6.5		
20													78	±1.9	3.4	4.3		
30													86	±1.1	1.9	2.2		
45													92	±0.7	1.2	1.3		
60													95	±0.5	1.0	1.0		
90													98	±0.4	0.7	0.7		
120													100	±0.3	0.6	0.6		

Table 9: Dissolution profiles of Darolutamide Tablets, 300 mg, in 0.01M HCl, with 1.0% SLS, Batch No. 1656119

Time [min]	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	AVG [%]	±CI (95%)	SD [%]	RSD [%]	Min. [%]	Max. [%]
10												(b) (4)	48	±3.0	5.4	11.2		(b) (4)
15													64	±1.7	2.9	4.6		
20													71	±1.4	2.5	3.5		
30													78	±1.2	2.1	2.7		
45													85	±1.0	1.8	2.2		
60													89	±0.9	1.6	1.8		
90													94	±0.7	1.3	1.4		
120													98	±0.5	0.9	0.9		

Figure 9. Dissolution profiles of three primary stability Darolutamide Tablets, 300 mg, batches

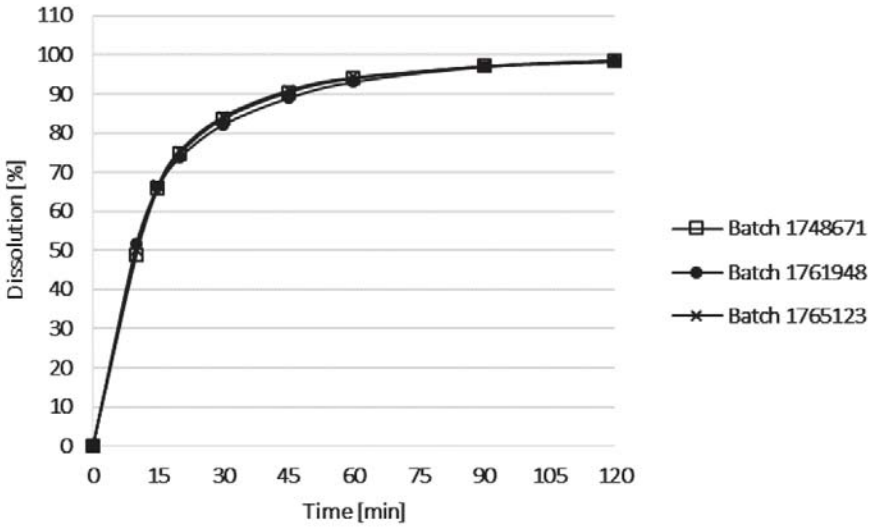


Table 10: Dissolution profiles of Darolutamide Tablets, 300 mg, in 0.01M HCl, with 1.0% SLS, Batch No. 1748671

Time [min]	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	AVG [%]	±CI (95%)	SD [%]	RSD [%]	Min. [%]	Max. [%]
10												(b) (4)	49	±3.1	5.5	11.2		(b) (4)
15													66	±2.4	4.2	6.3		
20													75	±1.7	3.1	4.1		
30													84	±1.2	2.1	2.6		
45													90	±0.7	1.2	1.3		
60													94	±0.6	1.0	1.1		
90													97	±0.4	0.6	0.7		
120													99	±0.3	0.5	0.5		

Table 11: Dissolution profiles of Darolutamide Tablets, 300 mg, in 0.01M HCl, with 1.0% SLS, Batch No. 1761948

Time [min]	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	AVG [%]	±CI (95%)	SD [%]	RSD [%]	Min. [%]	Max. [%]
10												(b) (4)	52	±1.6	2.9	5.6		(b) (4)
15													66	±1.3	2.4	3.6		
20													74	±0.9	1.7	2.2		
30													82	±0.6	1.1	1.4		
45													89	±0.5	0.8	0.9		
60													93	±0.4	0.7	0.8		
90													97	±0.4	0.6	0.6		
120													99	±0.2	0.3	0.3		

Table 12: Dissolution profiles of Darolutamide Tablets, 300 mg, in 0.01M HCl, with 1.0% SLS, Batch No. 1765123

Time [min]	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	AVG [%]	±CI (95%)	SD [%]	RSD [%]	Min. [%]	Max. [%]
10												(b) (4)	50	±2.3	4.0	8.1		(b) (4)
15													67	±1.7	3.0	4.5		
20													76	±1.2	2.2	2.9		
30													84	±0.8	1.5	1.8		
45													91	±0.5	0.9	1.0		
60													94	±0.2	0.4	0.5		
90													97	±0.3	0.5	0.5		
120													98	±0.3	0.5	0.5		

In the original submission, the Applicant did not provide full-profile dissolution data for stability samples. Via an Information Request (IR) dated 05/21/2019[7], the Applicant was requested to provide

[7] Application 212099 - Sequence 0014 - Response to IR 21May2019

these data. In response (dated 05/30/2019), the Applicant provided full-profile dissolution data for the registration batches collected over the duration of stability testing under long-term storage conditions[7].

Based on the provided information/data, the Applicant was recommended (via an IR sent on 06/06/2019[8]) to implement the dissolution acceptance criterion of 'NLT (b)(4)% (Q) at 45 minutes' for quality control testing of the proposed product. In response (dated 06/12/2019[8]), the Applicant provided additional dissolution data from validated batches[9] and proposed to retain the originally proposed dissolution acceptance criterion of 'NLT (b)(4)% (Q) at (b)(4) minutes' with the following justification:

- The main factor affecting the in vitro dissolution of Darolutamide Tablets, 300 mg, is the PSD of darolutamide (b)(4) drug substance. The data clearly demonstrate faster dissolution with smaller drug substance PSD d50 values. The clinical data provided in the submission suggest that the variation in in vitro release of darolutamide due to PSD variation is not reflected in vivo. The dissolution rate is not the limiting step in the absorption process in vivo. Since no in vitro/in vivo correlation (IVIVC) could be established, the dissolution method of Darolutamide Tablets, 300 mg, is only for quality control purposes with no in vivo relevance.
- The 60 min time point is adequate for quality control testing purposes due to the discriminatory power of the dissolution method.
- Based on the additional data, the requested dissolution acceptance criterion of Q=(b)(4) % in 45 minutes is considered too tight for the drug product as it would continuously require Stage 2 testing for batches with drug substance having particle size d50 above approximately (b)(4) µm.
- The requirement for Stage 2 and Stage 3 testing that the mean value is not less than (b)(4) % would not be fulfilled in some of the borderline batches[9]. This would lead to an increased number of out of specification results for tablets manufactured with drug substance batches having d50 close to the upper specification limit of (b)(4) µm.

Reviewer's Assessment

Upon further review of the provide information/data, this Reviewer determines that a tighter dissolution acceptance criterion of 'NLT (b)(4)% (Q) at 45 minutes' can lead to unnecessary stag-2 and stage-3 dissolution testing and/or failure of good-quality batches. The Applicant's proposed dissolution acceptance criterion of 'NLT (b)(4)% (Q) at 60 minutes' is appropriately justified and supported by the provided data and therefore is acceptable.

This Reviewer deems the dissolution method and acceptance criterion described in Table 3 adequate for quality control testing of the proposed product.

Formulation Bridging:

[8] Application 212099 - Sequence 0016 - Response to Authority Request 06Jun2019
[9] Application 212099 - Sequence 0016 - Additional Batch-Related Information - P.5.4.11#019707135

Two different dosage forms were used during the development of the proposed product—a 100 mg powder in-capsule for early Phase 1 / 2 studies, and a 300 mg tablet for subsequent clinical studies and commercial use. The Applicant performed a relative bioavailability study to demonstrate that the exposure of darolutamide from the capsule formulation was similar to that from an uncoated tablet (the data will be reviewed by the Office of Clinical Pharmacology). In all subsequent clinical studies, a film-coated tablet was used. During the development, Darolutamide Film-Coated Tablets were changed from blue tablets, which were used in the clinical studies, to white tablets, which are intended to be utilized for the commercial use. The change of the film-coating was performed (b) (4) . The Applicant provided comparative dissolution data with the pre-change and post-change products in multi-pH conditions to support the proposed change.

First, the comparative dissolution profiles of the blue and white Darolutamide Tablets, 300 mg, were collected using dissolution media at a pH of 1.2, 4.5, 6.5, 6.8, 7.5 conditions and in water. However, the dissolution level was low in each dissolution medium due to the poor solubility of darolutamide without a surfactant (Figure 10). To achieve adequate dissolution level (not less than 90%) to be able to evaluate the similarity of the blue and white tablets, The Applicant performed comparative dissolution studies at the different pH levels using dissolution media with addition of a surfactant (SLS) at concentrations of 1.0 % (Figure 11).

Figure 10. Dissolution profiles of blue and white Darolutamide Tablets, 300 mg, in media without SLS

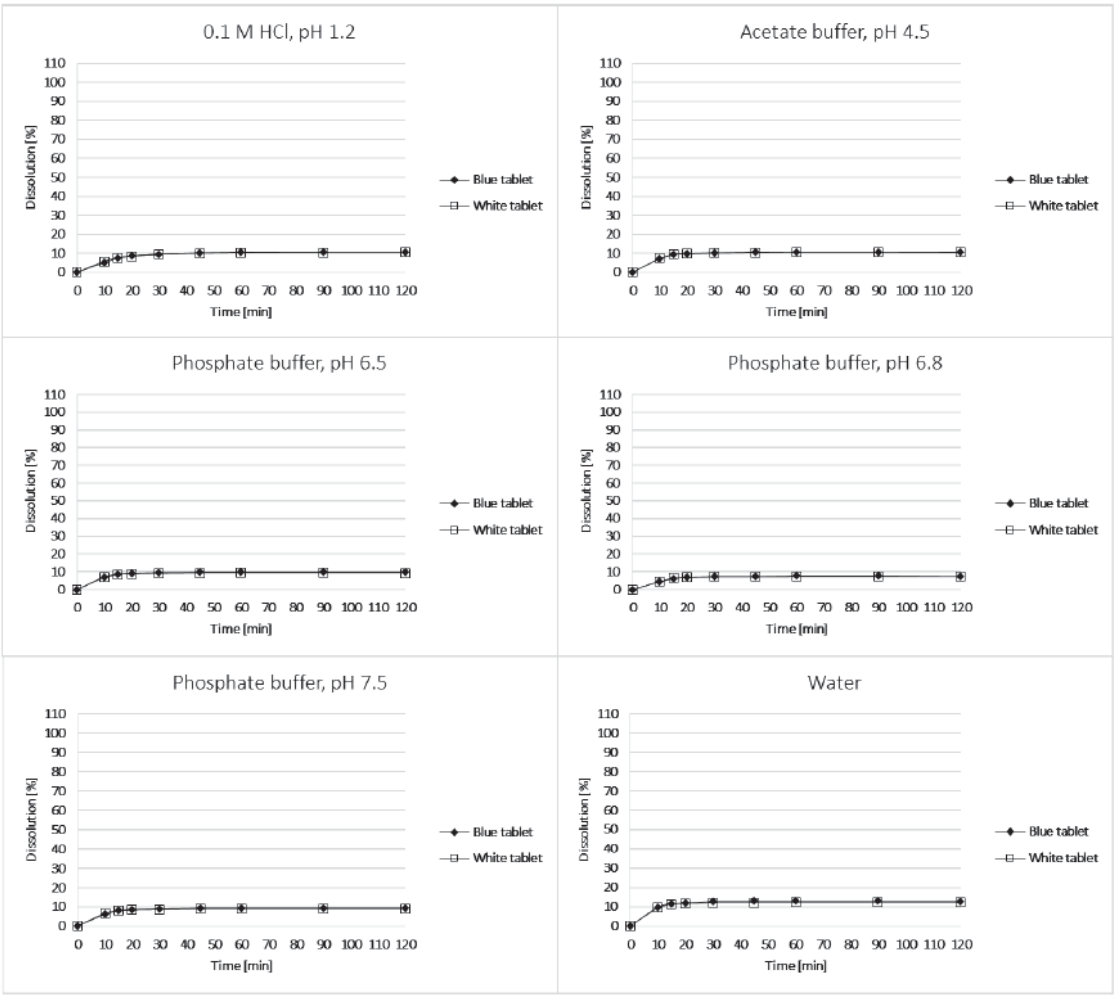
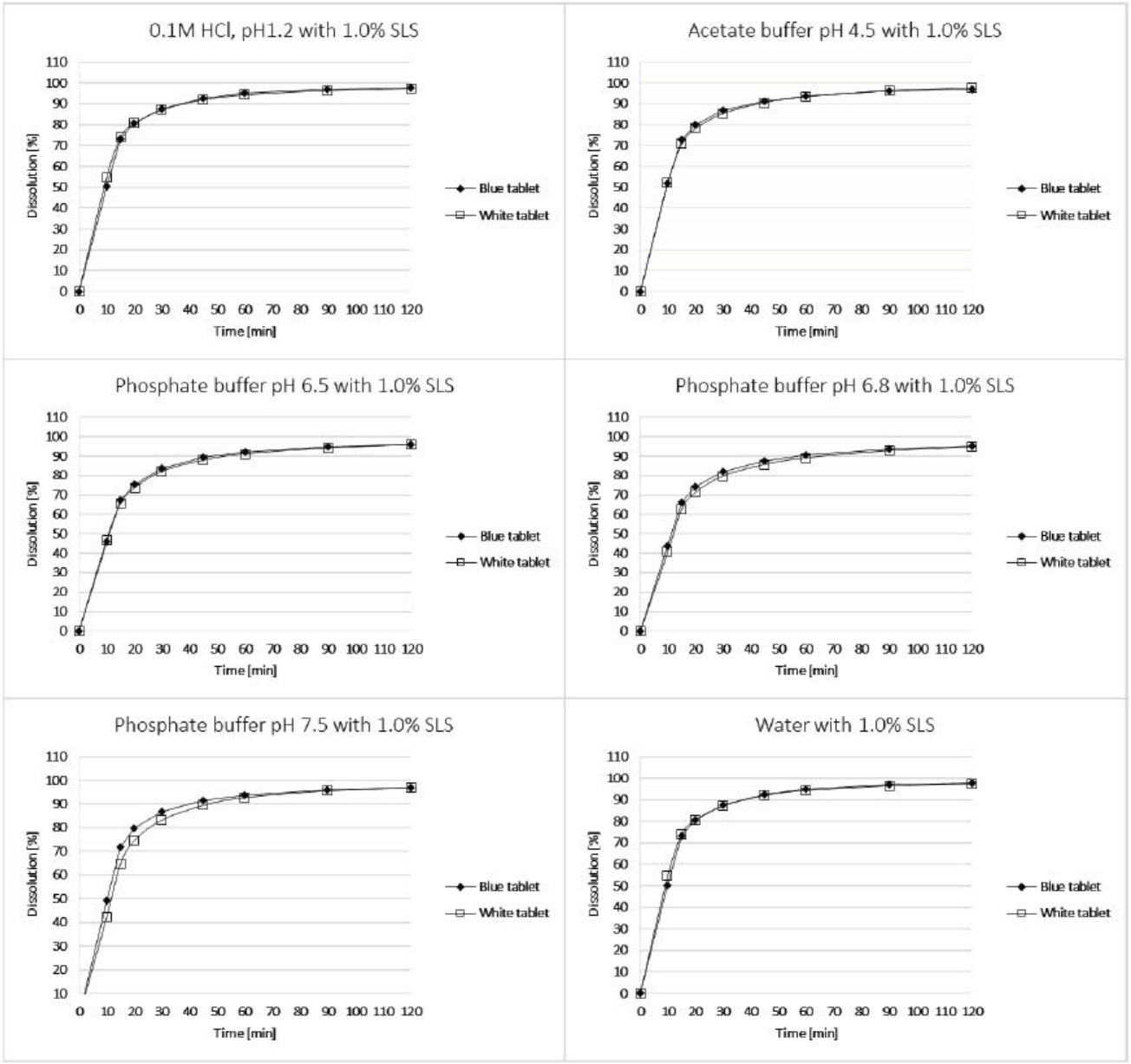


Figure 11. Dissolution profiles of blue and white Darolutamide Tablets, 300 mg, in media with SLS



Reviewer's Assessment

The provided multi-media dissolution data indicate that the dissolution of the pre-change and post-change tablets is very similar and not affected by the change in the color of the non-functional film-coating. There are no other changes, except the dye in non-functional film coating, between the studied and the proposed/commercial products. Based on the provided information/data, there is no significant difference between the pre-change (blue coting) and post-change (white coating) tablets in terms of their dissolution. From a biopharmaceutics perspective, the change in the color of the film-coating of the tablets from blue to while is considered appropriately bridged and therefore acceptable.

Biowaiver Request

Only one strength (300 mg) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

List of Deficiencies

None

Kaushalkumar Dave

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Date: 7/02/2019 11:08:17AM
GUID: 5575db68006e2262805f2e6449c54250

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 7/02/2019 11:56:29AM
GUID: 508da7270002a568e175a2c0dd90f334

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	NUBEQA	Adequate
Established name(s)	Darolutamide	Adequate
Route(s) of administration	Tablets, for oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	300 mg (b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Swallow tablets whole with food. Take any missed dose as soon as they remember prior to the next scheduled dose. Do not take two doses together to make up for a missed dose.	Acceptable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Acceptable
Strength(s) in metric system	300 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to off-white oval film-coated tablets marked with "300" on one side and "Bayer" on the other	Acceptable. Consistent with the description and specifications of the drug product.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	NUBEQA (darolutamide)	Acceptable.
Dosage form(s) and route(s) of administration	Tablet for oral use	The route of administration was not included. The applicant was asked to include it during labeling negotiations.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The applicant included all the ingredients as listed in the section 3.2.P.1	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Androgen receptor inhibitor	Acceptable
Chemical name, structural formula, molecular weight	Provided as indicated in the section 3.2.S.1	Acceptable
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	Not included.	Properties not included. The applicant was asked to include it during labeling negotiations.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Acceptable
Strength(s) in metric system	300 mg	Acceptable
Available units (e.g., bottles of 100 tablets)	Bottles of 120 tablets	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape provided as indicated in 3.2.P.1	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Includes statements: "keep the bottle tightly closed," and (b) (4)	The applicant was asked to remove the statement regarding (b) (4) The other sentence is acceptable based on the in-use data included in the submission.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Desiccant not used	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	USP controlled room temperature	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	
Include information about child-resistant packaging	Not included	Acceptable. Not a requirement per labeling review tool.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Not provided	The applicant was asked to include this information.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (Patient Information):

Appropriate storage conditions and the list of ingredients included. The applicant also included manufacturer information in Patient Information.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Appears prominently in the label	Acceptable
Dosage strength	300 mg	Acceptable
Route of administration	Not listed	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	120 tablets	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Yes	Acceptable
Lot number and expiration date	Yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Provided. Storage range not given	The applicant updated the carton container and label to include the range.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Yes	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Acceptable
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	NA	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	NA	

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

NA

Overall Assessment and Recommendation:

Acceptable, pending applicants response to labeling negotiations with the OND.

Primary Labeling Assessor Name and Date: Anamitro Banerjee, PhD, June 17, 2019

Secondary Assessor Name and Date: Thomas Oliver, PhD., June 17, 2019

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 6/17/2019 03:03:43PM
GUID: 5075764700003844b7bc89632228509f

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 6/18/2019 08:08:31AM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: just signed labeling

CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

The applicant submitted an environmental assessment (EA) for darolutamide. FDA concludes that the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment, per 21 CFR 25.15(a). FDA concludes that the proposed action does not significantly affect the environment, and thus a finding of no significant impact (FONSI) is recommended.

Environmental

(b) (4)

Bayer subsequently submitted an EA for darolutamide, dated 10 Dec 2018, with the following key observations:

1. Darolutamide is primarily released into the aquatic environment after oral administration and subsequent excretion.
2. Biodegradation or other elimination pathways do not significantly contribute to a reduction of the emitted drug.
3. No specific risks for the soil compartment are expected.
4. A sediment test showed that darolutamide did not affect the emergence and development of sediment settling midge larvae.

5. The introduction of darolutamide into the terrestrial environment due to agricultural sewage sludge use is considered to be highly unlikely, and consequently no terrestrial testing and assessment was performed for the compound.

6. The aquatic toxicity studies showed no indication of adverse effects at environmentally relevant concentrations. The ratio of the lowest no observed effect concentration (NOEC) to EEC, based on the study with fish as the most sensitive organism, was (b) (4) µg/L / (b) (4) µg/L = (b) (4), which indicated that there is no significant aquatic risk related to the environmental introduction of darolutamide.

References:

Ankley et al. 2010. Use of chemical mixtures to differentiate mechanisms of endocrine action in a small fish model. Aquatic Toxicology 99 (2010) 389–396.

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams. 2003. A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. Bulletin of Environmental Contamination and Toxicology, 96(5):580-584.

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Assessment: *Adequate*

The main goals of this review of the darolutamide EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly

affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA method, results, and conclusions were reviewed. FDA agrees that the EIC ((b) (4) µg/L) and EEC ((b) (4) µg/L) are considered worst case. The lowest NOEC among the assays and all endpoints, (b) (4) µg/L, result in a margin of exposure (MOE) of (b) (4) when compared to the EIC of (b) (4) µg/L. This EIC is considered worst-case because the calculation of the EIC did not take into consideration (1) metabolism, (2) degradation during wastewater treatment, or (3) dilution, degradation, or removal in surface water.

The EA for darolutamide contains sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The available data appear to be accurate and objective. Therefore, the EA is adequate for approval. Based on an evaluation of the information provided in the EA, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA. Based on the information available to date, a FONSI is recommended for this portion of the application.

Primary Environmental Assessor Name and Date: James Laurenson, July 6, 2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): M. Scott Furness, July 8, 2019

James Laurenson

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