

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213218Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 213218-Orig-1-Resub-26 SOAANZ (torsemide) Tablets

OPQ Integrated Quality Review

Recommendation: Recommended for Approval

Drug Name	SOAANZ (torsemide) Tablets
Dosage Form; Strength	Solid Oral; 20 mg and 60 mg film-coated tablets
Route of Administration	Tablets for oral use
Indication	Treatment of edema associated with heart failure and chronic renal failure
Rx/OTC Dispensed	Rx
Applicant	Sarfez Pharmaceuticals
Submissions (s) Reviewed	NDA 213218, and all the submitted CMC amendments

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Zhengfu Wang	OPQ/ONDP/DNDAPI/NDB3
Drug Product	Akm Khairuzzaman	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Liya Tang	OPQ/OPMA/DPMII/PMB6
Biopharmaceutics	Parnali Chatterjee	OPQ/ONDP/DB/BB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

1. Related/Supporting Documents:

Document	Application Number	Description
DMF	Type II #: (b) (4)	Reviewed and found adequate

2. Consults: None.

OPQ-XOPQ- NDA 213218-Orig-1-Resub-26: SOAANZ (torsemide) Tablets

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 213218 is recommended for approval. Based on the stability data submitted to date, the expiry dating period for Soanz (torsemide) tablets shall be 24 months from the date of manufacture, when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the proposed commercial packaging. Excursions are permitted from 15°C to 30°C (59°F to 86°F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

1. Background

The Applicant, Sarfez Pharmaceuticals, initially sought U.S. marketing approval for (b) (4) (torsemide) (b) (4) Tablets under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act. On January 10, 2020, the Agency issued a Complete Response Letter because of unresolved deficiencies regarding manufacturing facility (b) (4). Though not specifically related to manufacturing of torsemide, there was also a concern of potential (b) (4) contamination at (b) (4) facility. Additionally, based on (b) (4)

2. Product Quality

In this resubmission, the Applicant provided CMC updates (Module 3), including information about change of drug substance manufacturer from (b) (4) (b) (4). The drug product manufacturing process and manufacturer (b) (4) remain unchanged. Additionally, the resubmission includes a change in the drug product name from (b) (4) (b) (4) to Soanz (torsemide) Tablets. This Integrated Quality Review focuses on evaluation of the updated quality information in the resubmitted NDA. For a detailed quality assessment of 213218, refer to the previous Integrated Quality Review (DARRTS, November 25, 2019).

2.1. Drug Substance (Torsemide)

Torsemide, a small synthetic molecule with no chiral centers, is a compendial drug substance. It is practically insoluble in water. All CMC information about the drug

substance is referenced to the DMF (b)(4) which has been reviewed and found adequate. The drug substance exhibits polymorphism, and the manufacturing process described in DMF (b)(4) is designed to produce (b)(4) which is the same polymorphic form of the drug substance that was previously manufactured at the (b)(4) facility. Polymorph form is tested per release specification for the drug substance. The Applicant's acceptance criteria for testing critical quality attributes remain unchanged after changing the drug substance manufacturer. A comparison of batch analysis data of three batches of drug substance, manufactured at (b)(4) facilities, indicate that the drug substances from both manufacturers are comparable and representing (b)(4). The proposed specification, involving testing of critical quality attributes of the drug substance, conforms to the current USP monograph for torsemide and is adequate to ensure the quality of the drug substance.

2.2. Drug Product (Torsemide Tablets)

Per the CMC updates for this resubmission, there are no changes in drug product formulation, manufacturing process, manufacturing facility, specification, analytical methods validation, or the container closure system. Because of change in the drug substance source from (b)(4) the Applicant has manufactured four (4) drug product batches using the newly sourced drug substance. Two (2) batches for the 20 mg strength have been manufactured at a scale of (b)(4) tablets, and two (2) batches for the 60 mg strength have been manufactured at a scale of (b)(4) tablets. With no changes in the drug product manufacturing process and facility, information about the newly manufactured drug product batches (manufactured using the newly sourced substance), is adequate. Per batch analysis data, the newly manufactured batches meet specification, and all the tested attributes, including assay and impurity levels are similar to levels found in the earlier registration batches, manufactured using the former drug substance source. In conclusion, there is no meaningful impact on drug product quality because of the change in the drug substance source.

2.2.1. Biopharmaceutics Aspects: The Applicant relies on the FDA's findings of safety and efficacy of the immediate release Listed Drug (LD), Demadex™, 20 mg [NDA 020136, Approved on 08/23/1993]. The Biopharmaceutics review focused on evaluating the comparative dissolution profile data at release and on long-term stability and 'bridging' of drug product batches, manufactured with drug substance sourced from (b)(4) manufacturing facilities.

Bridging of Drug Product Batches: The 'bridge' between the 20 mg commercial-scale batch (EX-TOR-20TX-83) and 60 mg commercial scale batch (EX-TOR-60TX-84) manufactured with drug substance sourced from the new manufacturer ((b)(4) (b)(4) and the 20 mg batch (PTSB17001) administered in the pivotal clinical trials (study CLCD-058-15) and 60 mg drug product dosed in the food-effect study (CLCD-061-17) has been demonstrated based of similarity of the dissolution profiles and results from multivariate analysis. No significant change in the dissolution data is

observed for the 20 mg and 60 mg scale-up batches under long-term and accelerated stability conditions for up to at least 6 months.



2.2.2. Manufacturing and Manufacturing Facilities: The manufacturing process, involving (b) (4) (b) (4) (b) (4) is well controlled. The drug product manufacturing facility has experience with coated tablets and is currently GMP-compliant. The drug substance manufacturing site for commercial batches (b) (4) is recommended for approval based on-file-review of firm's manufacturing experience, recent inspection outcome, and district's recommendation.

2.2.3. Stability, Storage Conditions and Expiration Date: Six-month stability data for the four (4) newly manufactured batches, stored at 25°C/60% RH as well as under accelerated conditions of 40°C/75% RH, have been provided as additional supportive data. These data don't show any significant trend of product degradation. Previously, stability studies have been performed on 3 full-scale registration batches of each strength in 30-ct bottles, in accordance with ICH Q3B. The 30-ct bottles represent the worse-case for headspace-to-product ratio and therefore support the stability of the 90-ct bottles. No changes in polymorphic form of torsemide or any other critical quality attribute have been detected up to at least 24 months. Taken together, the stability data support an expiry dating period of 24 months for Soanz (torsemide) tablets, when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the proposed commercial packaging.

E. Any Special Product Quality Labeling Recommendations:

The product quality recommendations are included in the latest version of labeling, including the Prescription Information.

F. Life Cycle Knowledge Information

See Final Risk Assessment on the next page.

Final Risk Assessment

NDA 213218-Orig-1-Resub-26 SOAANZ (torsemide) Tablets

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	
Solid state Polymorphic form)/API Manufacturing	• Formulation • Raw materials • Process parameters • Scale/equipment/site	Moderate (M)		Acceptable	
Content Uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/equipment/site	Moderate (M)		Acceptable	Any proposed changes to formulation, manufacturing, or the control strategy will need to be evaluated for possible impact on content uniformity or release properties of the product.

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
(b) (4)	• Formulation • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	
Alcohol Dose Dumping	• Formulation • Process parameters • Scale/equipment/site	Low (L)		Acceptable	N/A
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment/site • API sources	Moderate (M)		Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment/site	Low (L)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 213218 is recommended for approval. Based on the stability data submitted to date, the expiry dating period for Soanz (torsemide) tablets shall be 24 months from the date of manufacture, when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the proposed commercial packaging. Excursions are permitted from 15°C to 30°C (59°F to 86°F).

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPB

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NDA 213218:

(b) (4)

OPQ Integrated Quality Review

Recommendation: Not Recommended for Approval

Drug Name	(b) (4)
Dosage Form; Strength	Solid Oral; 20 mg and 60 mg film-coated tablets
Route of Administration	Tablets for oral use
Indication	Treatment of edema associated with chronic congestive heart failure with or without chronic kidney disease, and the treatment of hypertension
Rx/OTC Dispensed	Rx
Applicant	Sarfez Pharmaceuticals
Submissions (s) Reviewed	NDA 213218, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	ONDP/DNDAPI/NDBI
Drug Product; Labeling; Environmental Assessment (EA)	Stephanie Emory	ONDP/DNDPI/NDPBI
Process and Facility	Allison Aldridge	OPF/DPAI/PABI
Biopharmaceutics	Kaushalkumar Dave	ONDP/DB/BBI
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

(b) (4)

1. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
DMF	Type II DMF #: (b) (4)	Reviewed and found adequate

2. CONSULTS:

None.

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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	(b) (4)	Adequate.
Established name(s)	torsemide)	
Route(s) of administration	tablets, for oral use	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 20 mg and 60 mg	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A – the tablets are not scored	N/A
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.	N/A	N/A

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)	None.	Patients should be instructed not to divide, crush, or chew tablets.

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)	(b) (4) is available as yellow tablets in 20-mg strength and pink tablets in 60-mg strength.	Include description of debossing (see section 16), shape, coating
Strength(s) in metric system		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
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.		

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	Adequate. "Tablets" is missing but would not be grammatically correct in this statement. The product is referred to as "tablets" later in this section
Dosage form(s) and route(s) of administration	(b) (4)	Remove compendial designations (USP, NF). List as "lactose monohydrate." Remove brand name (b) (4) and list individual coating components.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
Pharmacological/therapeutic class	diuretic of the pyridine-sulfonylurea class	Adequate
Chemical name, structural formula, molecular weight	Its chemical name is 1-isopropyl-3-[(4-m-toluidino-3-pyridyl) sulfonyl] urea and its structural formula is: [structure provided]. Its empirical formula is C ₁₆ H ₂₀ N ₄ O ₃ S, its pKa is 7.1, and its molecular weight is 348.43. Torsemide is a white to off-white crystalline powder.	Use a higher resolution image of structure. In section 3.2.S.1, the molecular weight is 348.42 and the pKa is 6.42 Add solubility info
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	None	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
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.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
If radioactive, statement of important nuclear characteristics.		
For oral prescription drug products, include gluten statement if applicable		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Information Provided in the NDA:

(b) (4)

Item	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section	
Available dosage form(s)	Adequate.
Strength(s) in metric system	Adequate.
Available units (e.g., bottles of 100 tablets)	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) (b) (4) and indicate that the debossing is "on one side"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A – not scored
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.	N/A
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.)	N/A
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."	Adequate – no desiccant
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Use standard USP range 20-25°C with excursions to 15-30°C
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."	N/A
Include information about child-resistant packaging	Missing

1.2.5 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	Manufactured For: Sarfez Pharmaceuticals Inc. Vienna, VA 22182	Adequate

1.2.6 Structured Product Labeling:

Assessment of SPL: Adequate, pending the following revisions:

- 1. In the Inactive Ingredients section, include all coating components*

2.0 PATIENT LABELING – N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label – the labels for all strengths (20 mg, 60 mg) and bottle counts (30 and 90 tablets) are essentially the same. The 20 mg 30-ct label is presented below.



3.2 Carton Labeling – No carton label is proposed. The bottles will be distributed without cartons.

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labels
Proprietary name, established name, and dosage form (font size and prominence)	See representative draft label above	Adequate
Dosage strength	See representative draft label above	Adequate
Route of administration	Not present	Not required for tablets
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	See representative draft label above	Adequate
"Rx only" displayed on the principal display	See representative draft label above	Adequate
NDC number	See representative draft label above	Adequate
Lot number and expiration date	Information not provided	Revise draft labels to show the placement of the lot number and expiration date
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	See representative draft label above	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Information not provided	Revise draft labels to include bar code
Name of manufacturer/distributor	See representative draft label above	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	No mention of overseal in Module 1 or Module 3	Clarify if overseal is used and if it contains text
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.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labels: Adequate, pending revisions above

ITEMS FOR ADDITIONAL ASSESSMENT

See above

Overall Assessment and Recommendation:

Adequate, pending revisions listed above.



Stephanie
Emory

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BIOPHARMACEUTICS

Application No: NDA 213218; [505(b)(2)]
Drug Product Name/Strengths: Torsemide Tablets; 20 mg, 60 mg
Route of Administration: Oral
Indication: Treatment of edema; treatment of hypertension
Applicant Name: Sarfez Pharmaceuticals, Inc.
Date of Submission: 03/14/2019 (Original)
Review Recommendation: Adequate

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Om Anand, Ph.D. for Jing Li, Ph.D.

REVIEW SUMMARY

Submission: In NDA 213218, the Applicant proposed, under a 505(b)(2) pathway, (b) (4) oral formulation of torsemide for the same indications as Demadex[®] (Torsemide) Immediate-Release (IR) Tablets, a loop diuretic indicated for the treatment of edema associated with heart failure, renal disease or hepatic disease, and for the treatment of hypertension to lower blood pressure.

Review Objective: The Biopharmaceutics review is focused on the evaluation of the data supporting the proposed dissolution method and acceptance criteria, formulation bridging and the (b) (4) for the proposed drug product.

Dissolution Method: ACCEPTABLE

The Applicant conducted drug substance solubility studies and drug product dissolution studies by altering the dissolution testing conditions to select the quality control (QC) dissolution method. The Applicant appropriately justified the selection of the dissolution testing parameters. The dissolution method for the Torsemide Tablets; 20 mg, 60 mg, is as follows: *900 mL of 0.1N HCl using USP Apparatus 2 (paddle) at 75 rpm*. The Applicant prepared several test batches to investigate the discriminating ability of the proposed product. The provided dissolution data show that the proposed dissolution method can discriminate between the target product and the deviant batch prepared with change in composition (b) (4). The dissolution method was not discriminating towards other studied variables. Due to the high solubility of torsemide in the proposed dissolution medium (0.1N HCl), it can be challenging to demonstrate discriminating ability of the dissolution method. Based on the Applicant's appropriate selection of the dissolution testing conditions, and the provided data demonstrating discriminating ability, the proposed dissolution method is deemed adequate for quality control testing of the proposed drug product.

Dissolution Acceptance Criteria: ACCEPTABLE

The Applicant's originally proposed dissolution acceptance criteria were not appropriately selected. However, the revised (in response to the FDA's recommendation) dissolution acceptance criteria are based on the dissolution data from the clinical and registration batches and are adequate to ensure

quality control testing of the proposed product at the time of release and during stability. The following dissolution acceptance criteria are acceptable for Torsemide Tablets; 20 mg, 60 mg:

1 Hour: NMT (b) (4)%; 3 Hours: NMT (b) (4)%; 6 Hours: NLT (b) (4)% and 10 Hours: NLT (b) (4)% (Q).

In vitro alcohol dose dumping: ACCEPTABLE

The results from the in vitro alcohol- induced dose dumping studies showed that Torsemide Tablets do not dose dump in ethanol solutions containing up to 40% ethanol.

Bridging: Not Applicable: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in i) composition of the proposed product between the pivotal clinical batch, exhibit batches, and the proposed commercial batches, ii) product manufacturing site, and iii) manufacturing process in the scale-up.

Biowaiver: Not Applicable: The Applicant provided pharmacokinetics data for both the strengths (20 mg and 60 mg) of the proposed drug product. Therefore, a biowaiver request is neither submitted nor required.

(b) (4)

RECOMMENDATION: From a Biopharmaceutics perspective, NDA 213218 for Torsemide Tablets; 20 mg, 60 mg is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	Received date	Document
0001	03/14/2019	Original NDA Submission
0006	07/24/2019	Quality/Response to Information Request
0010	09/11/2019	Quality/Response to Information Request
0011	09/16/2019	Quality/Response to Information Request
0013	09/26/2019	Clinical Pharmacology/Response to Information Request
0015	10/01/2019	Clinical/Response to Information Request
0017	10/21/2019	Quality/Response to Information Request

BACKGROUND

Torsemide is a loop diuretic indicated for the treatment of edema associated with heart failure, renal disease or hepatic disease, and for the treatment of hypertension to lower blood pressure.

The Applicant proposes to rely on the FDA’s previous finding of safety and efficacy of the LD product, Demadex® Tablets, [NDA 020136].

The Applicant submitted the following pivotal clinical studies with the proposed drug product:

- CLCD-058-015, which evaluated the pharmacokinetics (PK) and safety of 20 mg strength of the proposed product compared to Demadex® (torsemide in an IR formulation);
- CLCD-061-17, which evaluated the PK and safety of 60 mg strength of the proposed drug product under fasted and fed conditions;

The Applicant provided pharmacokinetics data for both the strengths (20 mg and 60 mg) of the proposed drug product. Therefore, a biowaiver request is neither submitted nor required.

The Biopharmaceutics review is focused on the evaluation of the (i) proposed dissolution method and acceptance criteria, (ii) formulation bridging, and (b) (4) for the proposed product, as presented below.

Formulation: The proposed product, Torsemide Tablets¹, 20 mg and 60 mg, was developed using a (b) (4)

[Redacted content]

¹ Note: the Applicant proposed to name the product as Torsemide (b) (4)
 [Redacted content] Torsemide Tablets has been used as the name in this Review document.

(b) (4) The 20 mg strength tablets have similar composition to the 60 mg tablets (Table 1) (b) (4)

Table 1. Composition of the proposed drug product

Ingredient	Nominal Amount				Function
	20 mg Tablet		60 mg Tablet		
	mg/ tablet	wt% of tablet	mg/ tablet	wt% of tablet	
Tablet core:					
Torsemide USP				(b) (4)	Active ingredient
Microcrystalline Cellulose (b) (4) NF					(b) (4)
Lactose (b) (4) NF					
Hypromellose (b) (4)					
(b) (4)					
(b) (4)					
Colloidal Silicon Dioxide NF					
Talc USP					
Magnesium Stearate NF					
Total					
Film coating:					
(b) (4)					
(b) (4)					
(b) (4)					
Overall total					(b) (4)

Proposed Dissolution Method and Method Development: The Applicant provided a detailed dissolution method development report in the proposed Type C meeting request (October 18, 2018, which was not granted mainly due to proximity of the request to the anticipated NDA submission timing) and is provided under Module 1.6.3². As per the dissolution method development report, the Applicant performed several studies to select the optimum dissolution method for the quality control testing of the proposed drug product.

The Applicant’s originally proposed dissolution method and acceptance criteria are summarized in Table 2.

Table 2: Originally proposed dissolution method and acceptance criteria

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	0.1N Hydrochloric acid
Temperature	37.0 ± 0.5 C
Acceptance Criteria	(b) (4)

For selection of the proposed dissolution study conditions, the Applicant performed the following studies:

² [Application 213218 - Sequence 0001 - Type C Meeting Background Materials 18OCT2018](#)

Drug Substance Solubility

Table 3. Solubility of torsemide in physiological pH conditions

S. No.	Medium	Solubility (mg/mL) at 37°C	Selected Medium Volume (mL)
1	Water	0.19	500
2	0.1N Hydrochloric acid (pH 1.0)	7.34	900
3	0.001N Hydrochloric acid (pH 3.0)	0.21	500
4	pH 3.0 Citrate buffer	0.27	750
5	pH 4.5 Acetate buffer	0.26	750
6	pH 3.0 Phosphate buffer	0.23	750
7	pH 6.8 Phosphate buffer	0.32	500
8	pH 7.2 Phosphate buffer	0.58	500

Dissolution Testing Conditions

[Redacted content] (b) (4)

[Redacted content] (b) (4)

³ [Application 213218 - Sequence 0001 - Type C Meeting Background Materials 18OCT2018](#), Section 5.3 (Page 12/114)

(b) (4)

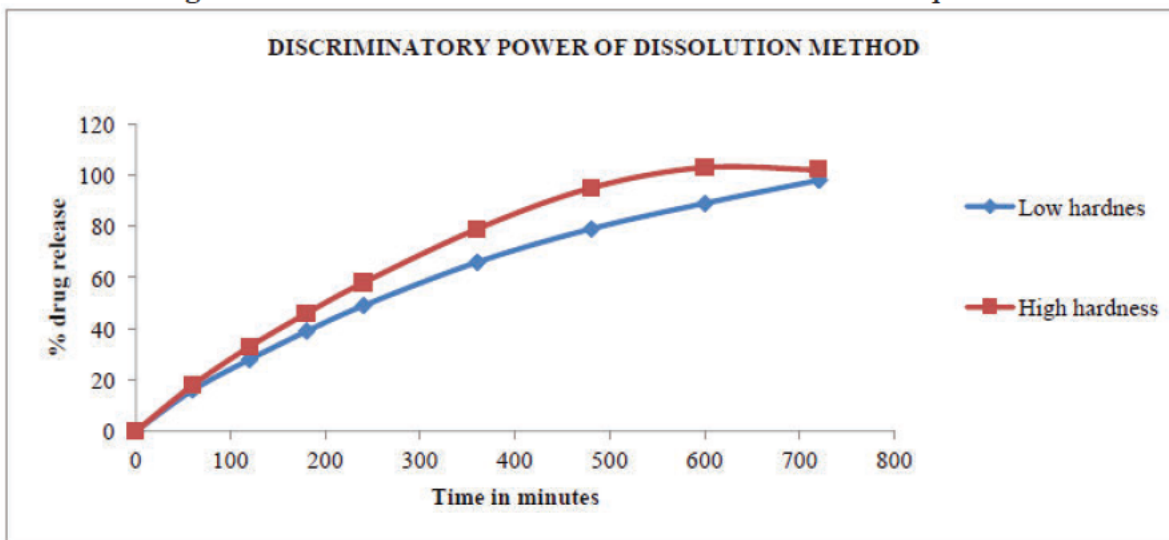
(b) (4)

Discriminating Ability of the proposed dissolution method

The Applicant studied the discriminating ability of the proposed method towards the following attributes/variables:

Tablet Hardness: To investigate the discriminatory ability of the proposed dissolution method, the Applicant prepared batches of the test product (target composition) with low hardness (b) (4) and high hardness (b) (4) and performed a comparative dissolution study. The study results are summarized in Figure 4.

Figure 4: Effect of tablet hardness on dissolution of the test product



No significant change in the dissolution profiles was observed between the studied test batches prepared with different levels of tablet hardness.

Based on the results from the above studies, the Applicant selected the proposed dissolution method for quality control testing of the proposed product.

Reviewer's Assessment:

(b) (4)

(b) (4)

(b) (4). The provided data support the Applicant's selection of 0.1N HCl as the dissolution medium for further testing.

The Applicant stated that torsemide exhibits polymorphism, but the manufacturing procedure described in Type II DMF (b) (4) (b) (4). The Applicant has proposed to use (b) (4) test as a drug substance specification test to ensure that Torsemide (b) (4) is used in the proposed product. The proposed drug substance specifications will be reviewed by the CMC Reviewer.

(b) (4)

Table 8: Mean dissolution of target/control and variant batches collected using (b) (4) mL of 0.1N HCl using USP Apparatus 2 at (b) (4) rpm

(b) (4)

The provided dissolution data indicate that no significant change in the dissolution profile was observed with the variant batches except for the batch prepared with (b) (4) (b) (4). Similar results were also reported with the proposed dissolution method (Table 2) when its discriminating ability was investigated (Figure 2-4). Except for the change in (b) (4) quantity, no other change led to significant difference in dissolution profiles in comparison to the target product. The proposed product is a relatively simple formulation and the drug has high solubility in the proposed dissolution medium. Due to these factors, it can be challenging to demonstrate discriminating ability of the dissolution method. The provided information/data adequately support the discriminating ability of the proposed dissolution method.

The Applicant's provided individual unit (n= 6) dissolution data (with (b) (4) mL of 0.1N HCl using USP Apparatus 2 at (b) (4) rpm) show that one of the units had (b) (4) dissolution profiles in comparison to the other 5 units³. Similar trends were also observed with the variant batches⁴. To understand whether such variability also exists with the currently proposed method, the Applicant was recommended to provide complete-profile dissolution data for all clinical and registration batches collected at the time of batch release using the proposed dissolution method (900 mL of 0.1N HCl using USP Apparatus 2 at 75 rpm). The Applicant provided the requested information on 10/01/2019⁵. The trends of (b) (4) dissolution profiles with one or two units were also consistent with the clinical/registration batches tested using the proposed dissolution method. This variability can be attributed to an error during dissolution testing (e.g., deviation in one of the dissolution vessels, sampling error etc.) or a variability in the product's quality. This Reviewer will ensure adequate selection of dissolution method and acceptance criteria to mitigate the risk of the product's dissolution failure. The provided dissolution data indicate that there is no significant change in dissolution profiles or discriminating ability with the

⁴ [Application 213218 - Sequence 0011 - AD-MISR-2019-047 Torsemide ER tablets Dissolution Report](#)

⁵ [Application 213218 - Sequence 0015 - Response to CMC Information Request 01OCT2019](#)

currently proposed dissolution method (900 mL of 0.1N HCl using USP Apparatus 2 at 75 rpm) and the method with (b) (4) volume and paddle speed ((b) (4) mL of 0.1N HCl using USP Apparatus 2 at (b) (4) rpm). In general, the later dissolution method is preferred in such situations. However, no dissolution data from the clinical batches (manufactured in May/June 2017) are available with the later method while full profile dissolution data from the clinical and exhibit batches at release and during stability testing are provided with the proposed method. Based on the totality of the provided information/data, the Applicant’s currently proposed dissolution method (Table 2) is deemed adequate for quality control testing of the proposed product.

During the process development, the Applicant studied dissolution (b) (4)
 (b) (4)
 (b) (4). The Applicant’s proposed acceptance criterion of D90 NMT (b) (4) microns for the drug substance particle size is acceptable from a Biopharmaceutics perspective.

Dissolution Acceptance Criteria

The Applicant’s currently proposed dissolution acceptance criteria are not adequately selected. Based on the provided information/data the following dissolution acceptance criteria are deemed appropriate for dissolution testing of the proposed product:

- 1 Hour: NMT (b) (4) %
- 3 Hours: NMT (b) (4) %
- 6 Hours: NLT (b) (4) %
- 10 Hours: NLT (b) (4) % (Q)

The following dissolution method and acceptance criteria are deemed adequate for QC testing of the proposed product:

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	75 rpm
Volume	900 mL
Medium	0.1N Hydrochloric acid
Temperature	37.0 ± 0.5 C
Acceptance Criteria	1 Hour: NMT (b) (4) % 3 Hours: NMT (b) (4) % 6 Hours: NLT (b) (4) % 10 Hours: NLT (b) (4) % (Q)

In an IR response (dated 10/21/2019), the Applicant agreed to implement the above dissolution acceptance criteria for quality control testing of the proposed product.

⁶ [Application 213218 - Sequence 0001 - Justification of Specification](#)

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the pivotal clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

In vitro alcohol dose dumping studies: Effect of alcohol on the dissolution profile of Torsemide Tablets; 20 mg, 60 mg: The dissolution profiles of Torsemide Tablets; 20 mg, 60 mg, in ethanol-containing media were determined over a 2-hour period with 15-minute sampling intervals and compared to the corresponding profiles in media without alcohol. Dissolution profile data of Torsemide Tablets dissolved in acidic (0.1N HCl) dissolution media containing 0%, 5%, 20% and 40% ethanol are presented below in Table 9.

Table 9: Summary of comparison of Torsemide Tablets dissolution profiles (up to 2 hours) in acidic (0.1 N HCl, paddle, 75 rpm) media containing 0%, 5%, 20% and 40% ethanol

Time (mins)	20 mg Tablets (Batch No. PTSB-17001)				60 mg Tablets (Batch No. PTSA-17001)			
	0.1 N HCl	0.1 N HCl, 5% EtOH	0.1 N HCl, 20% EtOH	0.1 N HCl, 40% EtOH	0.1 N HCl	0.1 N HCl, 5% EtOH	0.1 N HCl, 20% EtOH	0.1 N HCl, 40% EtOH
15	6 (5-7, 9)	6 (6-6, 4)	5 (4-6, 12)	6 (5-6, 7)	5 (3-6, 15)	8 (7-9, 11)	5 (4-6, 9)	5 (5-6, 6)
30	11 (10-13, 9)	12 (11-13, 4)	10 (8-11, 12)	10 (9-12, 7)	10 (6-11, 15)	12 (10-13, 9)	9 (7-10, 10)	9 (8-10, 7)
45	16 (15-19, 10)	18 (16-19, 5)	14 (11-16, 12)	15 (13-16, 7)	14 (9-16, 16)	16 (13-18, 10)	13 (10-15, 11)	13 (11-14, 7)
60	21 (19-24, 10)	23 (20-24, 5)	18 (14-24, 15)	19 (17-20, 7)	18 (11-22, 16)	21 (17-24, 10)	17 (13-19, 11)	17 (14-18, 8)
75	26 (23-30, 10)	28 (25-30, 5)	21 (17-25, 12)	22 (20-24, 7)	23 (14-27, 17)	27 (21-30, 11)	20 (16-23, 12)	20 (17-22, 8)
90	30 (27-35, 10)	33 (29-35, 5)	25 (20-29, 13)	26 (23-28, 7)	27 (16-31, 17)	31 (24-35, 11)	24 (18-28, 12)	24 (20-26, 9)
105	35 (30-40, 10)	37 (33-40, 5)	28 (22-33, 13)	29 (26-32, 7)	31 (19-36, 17)	36 (27-41, 11)	27 (21-32, 12)	27 (22-29, 9)
120	39 (34-45, 10)	42 (37-45, 5)	31 (25-37, 13)	32 (28-35, 7)	35 (21-41, 17)	41 (31-46, 11)	31 (23-36, 13)	30 (25-34, 10)

Though the Applicant also investigated the alcohol dose dumping potential of the proposed product and reported that alcohol (at the concentration of up to 40% v/v) had no effect on the drug release from the proposed product⁷. This Reviewer agrees that Torsemide Tablets do not dose dump in ethanol solutions containing up to 40% ethanol.

(b) (4)

⁷ Application 213218 - Sequence 0001 - Drug Product; Table 6



Om
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Dave

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/s/

MOHAN K SAPRU
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