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APPLICATION NUMBER:

218139Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	218139
Priority or Standard	Standard
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Office/Division	ORDPURM/DUOG
Reviewer Name(s)	Marjorie Dannis MD, Medical Officer Mark Hirsch MD, Medical Team Leader
Established/Proper Name	Terazosin Oral Solution
(Proposed) Trade Name	Tezruly
Applicant	NOVITIUM Pharma
Dosage Form(s)	Oral Solution 1mg/ml
Therapeutic Class	Alpha-1 adrenergic antagonist
Proposed Indication	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
Recommendation on Regulatory Action	Approval

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1. Executive Summary

1.1. Product Introduction

Terazosin is a nonselective alpha-1 adrenergic antagonist indicated for use alone or in combination with other agents for the management of hypertension and as monotherapy for the treatment of symptomatic BPH. Terazosin has been extensively studied in nonclinical and clinical studies, as referenced in the US Prescribing Information for HYTRIN capsules, the Listed Drug (LD), NDA 020347 (Abbott).

Terazosin was first approved in the US for the treatment of hypertension under the tradename HYTRIN 1, 2, 5 and 10 mg tablets (NDA 019057) on August 7, 1987, and as HYTRIN 1, 2, 5 and 10 mg capsules (NDA 020347) on December 14, 1994. Generic terazosin 1, 2, 5 and 10 mg tablets and capsules were first approved for the treatment of hypertension on Dec 31, 1998, and February 11, 2000, respectively.

On September 29, 1993, HYTRIN was approved in the US for the treatment of symptomatic BPH (”treatment of the signs and symptoms of BPH”) in adult males.

Twelve ANDAs to HYTRIN tablets (4) and capsules (8) dosage forms have been approved since inception. HYTRIN tablets and capsules are discontinued products. According to the Federal Register, HYTRIN was not discontinued or withdrawn for safety or efficacy reasons.

Novitium’s proposed drug product is Terazosin Oral Solution in a strength of 1mg/mL. This 505(b)(2) NDA relies in substantial part on FDA’s findings of safety and effectiveness for the listed drug HYTRIN capsules, 1 mg approved under NDA 020347 held by Abbott Laboratories. Terazosin capsules are marketed in most of world markets including USA, Europe and Canada and there is extensive postmarketing information on the efficacy and safety profile of this drug for both the hypertension and BPH indications.

This NDA relies on:

- Information from comparative fed-fasted relative bioavailability studies of the Applicant’s Terazosin Oral Solution, 1 mg/mL with Jubilant Cadista Pharmaceuticals Inc’s Terazosin capsules 1 mg (ANDA 075317) which is designated as the Reference Standard (RS) in the Orange Book in view of HYTRIN’s discontinued status.

- FDA’s prior findings of safety and effectiveness for HYTRIN capsules as the Listed Drug (LD).

- Nonclinical single and repeated dose bridging toxicity and toxicokinetic (TK) study data from studies conducted on behalf of the Sponsor.

- Nonclinical and clinical data in the public domain where the Sponsor does not have a right of reference.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The NDA application contains substantial evidence that the drug is effective for its intended use with the results of studies TERA-21-077 and TERA 23-003 showing comparable bioavailability of Terazosin Oral Solution to Jubilant Cadista's Terazosin capsules in both the Fed and Fasted states.

1.3. Benefit-Risk Assessment

See the Table that follows herein.

Benefit-Risk Integrated Assessment for BPH Indication

The results of studies TERA-21-077 and TERA 23-003 showing comparable bioavailability of Terazosin Oral Solution to Jubilant Cadista's Terazosin capsules in both the Fed and Fasted states. No new safety signals emerged from the relative bioavailability studies. A review of Postmarketing Experience was consistent with the known safety profile of the product. Based on substantial evidence of effectiveness and no new safety signals, we conclude that the benefit-risk assessment is acceptable for terazosin oral solution.

Benefit-Risk Dimensions BPH Indication

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HYTRIN is approved for the treatment of: • Benign Prostatic Hyperplasia (BPH) • Hypertension A pharmacokinetic bridge from the new oral solution is provided to HYTRIN capsules as the Listed Drug.	HYTRIN, the listed drug for this 505(b)(2) application, is approved for the treatment of benign prostatic hyperplasia (BPH). BPH is the benign enlargement of the prostate so that it obstructs the urethral flow of urine. This could result in symptoms of inadequate bladder emptying, frequent urination, straining to urinate, urgency and nocturia. Urinary tract infections and bladder calculi can also be caused by BPH. Blocking alpha-adrenergic receptors leads to relaxation of the smooth muscle of the bladder neck and the prostatic urethra and can potentially decease these urinary symptoms. Prostatic obstruction can progress to serious adverse outcomes including urinary retention,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		hydronephrosis and renal damage. Urinary tract infections can progress to sepsis which can be life-threatening.
Current Treatment Options	Current medical treatment options for BPH treatment include: • Alpha--1 receptor antagonists • 5-alpha reductase inhibitors • Phosphodiesterase type 5 inhibitors • Beta-3 adrenergic agonists • Antimuscarinics (anticholinergics) Other treatment options include: • Open surgery or transurethral resection of the prostate • Laser or temperature treatment of the prostate • UroLift or mechanical device separation of the obstructing prostate lateral lobes.	The benefit of terazosin oral solution is that a liquid may be easier to swallow for in patients with dysphagia or odynophagia. The product is anticipated to have the same risk: benefit profile as HYTRIN, the LD.
Benefit	• The advantage of terazosin oral solution is that in some patients this product may be easier to swallow.	Useful for patients who have difficulty swallowing capsules/tablets.
Risk and Risk Management	• No increased risk of dizziness or orthostatic hypotension observed in submitted clinical studies. • No new clinical safety signals were observed. • Observed laboratory abnormalities, including increased transaminases, increased eosinophils and decreased hemoglobin, were considered to be a consequence of baseline lab abnormalities, lab results variability, study design issues, and other factors.	Risks are the same as the Listed Drug, as is the risk management.

1.4. Patient Experience Data

This is a 505 (b)(2) application. Patient experience is provided by the experience for the listed drug.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include: This application is a 505 (b)(2) application. The submission consists of two relative bioavailability studies	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as:	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Benign prostatic hyperplasia (BPH) increases in prevalence as men age. Urinary symptoms include increased frequency of urination, nocturia, hesitancy, straining to urinate, urgency, and weak urinary stream. Treatment of BPH includes medical and surgical options.

Lifestyle modifications and behavioral interventions are first-line treatments for all patients. These should be tailored to symptoms but generally include avoiding fluids prior to bedtime or before going out, reducing consumption of mild diuretics such as caffeine and alcohol, and double voiding to empty the bladder more completely.

Treatment is indicated for symptomatic relief, if lifestyle and behavioral modifications do not suffice. In a smaller subset of men, treatment is required to manage refractory lower urinary tract symptoms (LUTS)/BPH and to reverse complication of bladder outlet obstruction, such as a rising post-void residual urine, bladder stones, associated hydronephrosis (with or without renal compromise), or recurrent urinary tract infection. Symptoms of BPH include those of storage (frequency, urgency, and nocturia) and emptying (slow or decreased force urinary stream, straining to void, intermittency, hesitancy, and splitting of the voiding stream).[1]

2.2. Analysis of Current Treatment Options

Alpha-adrenergic receptor antagonists are used as initial pharmacologic agents in most patients with lower urinary tract symptoms (LUTS)/BPH. In addition to bladder outlet obstruction caused by prostate bulk, bladder outlet obstruction (BOO) is primarily mediated by alpha-1 adrenergic receptors located on prostatic smooth muscle. Blocking signaling through the alpha-adrenergic receptors leads to relaxation of the smooth muscle of the bladder neck and the prostatic urethra.[2]

Beta-3 adrenergic agonists or antimuscarinics (anticholinergics) have be used for BPH patients in whom OAB symptoms (frequency, urgency, and incontinence) predominate.

Steroid 5-alpha reductase inhibitors (5-ARI) which block the conversion of testosterone (T) to dihydrotestosterone (DHT) are efficacious in the treatment of LUTS due to prostate enlargement as documented by digital rectal examination or transrectal ultrasonography.[3]

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[1] Up to Date: Medical Treatment of Benign Prostatic Hyperplasia: Literature review through May 2024, Topic last updated January 2024
[2] Up to Date: Medical Treatment of Benign Prostatic Hyperplasia: Literature review through May 2024, Topic last updated January 2024
[3] ibid

Phosphodiesterase type 5 inhibitors (PDE5i) can be used as monotherapy or as initial combination therapy with 5-ARIs in men with BPH-related symptoms. PDE5i are also used in men with BPH and erectile dysfunction.

See Table 1 below for currently available individual treatment options for BPH.

Table 1: Currently Available Medication for Treatment of BPH

Class	Medication
Phosphodiesterase -5 inhibitors	Tadalafil Sildenafil Vardenafil
Selective α-1 receptor antagonists	Alfuzosin Silodosin Tamulosin Doxazosin Terazosin
5-alpha reductase inhibitors	Finasteride Dutasteride
Beta-3 adrenergic agonists	Mirabegron Vibegron
Anticholinergic agents	Fesoterodine Tolterodine Oxybutrin Darifenacin Solifenacin

Source: Derived from Up to Date: Medical Treatment of Benign Prostatic Hyperplasia: Literature review through May 2024, Topic last updated January 2024

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Terazosin is a nonselective alpha-1 adrenergic antagonist indicated for use alone or in combination with other agents for the management of hypertension and as monotherapy for the treatment of symptomatic BPH. Terazosin has been extensively studied in nonclinical and clinical studies to support product approval, as referenced in the US Prescribing Information for HYTRIN capsules, the Listed Drug (LD), NDA 020347 (Abbott).

Terazosin was first approved in the US for the treatment of *hypertension* as HYTRIN 1, 2, 5 and 10 mg *tablets* (NDA 019057) on August 7, 1987, and as HYTRIN 1, 2, 5 and 10 mg *capsules* (NDA 020347) on December 14, 1994. Generic terazosin 1, 2, 5 and 10 mg tablets and capsules were first approved for the treatment of hypertension on Dec 31, 1998, and February 11, 2000, respectively.

On September 29, 1993, HYTRIN was approved in the US for the treatment of symptomatic BPH. Twelve ANDAs to HYTRIN tablets (4) and capsules (8) dosage forms have been approved since inception. HYTRIN tablets and capsules are discontinued products. According to the Federal Register, the NDA for HYTRIN was not discontinued or withdrawn for safety or efficacy reasons.

Novitium's proposed drug product is Terazosin Oral Solution in a strength of 1mg/mL. This 505(b)(2) NDA relies in substantial part on FDA's findings and safety and effectiveness for the listed drug HYTRIN capsules, 1mg approved under NDA 020347 held by Abbott Laboratories. Terazosin capsules are marketed in most of world markets, including USA, Europe and Canada and there is extensive postmarketing information on the efficacy and safety profile of this drug for both indications of hypertension and BPH.

3.2. Summary of Presubmission/Submission Regulatory Activity

- On October 21, 2021, DUOG provided Type B Pre-IND (PIND 157262) Meeting Written Responses: Various chemistry and manufacturing process questions and issues were answered. In addition, the Sponsor received guidance on non-clinical, clinical pharmacology, regulatory and clinical issues.
- On January 28, 2022, this IND was placed on Clinical Hold because the submission was "extremely insufficient and lacking in substance, such that a review of the submission and determination as to whether the proposed protocol in the submission is safe to proceed was not possible."
- On May 10, 2022, an Incomplete Response to Clinical Hold Letter was issued because the Sponsor had not provided results from a 28-day rat toxicity bridging study as they had been advised to submit in a letter dated February 28, 2022.
- On September 9, 2022, the Sponsor submitted a Complete Response to Clinical Hold which included the results of the 28-day rat toxicity study.
- On October 7, 2022, the planned relative bioavailability (BA/BE) study was deemed safe to proceed.
- On September 29, 2023, NDA 218139 was submitted.

3.3. Foreign Regulatory Actions and Marketing History

Terazosin oral solution is not approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) has determined that inspections were not needed for both the analytical and clinical sites (Bioequivalence Establishment Inspection Report Review dated 1/26/2023 in DARRTS). OSIS had conducted a Remote Regulatory Assessment for the analytical site in (b) (4) under the following submissions: ANDAs NON-RESPONSIVE and NON-RESPONSIVE. The Office of Regulatory Affairs conducted an inspection of the clinical site in August 2023 for ANDA NON-RESPONSIVE. These inspections did not identify any significant issues that would impact study integrity.

4.2. Product Quality

In their Integrated Quality Assessment (IQA), the Office of Pharmaceutical Quality (OPQ) recommended Approval of this NDA stating that" the applicant of this 505(b)2 NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug substance and the drug product". See IQA dated June 12, 2024, for full details.

4.3. Clinical Microbiology

Not applicable for this oral solution.

4.4. Nonclinical Pharmacology/Toxicology

In their Pharmacology/Toxicology review dated June 17, 2024, the Pharmacology/Toxicology review team concluded that "based on the 28-day toxicity rat study and the establishment of an acceptable clinical PK bridge between Terazosin 1 mg/mL oral solution and the Listed Drug allowing the reliance on the Agency's previous nonclinical findings of safety of HYTRIN, Pharmacology/Toxicology recommends Approval."

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4.5. Clinical Pharmacology

In their Office of Clinical Pharmacology review dated June 18, 2024, the Clinical Pharmacology review team concluded that application was acceptable for Approval from the Clinical Pharmacology perspective. Clinical Pharmacology confirmed that the requirement for bioequivalence was met when comparing "Applicant's proposed product containing terazosin 1 mg/mL to the RS Jubilant Cadista Pharmaceutical 1 mg capsules."

The Clinical Pharmacology review further noted that food intake decreased the Cmax of terazosin by 29% but did not affect the AUC of terazosin. Therefore, the effect of food on Cmax was not considered clinically relevant because 1) the proposed product was bioequivalent to the LD under both fasting and fed conditions and 2) food did not have a clinically meaningful effect on the PK of terazosin according to the approved label of the LD.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 : Clinical Trials Relevant to this NDA

Study Type	Study ID	Objectives	Design	Test Product¶ Regimen Route	N (M/F)	Subject Type
BA BE	TERA-21-077	*Clinical Bridge* Terazosin Oral Solution (Fasted [T] [B]) vs. Terazosin Capsules (Fasted [R] [C]) *Food Effect* Terazosin Oral Solution (Fed [T] [A]) vs. Terazosin Oral Solution (Fasted [T] [B])	SD, 3-way, X-over T (Fed [A]) T (Fasted [B]) R (Fasted [C]) 0-72 hr PK 28 samples .	Terazosin Oral Solution, Fed (1 mg) Terazosin Oral Solution, Fasted (1 mg) Terazosin Capsules, Fasted (1 mg)	**Enrolled**: 30 **M/F:** 22:8 **Dosed**: Period 01: 29 Period 02: 28 Period 03: 28 **Completed**: 28 B vs. C: 28 A vs. B: 28	Healthy Subjects

[T]=Test, [R]= Reference
[A] = Test fed, [B]=Test fasted, [C]= Reference fasted
Source: Derived from Applicant's Summary Clinical Safety

Study Type	Study ID	Objectives	Design	Test Product[¶] Regimen Route	N (M/F)	Subject Type
BA BE	TERA-23-003	*Food Effect* Terazosin Oral Solution (Fed [T] [A]) vs. Terazosin Capsules (Fed [R] [B])	SD, 2-way, X-over T (Fed [A]) R (Fed [B]) 0-72 hr PK 27 samples .	Terazosin Oral Solution, Fed (1 mg) Terazosin Capsules, Fed (1 mg)	**Enrolled**: 30 **M/F:** 16:14 **Dosed**: Period 01: 29 Period 02: 29 **Completed**: 29 A vs. B: 29	Healthy Subjects

[T]=Test, [R]= Reference
[A] = Test fed, [B]=Test fasted, [C]= Reference fasted
Source: Derived from Applicant's Summary Clinical Safety

5.2. Review Strategy

The two clinical trials relevant to this NDA are listed above in Table 2. The Applicant has established a clinical "bridge" by conducting two comparative BA studies to support its reliance on the Agency's findings of safety and efficacy for HYTRIN capsules. These two trials formed the basis for a scientific bridge to the FDA's prior determination of substantial evidence of effectiveness for the original HYTRIN application. Since samples of HYTRIN capsules are unavailable, the Sponsor has conducted its comparative BA studies using Jubilant Cadista Pharmaceuticals Inc's Terazosin capsules as the Reference Standard (RS) (following discussions with FDA's Division of Urology, Obstetrics, and Gynecology at a Type B PIND Meeting on October 21, 2021). The Jubilant Cadista product has been designated as the RS in the Orange Book and is acceptable as a reference product for the BA studies.

This NDA relied on:

- Information from comparative fed-fasted bioavailability and safety studies of the Sponsor's Terazosin Oral Solution, 1 mg/mL with Jubilant Cadista Pharmaceuticals Inc's Terazosin capsules 1 mg (ANDA 075317) which is designated as the Reference Standard (RS) in the Orange Book in view of HYTRIN's discontinued status.
- The Food and Drug Administration's (FDA) prior findings of safety and effectiveness for HYTRIN capsules as the Listed Drug (LD).
- Nonclinical single and repeated-dose bridging toxicity and toxicokinetic (TK) study data from studies conducted on behalf of the Sponsor.
- Nonclinical and clinical data in the public domain where the Sponsor does not have a right of reference, including information on the postmarketing experience with terazosin.

All available safety data are reviewed in the Safety section of this review.

Of note, as this NDA was submitted as a 505(b)(2) application and contained results from two bioavailability and food effect studies only, some subsections of this Clinical Review template are not applicable and have been omitted.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study TERA-21-077 (Single Dose Food Effect and BE study)

Trial Design

Study TERA-21-077 was a single-dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover study in healthy human adult subjects to assess oral bioavailability and to assess the effect of food on the test formulation of terazosin hydrochloride oral solution 1 mg/mL under fed (Treatment A) and fasted (Treatment B)

conditions with a Reference formulation of terazosin capsules USP 1 mg (Treatment C) under fasted conditions.

In this study, 30 subjects were enrolled. 29 subjects were dosed in period 01, 28 subjects were dosed in period 02 and period 03. Totally, 28 subjects were completed the study in accordance with the protocol

Subjects received a single dose of the proposed drug or RS following a 10-hour, overnight fast. For Treatment A, a high-fat high-calorie breakfast (995.5 kcal) was provided to subjects 30 min prior to administering the test product with about 240 mL water at ambient temperature. For Treatment B, the test product was administered with 240 mL of water at ambient temperature. For Treatment C, the reference product was administered with 240 mL of water at ambient temperature.

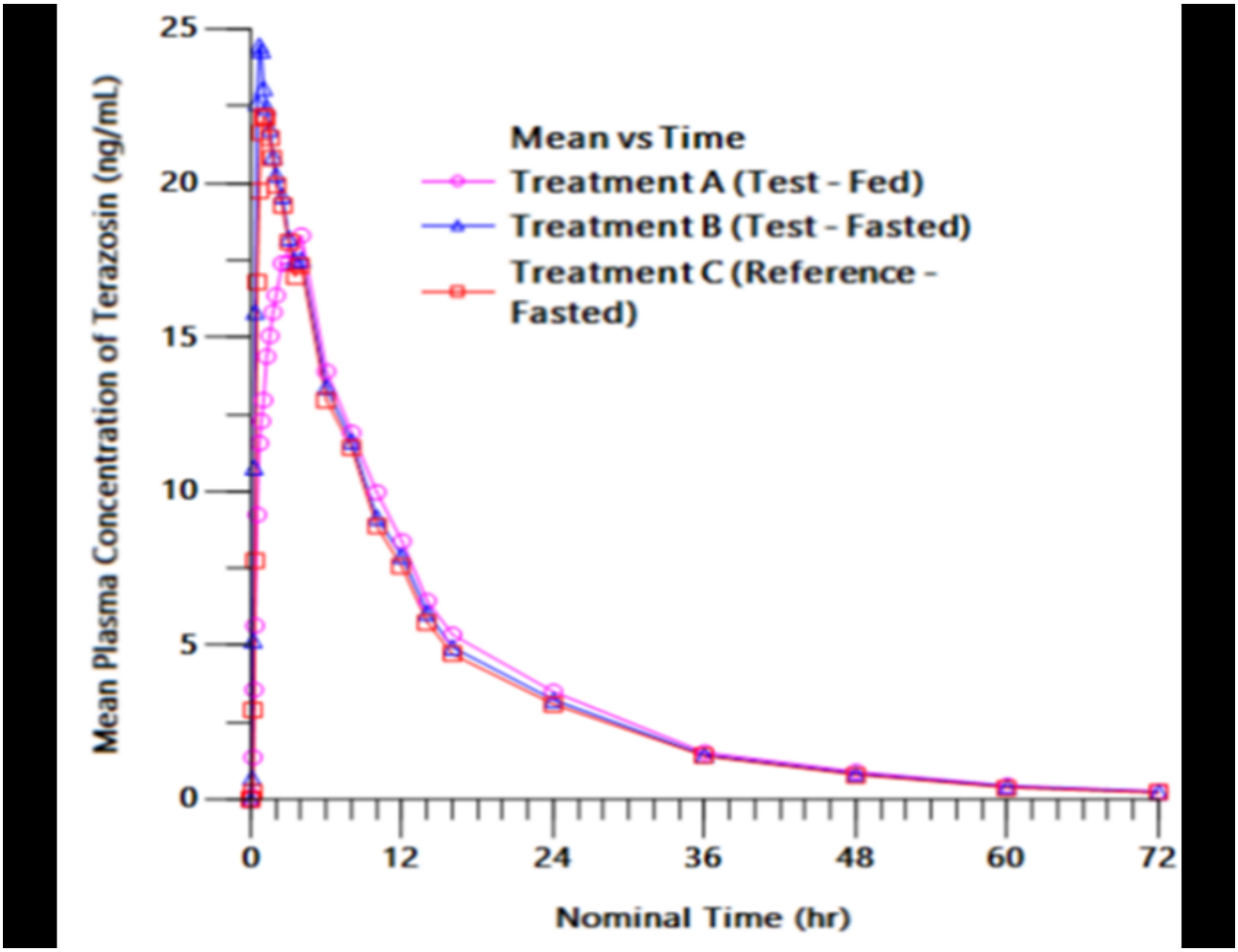
In each study period, a total of 28 venous blood samples were collected at pre-dose (0.0 hour) and at 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00, and 72.00 hours post-dose after administration of each dose.

The Clinical Pharmacology reviewers concurred that the PK sampling time points were adequate to capture the full PK profile of terazosin.

Results

The plasma concentration time profiles of terazosin (Figure 1) and statistical analyses (Tables 3 and 4) of the summary PK data are shown below. The results demonstrate that the proposed product is bioequivalent to the RS under fasting conditions and that food decreased the C_{max} by 29% but did not affect AUC for terazosin. This BA study supports a scientific bridge to the LD HYTRIN in the fasted state. These results were verified by the Clinical Pharmacology review team and they concurred with the bioequivalence determination.

Figure 1: Mean Plasma Concentration of Terazosin vs Scheduled Time Points in Study TERA-21-077



Source: Clinical Study Report TERA-21-077

Table 3: Results of Geometric Least Square Means, Power (%), Treatment (A)/Treatment (B) Ratios, ISCV (%), 90% Confidence Intervals of Test (Treatment B) versus Reference (Treatment C) in Study TERA-21-077

Parameters (Units)	Geometric mean		Power (%)	ISCV (%)
	Test (Treatment B)	Reference (Treatment C)		
C_{max} (ng/mL)	25.9790	25.2264	99.45%	16.90%
AUC_{0-t} (hr*ng/mL)	270.5851	261.0275	100.0%	10.31%
$AUC_{0-\infty}$ (hr*ng/mL)	276.2671	266.6007	100.0%	10.30%
Parameters	**Ratio (%)**	**90% Confidence Intervals for**	**Acceptance Criteria**	**Outcome of BE result**
	B/C	**B vs. C**		
C_{max}	102.98%	95.38% to 111.19%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	103.66%	98.9% to 108.65%	80.00% - 125.00%	
$AUC_{0-\infty}$	103.63%	98.87% to 108.61%	80.00% - 125.00%	

Test Product (Treatment B) – Terazosin Oral Solution 1 mg/mL under fasted conditions.
Reference Product (Treatment C) – Terazosin Capsules, USP 1 mg under fasted conditions
Source: Clinical Study Report TERA-21-077 Table 4

Table 4: Summary Statistics of PK Data Comparing Test (A & B) and Reference (C) in Study TERA-21-077

Parameters (Units)	Terazosin (Mean ± SD)		
	Treatment (A) under fed condition	Treatment (B) under fasting condition	Treatment (C) under fasting condition
C_{max} (ng/mL)	18.924 ± 4.5484	27.092 ± 7.8527	26.028 ± 7.5538
AUC_{0-t} (hr*ng/mL)	274.081 ± 66.6574	279.889 ± 73.7183	267.054 ± 61.6626
$AUC_{0-\infty}$ (hr*ng/mL)	280.280 ± 67.9262	285.616 ± 74.7694	272.618 ± 62.4492
t_{max} (hr) #	3.50 (0.67 – 4.02)	0.67 (0.50 – 1.75)	1.00 (0.50 – 2.50)
$t_{½}$ (hr)	13.265 ± 1.7994	12.977 ± 1.6070	12.871 ± 1.4460
K_{el} (1/hr)	0.0533 ± 0.00789	0.0543 ± 0.00730	0.0545 ± 0.00624
T_{lag} (hr) #	0.08 (0.00 – 0.17)	0.00 (0.00 – 0.17)	0.17 (0.08 – 0.25)
$AUC_{\_\%Extrap\_obs}$	2.24 ± 0.54	2.05 ± 0.45	2.08 ± 0.52
Cl/F ({mg/mL}/(ng/mL))	0.004 ± 0.0010	0.004 ± 0.0011	0.004 ± 0.0008
Vd/F ({mg/mL}/(hr*ng/mL))	0.071 ± 0.0157	0.069 ± 0.0169	0.071 ± 0.0154

#) T_{max} and T_{lag} are presented as Median (Minimum and Maximum)

Source: Clinical Study Report TERA-21-077

In summary, in the relative bioavailability part of study TERA-21-077, when comparing Treatment B (Test fasted) vs Treatment C (Reference fasted), the 90% CI of GMRs for Cmax, AUC0-t, and AUC0-∞ were 95.38% to 111.19%, 98.9% to 108.65%, and 98.87% to 108.61%, respectively. The 90% CI values are within the BE acceptance criteria of 80 to 125% and thus, the proposed product is bioequivalent to the RS under fasting conditions.

In the food effect part of the relative bioavailability study TERA-21-077, when comparing Treatment A (Test fed) vs Treatment B (Test fasted), the 90% CI of GMRs for Cmax, AUC0-t, and AUC0-∞ were 66.13% to 76.23%, 92.47% to 104.8%, and 92.64% to 105.01%, respectively. While food decreased the Cmax by 29%, it did not affect the AUC for terazosin.

The results of the clinical study reports from TERA-21-077 were verified by the Clinical Pharmacology review team and they concurred with the Applicant's conclusions of bioequivalence (refer to review dated June 18, 2024)

Compliance with Good Clinical Practices

In compliance with standard protocol and relevant standard operating procedures (SOPs) of

(b) (4), the research was carried out in accordance with the clinical research guidelines established principles enunciated in the Declaration of Helsinki. (b) (4) certified that (b) (4) employs all applicable Good Clinical Practice (GCP) standards. All drug accountability records, case report forms (CRFs), source data and related regulatory documents will be retained for at least 5 years from the date of completion of the study or as per regulatory requirements.

Financial Disclosure

The Sponsor provided financial disclosures for this NDA submission. A total of 3 investigators participated in this study and none had an issue with financial disclosure.

Data Quality and Integrity

According to Clinical Pharmacology review, terazosin concentration in plasma samples was assessed using a validated liquid-liquid extraction method with high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). For both studies, results showed that 95-100% of the samples met the criteria of reproducibility. In both studies, study samples were stored for up to 24 days before analysis. The storage stability of study samples is supported by the established long-term stability period of 99 days. Therefore, overall, the results of bioanalytical method validation and performance were acceptable.

6.2. Study TERA-23-003 (Relative BA/BE Study Under Fed Condition)

Trial Design

This was an open label, randomized, single dose, two-treatment, two-sequence, two-period, two-way crossover oral BA study to compare terazosin hydrochloride oral solution 1 mg/mL (test; T) with terazosin 1 mg capsules (reference; R) in healthy, adult, human subjects under fed conditions.

A total of 30 healthy adults were planned and enrolled in the study with 29 subjects completing the study. Subject (b) (6) had inadequate or incomplete consumption of the high fat, high calories breakfast in period 1 and was discontinued from the study. The Applicant based their final PK and statistical analysis on the 29 subjects that completed the study.

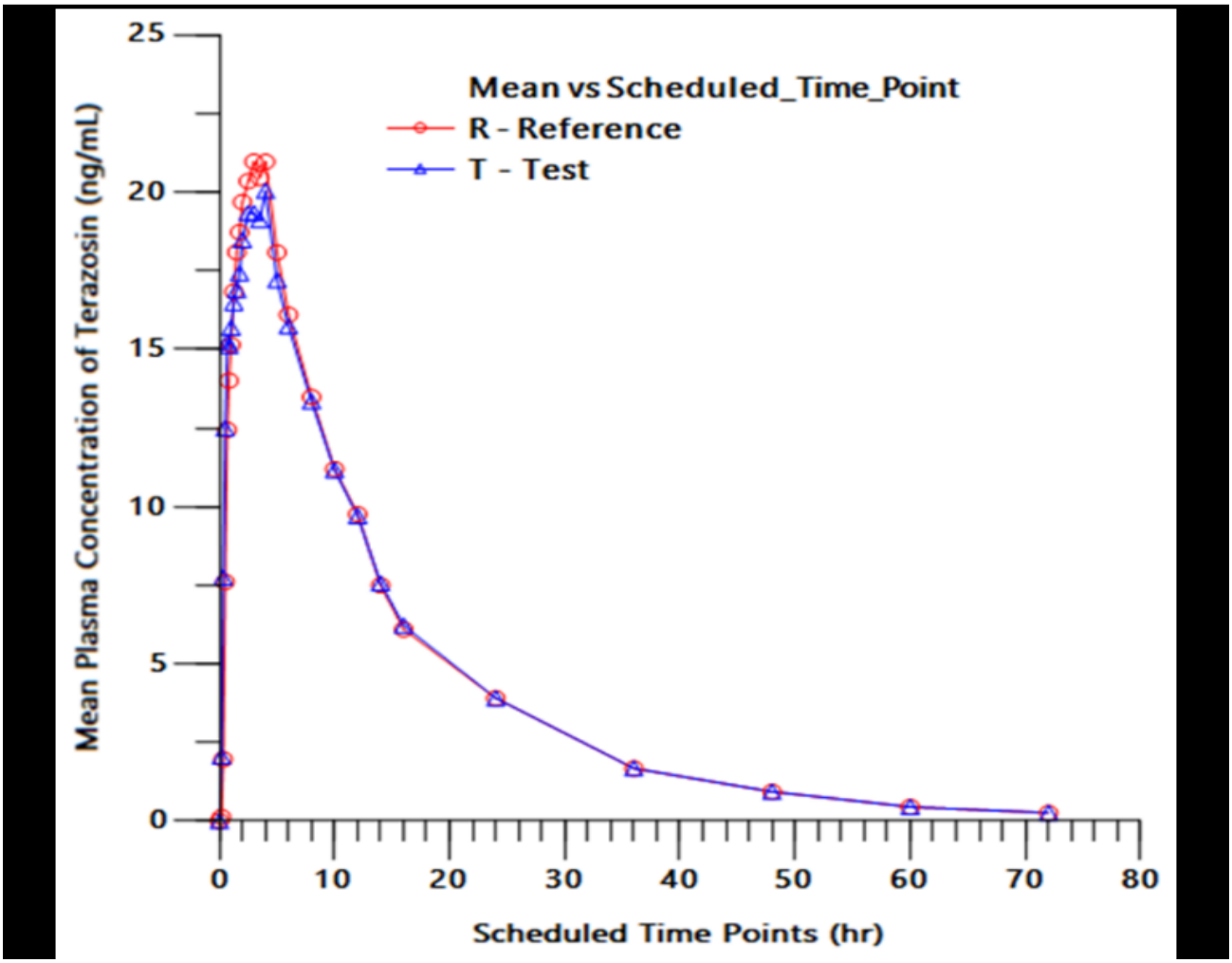
Following a 10-hour overnight fast, subjects received a single dose of the proposed drug (T) or RS (R) 30 minutes after a high fat, high calorie breakfast with 240 mL water at ambient temperature. In each period, a total of 27 venous blood samples were collected at pre-dose (0.0 hour) and at 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00, and 72.00 hours post dose after administration of each dose. The PK sampling time points were adequate to capture the full PK profile of

terazosin. The PK concentration measurements of terazosin in plasma PK samples were measured using validated LC-MS/MS method.

Results

The plasma concentration time profiles of terazosin (Figure 2) and statistical analyses for BE assessment (Table 5) are shown below.

Figure 2: Mean Plasma Concentration of Terazosin vs Scheduled Time Points in Study TERA-23-003



Source: Clinical Study Report TERA-23-003

Table 5: Results of Geometric Least Square Means, Power (%), Test/Reference Ratios, ISCV (%), 90% Confidence Intervals Based on Ln-transformed Data from Terazosin Under Fed Conditions in Study TERA-23-003

Parameters (Units)	Geometric mean		Power (%)	ISCV (%)
	Test (T)	Reference (R)		
C_{max} (ng/mL)	20.557	22.974	98.67	18.96
AUC_{0-t} (hr*ng/mL)	289.949	291.741	100.0	7.69
$AUC_{0-\infty}$ (hr*ng/mL)	295.744	297.410	100.0	7.70
Parameters	**Ratio (%)**	**90% Confidence Intervals**	**Acceptance Criteria**	**Outcome of BE result**
C_{max}	89.48	82.26% to 97.33%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	99.39	96.03% to 102.86%	80.00% - 125.00%	
$AUC_{0-\infty}$	99.44	96.08% to 102.92%	80.00% - 125.00%	

Test Product - Terazosin Oral Solution 1 mg/mL.
Reference Product - Terazosin Capsules, USP 1 mg.

Source: Clinical Study Report TERA-23-003

In summary, the plasma concentration time profiles of terazosin (Figure 2) and the Applicant's statistical analyses for BE assessment (Table 5) demonstrate that the proposed product is bioequivalent to the RS under fed conditions.

The results of the clinical study reports from TERA-23-003 were verified by the Clinical Pharmacology review team and they concurred with the Applicant's conclusions of bioequivalence (refer to review dated July 18, 2024).

Compliance with Good Clinical Practices

In compliance with standard protocol, relevant SOPs of (b) (4), research were carried out in accordance with the clinical research guidelines established principles enunciated in the Declaration of Helsinki. (b) (4) certified that (b) (4) employs all applicable Good Clinical Practice standards.

Financial Disclosure

The Sponsor provided financial disclosure for this NDA submission. For this study, three investigators participated, and none had none had an issue with financial disclosure.

Data Quality and Integrity

See Section 6.1 above.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

To support the application, the Applicant conducted two clinical studies, a pivotal, single dose, fasted, comparative bioavailability (BA)/bioequivalence (BE), and food effect study (TERA-21-077) and a single dose, fed, comparative BA/BE study (TERA-23-003). Both studies were conducted in healthy male and female subjects and used the to-be marketed formulation of the proposed product, aiming to establish a scientific bridge to the LD. As the LD HYTRIN capsules have been discontinued; the Applicant used Terazosin 1 mg Capsules (ANDA 075317, manufactured by Jubilant Cadista Pharmaceutical Inc.), the designated Reference Standard (RS) in the Orange Book, as the comparator in both studies.

Pharmacokinetic (PK) data results of the two studies demonstrated that the 90% confidence intervals (CI) and the geometric mean ratio (GMR) of the proposed Tezruly 1 mg/mL oral solution product compared to the RS product are within the pre-specified limit of 80% to 125% for primary PK endpoints (peak concentration (Cmax), Area Under the Curve from time zero to time t (AUC0-t), and Area Under the Curve from time zero to infinity (AUC0-∞)) for terazosin under both fasting and fed conditions.

The Clinical Pharmacology and Clinical reviewers concur that the results from these two BA studies support the conclusion that the proposed product and RS product are bioequivalent and a scientific bridge to the LD is established.

7.1.1. Primary Endpoints

In Study TERA-21-077, the results demonstrated that the proposed product was bioequivalent to the RS under fasting conditions and that food decreased the Cmax by 29% but did not affect AUC for terazosin. This study supports a scientific bridge to the LD HYTRIN in the fasted state.

In Study TERA-23-003, the results demonstrated that the proposed product was bioequivalent to the RS under fed conditions.

The reader is referred to Section 6 of this review for more detailed information regarding the individual studies.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional efficacy issues that require further consideration in the postmarketing setting.

7.3. Integrated Assessment of Effectiveness

The results from both studies TERA-21-077 and TERA-23-003 support the conclusion that the proposed product and RS product are bioequivalent and a scientific bridge to the LD has been established.

8. Review of Safety

8.1. Safety Review Approach

The Clinical review team conducted a review of all safety information generated in the Applicant's two single-dose, relative BA/BE clinical studies. In addition, a review of the postmarketing safety data (for terazosin as compiled by the Applicant) for adverse events reported in the published literature since 2009 was conducted.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

This NDA includes two comparative BA/BE studies of the Applicant's Terazosin Oral Solution.

The first comparative BA study (TERA-21-077) was a single-dose, open-label, randomized, three-period, three-sequence, three-way crossover bioavailability evaluation in 30 healthy adult male and female subjects with the following three-treatments: (i) the Sponsor's Terazosin Oral Solution (1 mg dose) administered under Fed conditions; (ii) the Sponsor's Terazosin Oral Solution (1 mg dose) administered under Fasted conditions; and (iii) Jubilant Cadista's Terazosin Capsules (1 mg dose) administered under Fasted conditions. A total of 28 subjects completed Study TERA-21-077 in accordance with the protocol.

The second comparative BA study (TERA-23-003) was a single-dose, open-label, randomized, two-period, two-sequence, two-way, crossover bioavailability evaluation in 30 healthy adult male and female subjects with the following two-treatments: (i) The Sponsor's Terazosin Oral Solution (1 mg dose) administered under Fed conditions; and (ii) Jubilant Cadista's Terazosin Capsules (1 mg dose) administered under Fed conditions. A total of 29 subjects completed all the periods of Study TERA-21-077 in accordance with the protocol)

While both studies were conducted in healthy Asian adult male and female subjects at the same contract research organization (CRO), and used the same bioanalytical method, dosage strengths and subject eligibility criteria, it is difficult to draw conclusions from cross-study data comparisons. In addition, test and reference products were administered in the Fed state only in one of the two studies (Study TERA-23-003).

8.2.2. Relevant characteristics of the safety population

Overall, subjects were healthy, young, Asian male and female volunteers.

8.2.3. Adequacy of the safety database

The safety database is adequate for this bioequivalence-based 505(b)(2) application. The Applicant cited and presented information on the extensive safety experience with the listed drug, as well as referencing the approved product prescriber and patient labeling.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant's assessment of adverse events in the two clinical studies appears adequate.

8.3.2. Categorization of Adverse Events

See adverse event information from the two clinical studies in Section 8.4.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points for collection of adverse events, vital signs (with additional positional blood pressure monitoring performed), clinical laboratories, and other routine laboratory testing obtained were adequate.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in either of the 2 studies submitted in this NDA.

8.4.2. Serious Adverse Events

There were no serious adverse events reported in either of the 2 studies submitted in this NDA.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to adverse events in either of the 2 studies submitted in this NDA.

Significant Adverse Events

There was no significant adverse event reported in either of the 2 studies provided in this NDA. Thus, there were no safety data or trend in the safety data that would raise concerns that this proposed product will have a different safety profile when compared to the approved terazosin products.

8.4.4. Treatment-Emergent Adverse Events and Adverse Reactions

Study TERA-21-077
A total of 4 post-dose adverse events (dizziness-3 events and orthostatic hypotension-1 event) were reported by 2 subjects during the study; all 4 post-dose adverse events were mild in severity.

A total of 3 post-study adverse events (elevated SGPT-1 event, decreased memoglobin-1 event and elevated eosinophil count percentage-1 event) were reported by 3 subjects. All 3 post-study adverse events were mild in severity and judged by the investigator as possibly related to the investigational products.

See Table 6 below for more details on the 7 reported adverse events in 6 subjects.

Table 6: On-Study and Post-Study Adverse Events in Study TERA-21-077 (N=28)

Sub. No.	Last Treatment Received	Period	Adverse Event	Description
(b) (6)	Test (fed)	01 (Post-Dose)	Dizziness	Mild dizziness, lasted 41 minutes, no associated symptoms, resolved spontaneously
	Reference	02	Orthostatic Hypotension	Supine BP- 122/72 to Standing BP-110/60

(b) (6)	(fasted)	(Post-Dose)	Dizziness	Associated with the orthostatic hypotension event shown immediately above
	Test (fed)	03 (Post- Dose)	Dizziness	Mild dizziness, lasted 30 minutes, no associated symptoms, resolved spontaneously
(b) (6)	Test (fast)	Post-Study	Elevated SGPT Level	Post Study SGPT-75 U/L Baseline SGPT-58 U/L

(b) (6)	Reference (fasted)	Post-Study	Decreased Hemoglobin Level	Male Subject Post-study Hb -10.7 gm/dL Baseline Hb-11.4 gm/dL (*Reviewer's Comment: The subject's Hb started low and ended slightly lower*)
(b) (6)	Test (fasted)	Post-Study	Elevated Eosinophil Level	Post-study Eosinophil percentage -14% Baseline Eosinophil percentage -8%

Source: Derived from Study TERA-21-077 final study report and individual Case Report Forms (CRFs)

Reviewer's Comments: There were 2 subjects with mild dizziness after taking Tezruly vs. 1 subject with mild dizziness after taking the Reference Standard (RS). In the RS subject, mild orthostatic hypotension was also reported (see details in Table 6). The adverse events of dizziness and orthostatic hypotension are included in the current labeling for terazosin and of note, they occurred in the Fed state in the Tezruly patients. Again, all 4 post-dosing events were mild and all 4 resolved spontaneously.

Post-study, 1 subject had a mildly elevated SGPT level (75 U/L) yet the subject also a mildly elevated SGPT at Baseline (58 U/L). This event was not associated with any other liver function test abnormalities and subsequently resolved. It is not uncommon to have random isolated mild elevations in liver function tests, which resolve spontaneously without sequelae. It is difficult to assess whether the subject's baseline, or which of the 2 treatments, if either, may have contributed to the mildly elevated post-study SGPT level.

Post-study, 1 subject had an elevated eosinophil percentage level (14%) yet the subject also had an elevated eosinophil percentage level at Baseline (8%). The increase from Baseline to Post-study eosinophil level was small and not associated with any other adverse event. This subject appeared to have some degree of underlying eosinophilia and the small increase in level did not appear to be clinically meaningful. It is difficult to assess whether the subject's baseline, or which treatment, if either, may have contributed to the mildly elevated posy-study eosinophil percentage level.

Post-study, 1 male subject had a decreased hemoglobin level (10.7%); however, the subject also had a decreased Baseline hemoglobin level (11.4%). It appears that this subject has some underlying anemia that was present prior to the start of the study. In addition, this degree of decrease in hemoglobin level was not associated with any other adverse events and thus did not appear to be clinically significant. It is difficult to assess whether the subject's baseline, or which of the 2 treatments, if either, may have contributed to the mildly decreased post-study hemoglobin level.

Study TERA-23-003

A total of 7 post-study adverse events (elevated SGPT-1, decreased hemoglobin-3 and elevated eosinophil level-2, elevated random glucose-1) were reported by 6 subjects. See Table 7 below for case details. All 7 events were mild in severity and judged by the investigator as possibly related to the investigational products.

Table 7: Post Study TERA- 02-023 Adverse Events

Body System / Adverse Event	**Test (T) N=29 n (%)**	**Reference (R) N=29 n (%)**	**Post-Study N=29 n (%)**	**Description**
Hepatic System				
Elevated SGPT Level	0	0	1 (4%)	Post-studySGPT-87 U/L Baseline SGPT-47 U/L
Gastrointestinal System				
Elevated Random Glucose Level	0	0	1 (4%)	Post-study random glucose- 223mg/dL Baseline random glucose-157 mg/dL
Circulatory System				
Decreased Hemoglobin Level	0	0	3 (10%)	Female- Post-study Hb -10.2 gm/dL Baseline Hb-11.3 gm/dL Female- Post-study Hb -10.2 gm/dL Baseline Hb- 11.0 gm/dL Female* Post-study Hb-10.4 gm/dL Baseline Hb-10.9 gm/dL
Elevated Eosinophil Level	0	0	2 (7%)	Post-study eosinophil percentage 18% Baseline Eosinophil percentage -11% *Post-study Eosin 15% Baseline Eosin -12%
Total	-	-	7 (24%)	

Source: Derived from Study TERA-23-003 study report and individual Case Report Forms

Reviewer's Comments: The only reported adverse events in Study TERA-23-003 were Post-study adverse events.

There were three cases of decreased hemoglobin levels. Each small decrease occurred in a healthy, young reproductive age woman who also had mildly decreased hemoglobin level at Baseline. It is not uncommon for menstruating females to have a mild anemia often due to iron deficiency. In addition, this degree of decrease in hemoglobin level was not associated with any other adverse events and thus did not appear to be clinically significant.

There was one subject who had a Post-study elevated random glucose level of 233 mg/dL. This subject had a Baseline-elevated random glucose level of 157 mg/dL and therefore shows some level of pre-treatment glucose intolerance. Study treatment was most probably not the underlying etiology of the subject's post-study elevated random glucose level. It is increasingly common to see elevated glucose levels in the general population and checking random blood glucose levels without knowing the relation to food intake does not provide a full picture of diabetic status; it only shows some level of glucose intolerance.

There were two subjects with elevated eosinophil percentage levels; both also had elevated eosinophil percentage levels at Baseline. The increase from Baseline to Post-study eosinophil levels was very small and not associated with any other adverse event. Both patients appeared to have some degree of underlying eosinophilia and the small increase in level does not appear to be clinically meaningful.

One subject had a mildly elevated Post-study SGPT level (87 U/L) yet also a mildly elevated SGPT at Baseline (47 U/L). This was not associated with any other liver function test abnormalities and subsequently resolved. It is not uncommon to have random isolated mild elevations in liver function tests, which resolve spontaneously without sequelae.

8.4.5. Laboratory Findings

See Section 8.4.4 for all laboratory-related adverse events.

8.4.6. Vital Signs

See Section 8.5.5 for full details regarding vital signs.

8.4.7. Electrocardiograms (ECGs)

There were no notable ECG findings.

8.4.8. QT

There were no notable QT findings reported in the studies and a tQT study was not required for this 505(b)(2) NDA submission.

8.4.9. Immunogenicity

This submission is not for a biologic product or peptide and no data on immunogenicity was required.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Orthostatic BP/HR Changes

At the request of FDA, the Applicant assessed the potential for clinically significant orthostatic BP/HR changes in Studies TERA-21-077 and TERA-23-003.

In Study TERA-21-077, the following schedule of assessments was performed: Supine blood pressure, pulse rate and well-being assessment were assessed at check- in, prior to dosing (≤ 60 minutes), at 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.25, 04.50, 04.75, 05.00 and 08.00 hours post dose.

Orthostatic hypotension (supine blood pressure, standing blood pressure), pulse rate and well-being assessment was confirmed at 00.50, 01.00, 02.00 and 04.00 hours post-dose. A 12 lead ECG was performed at 02.00, 08.00 hours post dose and at check-out (72.00 hours) in each period.

The following statistical comparisons were performed:

- Baseline sitting SBP, DBP and pulse rate were compared using a 1-way analysis of variance (ANOVA) with treatment as the factor.
- Changes in supine SBP, supine DBP and supine PR from baseline to 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75 and 04.00 hours post-dose.
- Change in supine systolic blood pressure, supine diastolic blood pressure and supine pulse rate from 00.25 to 04.00 hours were analyzed using a 1-way ANOVA with treatment as a factor.
- Changes in supine minus standing systolic blood pressure and changes in supine minus standing diastolic blood pressure at 00.50, 01.00, 02.00 and 04.00 hours post dose were analyzed using a 2-way ANOVA with treatment and time point as factors, were analyzed using a 2-way ANOVA with treatment and time point as factors.

Results

Baseline Comparison: Statistical comparison of Baseline (Pre-dose) sitting SBP, DBP and PR between treatments (Test fasted [A] Vs Test fed [B]) showed no significant differences between treatments. These results are summarized below in Table 8.

Table 8: Baseline (Pre-dose) Sitting SBP, DBP and PR Between Treatments in Study TERA-21-077

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Treatment A	119.172414	6.64437982	75.3793103	4.34588305	75.1034483	4.32884699
Treatment B	118.214286	7.74289229	76.6428571	4.74704029	73.7857143	4.93931426
p-Value Treatment (A vs B)	0.6177		0.2989		0.2883	

Source: CSR: Study TERA-21-077

Changes from Baseline to Post-dose (Up to 04.00 Hours) in Sitting Vital Signs: Statistical comparison of supine SBP, supine DBP and supine PR from baseline to 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75 and 04.00 hours post-dose between treatments (Test fasted [A] Vs Test fed [B]), results showed SBP had no significant differences between treatment groups in change from baseline to post-dose time points (up to 4.00 hours) when the subject were dosed in different conditions (fasted & fed). However, statistically significant differences between treatment groups (fasted vs fed) in changes from baseline (up to 4 hours) were observed for DBP and PR .Changes from baseline to post-dose (up to 04.00 hours) for SBP, DBP and PR results are summarized below in Table 9.

Table 9: Changes from Baseline to Post-dose (Up to 04.00 Hours) in Sitting SBP, DBP and PR Between Treatments in Study TERA-21-077

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Treatment A	-0.55803571	7.68514810	0.21428571	5.71262360	0.42410714	4.95424696
Treatment B	-0.95535714	8.10544424	1.48660714	6.22291350	-1.20982143	5.77045565
p-Value Treatment (A vs B)	0.4500		0.0014		<.0001	
p-Value Time (A vs B)	0.1152		0.0415		0.4330	

Source: CSR: Study TERA-21-077

Reviewer's Comment: The differences in changes from baseline observed in Table 9 between Test fasted and Test fed are small and not clinically meaningful.

Change from 00.25 to 04.00 Hours in Supine Vital Signs: Statistical comparison of change in supine systolic blood pressure, supine diastolic blood pressure and supine pulse rate from 00.25 to 04.00 hours between treatments (Test fasted [A] Vs Test fed [B]) showed no significant difference between treatments in SBP, DBP and PR. Changes from 00.25 to 04.00 hours for SBP, DBP and PR are summarized below in Table 10.

Table 10: Change from 00.25 to 04.00 Hours in Sitting SBP, DBP and PR Between Treatments in Study TERA-21-077

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Treatment A	0.78571429	6.14248799	-1.07142857	4.56985753	2.42857143	4.93984984
Treatment B	1.92857143	7.70727685	-1.92857143	5.14909968	0.71428571	5.05420355
p-Value Treatment (A vs B)	0.5421		0.5128		0.2048	

Source: CSR: Study TERA-21-077

Vital Signs Changes Associate With Changes in Posture (Supine – Standing): Statistical comparison of changes in supine minus standing systolic blood pressure and changes in supine minus standing diastolic blood pressure at 0.05. 01.00, 02.00 and 04.00 hours post-dose were compared between treatments (Test fasted [A] Vs Test fed [B]) showed a statistically significant difference between treatment groups for SBP change from supine to standing posture in each time point (00.50, 01.00, 02.00 and 04.00) when the subject is dosed in different conditions (fasted & fed) but DBP showed no statistically significant difference between treatment groups in change from supine to standing posture in each time point (00.50, 01.00, 02.00 and 04.00) when the subject is dosed in different conditions (fasted & fed). Changes in supine minus standing SBP and DBP are summarized below in Table 11.

Table 11: Change in SBP and DBP Associated With Change in Posture (Supine – Standing) between Treatments in Study TERA-21-077

Treatment	SBP		DBP	
	Mean	Std Dev	Mean	Std Dev
Treatment A	6.30357143	3.38741520	3.98214286	2.75740491
Treatment B	5.18750000	4.44694702	3.23214286	3.23545155
p-Value Treatment (A vs B)	0.0316		0.0625	
p-Value Time (A vs B)	0.0041		0.2425	

Source: CSR: Study TERA-21-077

Reviewer's Comment: Multiple comparisons of vital signs from pre-treatment to post-treatment were done at multiple timepoints and in multiple positions in Study TERA-21-077. Although some changes were noted throughout these analyses, the changes were negligible and not clinically significant. This conclusion was also confirmed by the Division of Cardiology and Nephrology (DCN) consultant team (See DCN Memo dated June 28, 2024). Additional summary vital sign data for all 3 treatment groups, including Reference fed (Treatment C) , are presented

below in Table 12. In response to an FDA IR, the Applicant also submitted individual listings of vital sign data for each subject in Study TERA-21-077. These data were also reviewed and did not show any clinically meaningful changes per individual patient or between treatment group

Table 12: Summary of Vital Signs for All Treatments (A, B & C) – Mean ± SD (TERA-21-077)

Description	Treatment	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (beats/minute)
Baseline	A	119.1724 ± 6.64438	75.3793 ± 4.34588	75.1035 ± 4.32885
	B	118.2143 ± 7.74289	76.6429 ± 4.74704	73.7857 ± 4.93931
	C	119.5714 ± 7.91355	76.06429 ± 4.96069	74.7143 ± 5.11249
Changes from Baseline to Post-dose (Up to 04.00 Hours in Supine)	A	-0.5580 ± 7.68515	0.2143 ± 5.71262	0.4241 ± 4.95425
	B	-0.9554 ± 8.10544	1.4866 ± 6.22291	-1.2098 ± 5.77046
	C	-0.2098 ± 7.69094	1.5179 ± 5.84357	0.0357 ± 5.95273
Change from 00.25 to 04.00 Hour Post-dose (In Supine)	A	0.7857 ± 6.14249	-1.0714 ± 4.56986	2.4286 ± 4.93985
	B	1.9286 ± 7.70728	-1.9286 ± 5.14910	0.7143 ± 5.05420
	C	-0.2143 ± 6.67420	-0.7143 ± 4.62567	0.0000 ± 5.68298
Change In Posture (Supine – Standing)	A	6.3036 ± 3.38742	3.9821 ± 2.75740	-
	B	5.1875 ± 4.44695	3.2321 ± 3.23545	-
	C	5.9643 ± 4.05353	3.8036 ± 3.53066	-

Test Product (Treatment A & B): Terazosin Oral Solution 1 mg/mL

Reference Product (Treatment C): Terazosin Capsules, USP 1 mg

Source: Applicant Response to IR

Reviewer's Comment: There are no clinically meaningful difference between treatment groups in any vital assessment in Study TERA-21-077 as shown in Table 12.

In Study TERA-23-003, sitting blood pressure, pulse rate and body temperature (measured with an infrared thermometer) were measured and questioning for well-being (including ambulatory visit) was confirmed prior to check-in of each period, prior to dosing (within 60 minutes) and prior to check out of each period.

Supine blood pressure, pulse rate and questioning for well-being were confirmed prior to check-in, prior to dosing at 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.25, 04.50, 04.75, 05.00 and 08.00 hours post dose.

Orthostatic hypotension (supine blood pressure, standing blood pressure), pulse rate and questioning for well-being were confirmed at 00.50, 01.00, 02.00 and 04.00 hours post dose.

Sitting blood pressure, pulse rate was measured and questioning for well-being was confirmed at 12.00, 16.00, 24.00 and 48.00 hours (with the window period of ± 40 minutes) post-dose in each period.

The following statistical comparisons were performed:

- Baseline supine SBP, DBP and pulse rate were compared between treatments (Test [T] and Reference [R]) using a 1-way analysis of variance (ANOVA) with treatment as the factor.
- Changes in supine SBP, supine DBP and supine PR from baseline to 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75 and 04.00 hours post-dose were analyzed using a 2-way ANOVA with treatment and time point as factors.
- Change in supine SBP, supine DBP and supine PR from 00.25 to 04.00 hours were analyzed using a 1-way ANOVA with treatment as a factor.
- Changes in supine minus standing SBP and changes in supine minus standing DBP and changes in supine minus standing PR at 00.50, 01.00, 02.00 and 04.00 hours post-dose were analyzed using a 2-way ANOVA with treatment and time point as factors.

Results

Baseline Comparison: Statistical comparison of Baseline (Pre-dose) supine SBP, DBP and PR between treatments (T vs. R) showed no significant differences between treatments in SBP, DBP and PR. Baseline (Pre-dose) supine SBP, DBP and PR results are summarized in Table 13.

Table 13: Baseline (Pre-dose) supine SBP, DBP and PR Between Treatments in Study TERA-23-003

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
T (Test)	116.551724	4.89596194	73.9310345	4.01720438	72.6206897	3.12151283
R (Reference)	116.620690	6.32689155	75.4482759	5.34245935	72.9655172	3.64968451
p-Value Treatment (T vs. R)	0.9631		0.2267		0.7005	

Source: CSR: Study TERA-23-003

Changes from Baseline to Post-dose (Up to 04.00 Hours): Statistical comparison of supine SBP, supine DBP and supine PR from baseline to 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75 and 04.00 hours post-dose between treatments (T vs. R), results showed SBP and PR had no significant changes from baseline to post-dose time points (up to 4.00 hours) between treatments (T vs. R) but statistically significant changes were observed for DBP from baseline to post-dose time points (up to 4.00 hours) between treatments (T vs. R). Changes from Baseline to Post-dose (Up to 04.00 Hours) for SBP, DBP and PR results are summarized below in Table 14.

Table 14: Changes from Baseline to Post-dose (Up to 04.00 Hours) in Sitting SBP, DBP and PR Between Treatments in Study TERA-23-003

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
T (Test)	0.08405172	5.87591673	-0.75862069	5.42869854	-1.42672414	4.92613005
R (Reference)	-0.40948276	7.15731864	0.37500000	6.61870345	-0.90086207	5.19416512
p-Value Treatment (T vs. R)	0.2414		0.0040		0.1118	
p-Value Time (T vs. R)	<.0001		0.0008		0.0382	

Source: CSR: Study TERA-23-003

Reviewer's Comment: The difference between groups in change-from-baseline to 4 hours in sitting DBP is not considered to be clinically meaningful.

Change from 00.25 to 04.00 Hours: Statistical comparison of changes in supine SBP, DBP and PR from 00.25 to 04.00 hours between treatments (T vs. R) showed no significant difference between treatments in SBP, DBP and PR. Changes from 00.25 to 04.00 hours for SBP, DBP and PR results are summarized in Table 15.

Table 15: Change from 00.25 to 04.00 Hours in Sitting SBP, DBP and PR Between Treatments in Study TERA-23-003

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
T (Test)	-2.41379310	6.70563325	-4.27586207	5.57351230	1.86206897	3.96163871
R (Reference)	-1.79310345	7.80741090	-2.48275862	5.22781496	1.17241379	3.40240425
p-Value Treatment (T vs. R)	0.7466		0.2116		0.4799	

Source: CSR: Study TERA-23-003

Vital Signs Changes Associated with Changes in Posture (Supine – Standing): Statistical comparison of changes in supine minus standing SBP and changes in supine minus standing DBP at 0.05. 01.00, 02.00 and 04.00 hours post-dose between treatments (T vs. R) showed SBP, DBP and PR had no significant changes from supine to standing posture in each time point (00.50, 01.00, 02.00 and 04.00) with the subject dosed in fed conditions (T vs. R). Changes in supine minus standing SBP, DBP and PR results are summarized below in Table 16.

Table 16: Change in Vital Signs With Changes in Posture (Supine – Standing) between Treatments in Study TERA-23-003

Treatment	SBP		DBP		PR	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
T (Test)	3.46551724	2.86942210	2.43103448	3.24967995	1.50000000	4.43601858
R (Reference)	3.24137931	3.15021239	2.29310345	3.45157114	1.05172414	5.04216107
p-Value Treatment (T vs. R)	0.5725		0.7543		0.4728	
p-Value Time (T vs. R)	0.5823		0.3822		0.3746	

Source: CSR: Study TERA-23-003

Reviewer's Comment: Similar to in Study TERA-21-077, multiple comparisons in SBP, DBP and PR were made between treatment groups at multiple timepoints and in multiple positions. Few changes were noted throughout these analyses, and those were negligible and not clinically significant. This Clinical review conclusion was also confirmed by the Division of Cardiology and Nephrology (DCN) consultant (See DCN Memo dated June 28, 2024).

8.6. Safety Analyses by Demographic Subgroups

Not Applicable.

8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies conducted to support this 505(b)(2) NDA.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

This is a 505(b)(2) application. See the Listed Drug's approved labeling as well as the final agreed-upon label for the proposed product, where relevant language in this section was updated.

8.8.2. Human Reproduction and Pregnancy

This is a 505(b)(2) application. See the Listed Drug's approved labeling as well as the final agreed-upon label for the proposed product, where relevant language in this section was updated.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable. BPH is a condition of adult men. A full waiver of required pediatric studies was granted.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable. This is a 505(b)(2) application. See the Listed Drug's approved labeling.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As part of their Integrated Summary of Safety (ISS), the Applicant submitted a robust review of the HYTRIN postmarketing experience (MEDLINE via PubMed), which included searches of the published medical literature. The Applicant's postmarketing safety review covered the period from 2008 to 2022. According to the Applicant and the Clinical review team, the results of their searches were generally consistent with the safety information already shown in the approved HYTRIN USPI.

Of note, one observational study from Italy reported a case series of gynecomastia reported in users of alpha-1 adrenergic antagonists. The cases were obtained from the Italian spontaneous reporting system database and the World Health Organization ICSRs database. The study focused on tamsulosin use. The report stated that the World Health Organization ICSRs database contained 6,048 adverse event reports for terazosin, submitted from 4 countries. Of that total, 46 reports were of gynecomastia. The time to onset of gynecomastia was six days to four years and the average age of the patient was 64.5 years. Overall, while a small number of postmarketing cases of gynecomastia have been reported from worldwide databases, it is impossible to draw conclusions on drug causality from this information, based on a small number of cases from just one case series, the background incidence of gynecomastia in the BPH target population, and the possible effect of concomitant medications (e.g., 5-ARIs) and co-morbidities (e.g., hypogonadism). Given that causality of gynecomastia to terazosin was not established, this AE term was not included in labeling.

8.9.2. Expectations on Safety in the Postmarket Setting

The Clinical review team did not identify a change in the safety profile for use of this product compared to the Listed Drug. For details on the Postmarketing Experience, the reader is referred to the Postmarketing Experience section of the Listed Drug's labeling and the final agreed-upon Tezruly labeling, which was revised to comply with Physician's Labeling Rule (PLR) format.

8.9.3. Additional Safety Issues From Other Disciplines

There are no additional safety issues identified by other disciplines.

8.10. Integrated Assessment of Safety

The Applicant has adequately established a scientific bridge to the listed drug, HYTRIN, based on data generated in their two comparative bioavailability studies TERA-23-003, TERA-21-077 that demonstrated bioequivalence of Tezruly to the LD under fasted and fed conditions.

Based on the successful establishment of bioequivalence, all safety information shown in approved terazosin/HYTRIN labeling is applicable to Tezruly and may be relied upon in support of product safety and class labeling.

The Applicant also submitted a robust review of the post marketing safety experience for the listed drug, HYTRIN. The reported adverse events appeared to be comparable between the published reports and the safety information shown in the approved USPI for HYTRIN and consistent with the pharmacologic effects of terazosin. No new safety signals or trends in the safety profile for HYTRIN were identified by the Applicant or by the Clinical review team.

In summary, the results of the 2 completed BA/BE studies, all safety information shown in approved terazosin/HYTRIN labeling, and the compiled postmarketing data from 2006-2022 support the safety of Tezruly.

Overall, there were no clinical findings, new safety signals or safety trends that alter the benefit/risk considerations of the listed drug product, HYTRIN.

Advisory Committee Meeting and Other External Consultations

Neither an Advisory Committee meeting nor external consultations were considered necessary for this new formulation 505(b)2 NDA.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

On June 17, 2024, after several multidisciplinary internal labeling meetings, DUOG conveyed FDA-proposed labeling edits and comments to the Prescribing Information (PI) to the Applicant. The majority of the edits related to updating the label to ensure compliance with PLR format requirements.

On June 19, 2024, the Applicant responded by acknowledging FDA's proposed labeling edits/comments and agreed to accept all of FDA's proposed changes. Subsequently, FDA-proposed edits on the Patient Package Insert (PPI) were conveyed to Applicant, who rapidly provided their full agreement.

On July 12, 2024, one additional request was sent to the Applicant asking them to revise the container labels to include equivalency statements as per the USP salt policy, "TEZRULY contains 1 mg/mL of terazosin (equivalent to 1.1 mg/mL of terazosin hydrochloride)"

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

There are no risk evaluation and mitigation strategies (REMS) necessary to support approval of this 505(b)2 NDA.

11. Postmarketing Requirements and Commitments

No PMR or PMCs are necessary to provide further support for this 505(b)2 NDA.

12. Appendices

12.1. References

Not Applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARJORIE F DANNIS
07/15/2024 10:50:46 AM

MARK S HIRSCH
07/15/2024 10:58:26 AM
I concur.

AUDREY L GASSMAN
07/16/2024 12:10:37 PM