CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 218139
Supporting document/s:	eCTD 0001
Applicant's letter date:	09/29/23
CDER stamp date:	09/29/23
Product:	Terazosin Oral Solution, 1 mg/mL (TEZRULY)
Indication:	The treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension
Applicant:	Novitium Pharma LLC (East Windsor, NJ)
Review Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM)
Reviewer:	Miyun Tsai-Turton, PhD, MS
Supervisor/Team Leader:	Andrea Benedict, PhD
Deputy Division Director:	Audrey Gassman, MD
Project Manager:	Sydney Tran

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Applicant, Novitium Pharma LLC (Novitium), submitted Terazosin Oral Solution, 1 mg/mL (proposed trade name of TEZRULY) for the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension. Since this is a 505(b)(2) NDA submission, the Applicant relies on NDA 020347 (HYTRIN, Terazosin Capsules, 1 mg, by Abbott Laboratories, which was discontinued in late 2013 not due to reasons of safety or efficacy) as the Listed Drug (LD) and ANDA 075317 (Terazosin Capsules 1 mg, by Jubilant Cadista Pharmaceuticals) as the Reference Standard (RS). Terazosin is currently available as oral capsules that can be used alone or in combination with other antihypertensive agents such as diuretics or β-adrenergic blocking agents.

Terazosin is an α-1-adrenoceptor blocking agent. The reduction in symptoms and improvement in urine flow rates following terazosin administration in BPH patients is related to relaxation of smooth muscle produced by blockade of α-1-adrenoceptors in the bladder neck and prostate. The active ingredient in Novitium drug product is the same as in the LD and the route of administration is the same as that of the LD. However, the Applicant has changed the drug product dosage form from 1 mg capsule (LD) to 1 mg/mL oral solution (Novitium drug product). The Filing meeting was held on 11/13/23 and the 74-day letter was issued on 11/29/23 with filing issues enclosed. There were no filing issues from Pharm/Tox.

To rely on the FDA's findings on safety and effectiveness for HYTRIN, the Applicant proposed to establish a clinical bridge by conducting two comparative bioavailability clinical studies in healthy adult subjects (Study No. TERA-21-077 and Study No TERA-23-003). Based on internal discussion with the Clinical Pharmacology team, Terazosin 1 mg/mL oral solution was bioequivalent to the RS Terazosin 1 mg capsules under fasted and fed conditions. Refer to the Clinical Pharmacology review for full details. Therefore, the clinical bridge was considered adequate to allow reliance on the nonclinical information as stated in the LD approved drug product labeling.

Additionally, considering the change in dosage form from capsules to oral solution, Novitium drug product is a reformulation drug product. A 28-day bridging study in the rat (Study No. (b) (4) /0422/G/T074) was conducted to evaluate the nonclinical pharmacokinetics and/or toxicokinetics of the oral solution and the safety of the reformulated Novitium drug product. This 28-day rat study was reviewed under IND 157262 (eCTD 0013) and the Pharm/Tox review can be found in DARRTS dated 09/30/22 under IND 157262.

Summary of Clinical Bridging BA Studies Provided by the Applicant

Study No.	TERA-21-007	TERA-23-003
Study Design	Single-dose open-label randomized balanced, three-period, three-sequence, three-way crossover bioavailability Study	Single-dose open-label randomized balanced, two-period, two-sequence, two-way crossover bioavailability study

<table>
<tr><td>Target Population</td><td>30 healthy adult male subjects</td><td>30 healthy adult male subjects</td></tr>
<tr><td>Treatments</td><td>▪ Terazosin Oral Solution 1 mg dose, fed.
▪ Terazosin Oral Solution 1 mg dose, fasted.
▪ Jubilant Cadista's Terazosin Capsule 1 mg dose, fasted.</td><td>▪ Terazosin Oral Solution 1 mg dose, fed.
▪ Jubilant Cadista's Terazosin Capsule 1 mg dose, fed.</td></tr>
<tr><td>Summary of Human PK Parameters from Two Clinical BA Studies</td><td colspan="2">
Comparative Pharmacokinetic Parameters in TERA-21-077 and TERA-23-003
<table>
<tr><th rowspan="2">Study No.</th><th colspan="2">Formulation (mg)</th><th rowspan="2">N</th><th rowspan="2">AUC_{0-t} (ng*hr/mL)§</th><th rowspan="2">$AUC_{0-\infty}$ (ng*hr/mL)§</th><th rowspan="2">C_{max} (ng/mL)§</th><th rowspan="2">t_{max} (hr)¶</th></tr>
<tr><th>Form</th><th>Dose (mg)</th><th>Fed or Fasted</th></tr>
<tr><td>TERA-21-077</td><td>T</td><td>1</td><td>Fed</td><td>28</td><td>274.081 ± 66.6574</td><td>280.280 ± 67.9262</td><td>18.924 ± 4.5484</td><td>3.50 (0.67 – 4.02)</td></tr>
<tr><td>TERA-21-077</td><td>T</td><td>1</td><td>Fasted</td><td>28</td><td>279.889 ± 73.7183</td><td>285.616 ± 74.7694</td><td>27.092 ± 7.8527</td><td>0.67 (0.50 – 1.75)</td></tr>
<tr><td>TERA-21-077</td><td>R</td><td>1</td><td>Fasted</td><td>28</td><td>267.054 ± 61.6626</td><td>272.618 ± 62.4492</td><td>26.028 ± 7.5538</td><td>1.00 (0.50 – 2.50)</td></tr>
<tr><td>TERA-23-003</td><td>T</td><td>1</td><td>Fed</td><td>29</td><td>308.050 ± 108.4952</td><td>313.939 ± 109.8165</td><td>21.343 ± 5.8421</td><td>3.02 (0.50 – 4.10)</td></tr>
<tr><td>TERA-23-003</td><td>R</td><td>1</td><td>Fed</td><td>29</td><td>309.916 ± 106.5908</td><td>315.781 ± 108.2930</td><td>24.713 ± 10.1428</td><td>3.00 (0.67 – 6.00)</td></tr>
</table>
T- Test Formulation (Terazosin Oral Solution 1 mg); R = Reference Formulation (Terazosin Capsules 1 mg); ¶ = Median (min-max); § = Mean ± SD
</td></tr>
</table>

Nonclinical Bridge 28-day Rat Study

Study No.	(b) (4)0422/G/T074
Study Design	A single and repeated-dose (28-day) oral gavage toxicity and toxicokinetic (TK) study with a 14-day recovery period
Species	Wistar rats
Treatments	▪ Terazosin Oral Solution (1 mg/mL) at 0.5, 2.07 and 20.7 mg/kg. ▪ Jubilant Cadista's Terazosin Capsule (1 mg/mL oral suspension made from 10 mg capsules in purified water) at 20.7 mg/kg.
Findings	This rat study showed Terazosin Oral Solution appeared to have a similar safety profile when compared to Jubilant Cadista's Terazosin Capsules. However, based on lower systemic exposure to Terazosin Oral Solution, this formulation might not have the same efficacy as compared to Jubilant Cadista's Terazosin Capsules.

1.2 Brief Discussion of Nonclinical Findings

Terazosin Oral Solution, 1 mg/mL was developed by Novitium Pharma for the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension. Terazosin Capsules 10 mg was approved under NDA 020347 (discontinued in 2013 not due to safety or efficacy reasons) and ANDA 075317. The Applicant conducted two clinical BA studies and one 28-day oral toxicity and toxicokinetic rat study to bridge their new formulation (Terazosin Oral Solution, 1 mg/mL) to the reference formulation (Terazosin Capsules 1 mg).

In the 28-day rat study, Terazosin Oral Solution, 1 mg/mL (at 0, 0.5, 2.7, and 20.7 mg/kg) was given to rats for 28 days, with a 14-day recovery period. Terazosin Capsules 10 mg (at 20.7 mg/kg) was used as a reference. Both formulations were well tolerated in rats and there were no new safety concerns raised with Terazosin Hydrochloride Oral Solution. The NOAEL for the Terazosin Hydrochloride Oral Solution

= 20.7 mg/kg, corresponding to $AUC_{0\text{-}24h}$ of 6368.29 ng•h/mL and C_{max} of 472.23 ng/mL in males and 6969.23 ng•h/mL and 618.34 ng/mL in females on Day 28).

In addition, the TK analysis showed that the test item, Terazosin Oral Solution, has lower systemic exposure (AUC and C_{max}) than the reference item, Terazosin Capsules, corresponding to $AUC_{0\text{-}24h}$ of 7775.55 ng•h/mL and C_{max} of 1245.96 ng/mL in males and 15213.17 ng•h/mL and 2092.44 ng/mL in females on Day 28) at the dose of 20.7 mg/kg/day. A sex-related difference in systemic exposure was observed for the reference item but was not observed for the oral solution test item.

TK Parameters on Day 28

Terazosin	Oral Solution 1 mg/mL @ NOAEL = 20.7 mg/kg		Oral Capsules 10 mg @ 20.7 mg/kg/day	
	M	F	M	F
$AUC_{0\text{-}24h}$ (ng•h/mL)	6368.29	6969.23	7775.55	15213.17
C_{max} (ng/mL)	472.23	618.34	1245.96	2092.44

Overall, the 28-day rat study showed Terazosin Oral Solution appeared to have a similar safety profile, but with lower systemic exposure, when compared to Terazosin Capsules when given at the equivalent dose of 20.7 mg/kg.

1.3 Recommendations

1.3.1 Approvability

Pharm/Tox recommends approval.

1.3.2 Additional Non-Clinical Recommendations

None.

1.3.3 Labeling

TEZRULY's Prescribing Information is in the required PLLR format. However, the current HYTRIN label is not in PLLR format. There is a separate review for labeling.

2 Drug Information

2.1 Drug

CAS Registry Number

70024-40-7

Generic Name

Terazosin Hydrochloride

Code Name

Terazosin Oral Solution, 1 mg/mL

Chemical Name

Piperazine,1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-monohydrochloride, dihydrate (As per USP).

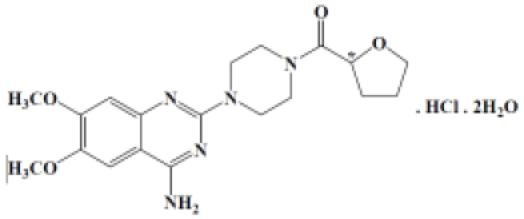
1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl)piperazine monohydrochloride dihydrate (As per USP).

Molecular Formula/Molecular Weight

$C_{19}H_{25}N_5O_4$. HCl. $2H_2O$

459.92

Structure or Biochemical Description



* asymmetric centre

Pharmacologic Class

α-adrenoceptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 157262
- NDA 020347 (Terazosin capsules, discontinued in 2013)
- ANDA 075317
- DMF (b) (4)
- DMF (b) (4)

2.3 Drug Formulation

The drug composition and function of each component in the drug product are listed below.

Composition of Drug Product

Item #	Ingredients	Functions	Amount Per Unit, mg /mL	%w/v	%w/w
1	Terazosin Hydrochloride, USP	Active	1 (b) (4) [#]	0.11	0.11
2	Methylparaben, NF	(b) (4)			
3	Propylparaben, NF				
4	Glycerin, USP				
5	Sucralose, NF				
6	Citric acid anhydrous, USP				
7	Sodium citrate dihydrate, USP				
8	Artificial Cherry Flavor (b) (4)				
9	Purified water, USP	(b) (4)		NA	NA

Density of solution: (b) (4)

2.4 Comments on Novel Excipients

No novel excipients. The Applicant also provided the table below to show the amount allowed per FDA's Inactive Ingredient Report (IIG in the table below) for each inactive ingredient used in the drug product. Pharm/Tox has no concern with these inactive ingredients.

The Amount of Inactive Ingredients Allowed per IIG

Composition of Inactive Ingredients and amounts as per Maximum IIG Limits:

S. No	Ingredients	Functions	mg/mL	% w/v	% w/w	Amount based on MDD (mg)	Route of administration dosage form	Maximum Daily Exposure/ Maximum potency per unit dose) (mg) [1]
1.	Terazosin Hydrochloride, USP	Active	1 (b) (4)	0.11	0.11	21.88	NA (Active)	
2.	Methylparaben, NF	(b) (4)					Oral/Suspension	1000mg/5mL (Maximum Potency per unit)
3.	Propylparaben, NF						Oral/Suspension	200mg/5mL (Maximum Potency per unit)
4.	Glycerin, USP						Oral/Solution	32400mg (MDE)
5.	Sucralose, NF						Oral/Tablet, Effervescent	1080mg (MDE)
6.	Citric acid anhydrous, USP						Oral/ Solution	743 (MDE)
7.	Sodium citrate dihydrate, USP						Oral/Suspension	5013mg (MDE)
8.	Artificial Cherry Flavor (b) (4)						Oral/Suspension	(b) (4) (MDE)
9.	Purified water, USP	(b) (4)		NA	NA	NA	NA	NA

(b) (4)

Note: (b) (4)

Amount calculated based on the maximum daily dose of Terazosin which is 20 mg.

[1] Based on the FDA' s Inactive Ingredient database updated on July 06,2023

[2]The composition breakdown of the flavor is provided in this Module as well the LoA from the manufacturer is provided in Module 1.4.2.

The (b) (4) Cherry flavor (b) is also specifically approved in another CDER approved drug product for the same route of administration (oral). (b) (4)

(b) (4)

Reviewer's Note: During the 11/17/23 filing meeting, the use of cherry flavor- (b) (4) was brought up by the Clinical Team. As addressed in a follow-

up 11/28/23 email to the Clinical Team, Pharm/Tox had no concerns about any of the excipients in the formulation. We confirmed that the cherry flavor (b) (4) excipient was covered by levels currently used in approved products in the FDA's Inactive Ingredient Report.

2.5 Comments on Impurities/Degradants of Concern

Drug substance impurities and (b) (4) risk assessment are included in Module 3.2.s. There are two manufacturing facilities. (b) (4) Therefore, there are two separate analyses in drug product impurities. Drug product impurities are included in Module 3.2.p.5.5. In this submission, there are no nonclinical study specifically conducted for any impurity. The drug substance and drug product impurity specifications were acceptable, per ICH Q3A and ICH Q3B.

Reviewer's Note: During the 11/17/23 filing meeting, a potential (b) (4) concern was also brought up by the Clinical Team. As addressed in a follow-up 11/28/23 email to the Clinical team, Pharm/Tox had no concern regarding (b) (4) impurities at this time, as no (b) (4) have been detected in the drug substance or drug product. An excerpt of the internal email that was communicated to the Clinical Team is provided below.

(b) (4)

In response to the CMC comments to the Applicant in the 74-day letter, the Applicant has agreed to establish the AI limit for the potential (b) (4) at no more than (b) (4) for the maximum daily dose of 20 mL which is equal to 20 mg of Terazosin). This is acceptable from the Pharm/Tox perspective.

2.6 Proposed Clinical Population and Dosing Regimen

Terazosin hydrochloride (oral solution 1 mg/mL) is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) and the treatment of hypertension alone or with other antihypertensive agents, to lower blood pressure.

- For BPH, an initial dose is 1 mg at bedtime and can be titrated up to 10 mg once daily, which is generally required for a clinical response.

- For hypertension, an initial dose is 1 mg at bedtime with a recommended dose up to 5 mg once daily and can be titrated up to 20 mg once daily if needed.

2.7 Regulatory Background

- September 2021 – PIND Type B meeting.
- September 2022 – Opening IND submission.
- September 2023 – NDA submission
- November 2023 – NDA filing meeting. NDA was filable with potential review issues, addressed in the 74-day letter, dated 11/29/23 in DARRTS.
- January 2024 – Applicant provided responses to review issues identified during filing review, dated 1/26/24 (SDN 5, eCTD 0005).
- February 2024 – NDA Mid-Cycle Review meeting.
- March 2024 - FDA had a teleconference to discuss the drug substance manufacturing facility (b) (4) that is still under OAI. The Applicant agreed to remove (b) (4) from FDA Form 356h, update Module 3 of the application in accordance with 21 CFR 314.50(d), and indicate that (b) (4) is not for commercial use. The Applicant may submit a supplement to use the (b) (4) site after the site is determined to be compliant.

3 Studies Submitted

3.1 Studies Reviewed

All nonclinical studies have been reviewed under IND 157262.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Below table summarizes the nonclinical memos and reviews under IND 157262, with regards to this NDA.

Nonclinical Memo and Reviews under IND 157262

Review	Reviewer	Reviews	Comments
PIND 157262 eCTD 0002 09/23/21 Type B pre-IND meeting	Miyun Tsai-Turton	2021 1022 - PIND 157262 pt memo.pd 2021 1021 - Final Meeting Minutes [W	Considering the change in dosage form from capsules to oral solution, this product is a re-formulation. The Pharm/Tox requested that the Sponsor conduct a short-term, repeat-dose bridging study to establish relative safety of the new formulation and to evaluate the nonclinical PK/TK of the oral solution.
PIND 157262 eCTD 0009 02/03/22 Clarifying Questions from the 10/21/21 IR letter	Miyun Tsai-Turton	2022 0301 - PIND 157262 pt memo.pd 2022 0228 - Final-Advice-Clarifyi	The Pharm/Tox also advised the Sponsor that the 28-day rat bridging study be conducted BEFORE initiation of their clinical BA/BE study.
PIND 157262 eCTD 0010 02/24/22	Miyun Tsai-Turton	2022 0328 - PIND 157262 pt memo re 2 2022 0413 - Final-March2022-28	Pharm/Tox reviewed the 28-day rat study protocol and found the proposed study design for the 28-day toxicity study in rats reasonable. The Sponsor was advised that their dosing solution should be the intended to-be-marketed clinical formulation. However, Pharm/Tox could not comment on the adequacy of the study parameters and endpoints since in-life parameters and terminal endpoints were not provided in their submission.
IND 157262 eCTD 0013 09/09/22	Miyun Tsai-Turton	2022 0930 - PharmTox_IND 1572	The 28-day rat study showed that terazosin hydrochloride oral solution appeared to have a similar safety profile when compared to Terazosin Hydrochloride Capsules at equivalent doses of 20.7 mg/kg. However, based on lower systemic exposure to Terazosin Hydrochloride Oral Solution, this formulation might not have the same efficacy as compared to Terazosin Hydrochloride Capsules. In addition, a sex-related difference in systemic exposure was observed for the reference item but was not observed for the oral solution test item. A review of information for other alpha-1 adrenoreceptor antagonists (e.g., tamsulosin, doxazosin, silodosin, alfuzosin) did not show consistent sex-related effects on systemic exposure across the nonclinical species tested. Therefore, this sex-related effect on systemic exposure in the Terazosin Hydrochloride

			Capsules reference item does not appear to be an established class effect.

4 Pharmacology

No pharmacology studies were conducted by the Applicant. The Applicant relies on the Agency's findings on safety and effectiveness of HYTRIN Capsules.

Mechanism of Action for BPH

The reduction in the symptoms associated with BPH following administration of terazosin hydrochloride may be related to the changes in muscle tone produced by a blockade of alpha-1 adrenoceptors in the smooth muscle of the bladder neck and prostate. Because there are relatively few alpha-1 adrenoceptors in the bladder body, terazosin can reduce the bladder outlet obstruction without affecting bladder contractility.

Mechanism of Action for Hypertension

Terazosin may decrease in blood pressure by decreasing total peripheral vascular resistance, mainly produced by antagonism of α-1 adrenoceptors. In animals, terazosin decreases blood pressure within 15 minutes following oral administration.

5 Pharmacokinetics/ADME/Toxicokinetics

No nonclinical pharmacokinetic studies were conducted by the Applicant. The Applicant relies on their own clinical BA studies in addition to the Agency's findings on safety and effectiveness of HYTRIN Capsules.

Absorption

Terazosin is a highly soluble drug in BCS Class I or III. It is rapidly and almost completely absorbed following oral administration, with an oral bioavailability of about 90%. Following oral administration, the plasma levels peak about one hour after dosing, and then decline with a half-life of approximately 13 hours. Terazosin Oral Solution and terazosin hydrochloride capsules have comparable rate (C_{max}) and extent (AUC) of absorption following single-dose administration to healthy subjects in the fed and fasted states. In addition, following administration of Terazosin Oral Solution to healthy volunteers, the C_{max} decreased 29%, while the AUC remained unchanged with a high-fat meal (1000 calories, 50% fat) compared to fasted conditions. However, this concentration decrease is not clinically significant.

Distribution

Approximately 90 to 94% of the drug is bound to plasma proteins and binding is constant over the clinically observed concentration range.

Metabolism

Hepatic metabolism is extensive with major biliary elimination.

Excretion

Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is excreted in the feces. The remainder is eliminated as metabolites.

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

The Applicant conducted one 28-day rat study (Study No. (b) (4)0422/G/T074). comparing their Terazosin Oral Solution, 1 mg/mL (0, 0.5, 2.07, and 20.7 mg/kg) to Terazosin Capsules 10 mg (20.7 mg/kg) to support a formulation change. In both formulations, there was no test article related adverse findings. This 28-day rat study was reviewed under IND 157262 (eCTD 0013) and the Pharm/Tox review can be found in DARRTS dated 09/30/22.

28-day Toxicity/TK Rat Study

Species/ Dose/ Duration	NOAEL	Key Study Findings
28-day rat study with 14-day recovery Test Article: Terazosin Oral Solution: (1 mg/mL) at 0.5, 2.07 and 20.7 mg/kg. Reference: Jubilant Cadista's Terazosin Capsule: (1 mg/mL oral suspension made from 10 mg capsules in purified water) at 20.7 mg/kg.	20.7 mg/kg Terazosin Oral Solution $AUC_{0\text{-}24h}$ (ng•h/mL) 6368.29 (male) 6969.23 (female) C_{max} (ng/mL) 472.23 (male) 618.34 (female)	▪ Both formulations were well tolerated. ▪ No new adverse findings were identified with Terazosin Hydrochloride Oral Solution, 1 mg/mL. ▪ Terazosin Hydrochloride Oral Solution, 1 mg/mL had lower systemic exposure (C_{max} and AUC) than Terazosin Hydrochloride Capsules 10 mg when given at an equivalent dose of 20.7 mg/kg.

The exposure profile of Terazosin Hydrochloride Oral Solution, 1 mg/mL and Terazosin Hydrochloride Capsules 10 mg were as follow:

Dose (mg/kg)	Trea. Days	Male					Female				
		T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC 0-inf (ng.h/mL)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC 0-inf (ng.h/mL)	$T_{1/2}$ (h)
0.5*	Day 1	6	16.78	59.99	NR	NR	2	15.84	65.58	NR	NR
	Day 28	6	9.12	31.35	NR	NR	2	14.77	49.99	NR	NR
2.07*	Day 1	4	53.11	223.94	NR	NR	4	49.24	230.53	NR	NR

Dose (mg/kg)	Trea. Days	Male					Female				
		T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC 0-inf (ng.h/mL)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC 0-inf (ng.h/mL)	$T_{1/2}$ (h)
	Day 28	6	56.78	215.91	NR	NR	4	161.59	760.03	NR	NR
20.7*	Day 1	4	462.28	6591.02	NR	NR	2	596.53	6527.02	6634.4	4.05
	Day 28	2	472.23	6368.29	6748.99	6.25	2	618.34	6969.23	7311.56	5.79
20.7**	Day 1	0.5	1395.82	8367.37	8500.13	4.1	0.5	1342.03	9072.14	9138.92	3.53
	Day 28	2	1245.96	7775.55	8176.06	6.02	0.5	2092.44	15213.17	15462.45	4.21

Note: Trea. Days =Treatment Days, * = Terazosin Hydrochloride Oral Solution, 1 mg/mL, ** = Terazosin Hydrochloride Capsules 10 mg, NR: Not reportable due to improper elimination phase.

7 Genetic Toxicology

No genetic toxicology studies were conducted by the Applicant. The Applicant relies on the Agency's findings on safety and effectiveness of HYTRIN Capsules. In vitro and in vivo studies were conducted for HYTRIN® (terazosin hydrochloride tablet). The text below is extracted from the HYTRIN® label.

> HYTRIN was devoid of mutagenic potential when evaluated in vivo and in vitro (the Ames test, in vivo cytogenetics, the dominant lethal test in mice, in vivo Chinese hamster chromosome aberration test and V79 forward mutation assay).

8 Carcinogenicity

No carcinogenicity studies were conducted by the Applicant. The Applicant relies on the Agency's findings on safety and effectiveness of HYTRIN Capsules. Studies were conducted in rats and mice for HYTRIN® (terazosin hydrochloride tablet). The text below is extracted from the HYTRIN® label. The MRHD for HYTRIN® is 20 mg.

> HYTRIN, administered in the feed to rats at doses of 8, 40, and 250 mg/kg/day (70, 350, and 2100 mg/m^2/day), for two years, was associated with a statistically significant increase in benign adrenal medullary tumors of male rats exposed to the 250 mg/kg dose. This dose is 175 times the maximum recommended human dose of 20 mg (12 mg/m^2). Female rats

were unaffected. HYTRIN was not oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day (110 mg/m^2; 9 times the maximum recommended human dose). The absence of mutagenicity in a battery of tests, of tumorigenicity of any cell type in the mouse carcinogenicity assay, of increased total tumor incidence in either species, and of proliferative adrenal lesions in female rats, suggests a male rat species-specific event. Numerous other diverse pharmaceutical and chemical compounds have also been associated with benign adrenal medullary tumors in male rats without supporting evidence for carcinogenicity in man.

9 Reproductive and Developmental Toxicology

No reproductive and development toxicology studies were conducted by the Applicant. The Applicant relies on the Agency's findings on safety and effectiveness of HYTRIN Capsules. Studies were conducted in rats and rabbits for HYTRIN® (terazosin hydrochloride tablet). Below text is extracted from the HYTRIN® label. The MRHD for HYTRIN® is 20 mg.

HYTRIN was not teratogenic in either rats or rabbits when administered at oral doses up to 280 and 60 times, respectively, the maximum recommended human dose. Fetal resorptions occurred in rats dosed with 480 mg/kg/day, approximately 280 times the maximum recommended human dose. Increased fetal resorptions, decreased fetal weight and an increased number of supernumerary ribs were observed in offspring of rabbits dosed with 60 times the maximum recommended human dose. These findings (in both species) were most likely secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women and the safety of terazosin in pregnancy has not been established. HYTRIN is not recommended during pregnancy unless the potential benefit justifies the potential risk to the mother and fetus.

In a peri- and post-natal development study in rats, significantly more pups died in the group dosed with 120 mg/kg/day (> 75 times the maximum recommended human dose) than in the control group during the three-week postpartum period.

The effect of HYTRIN on fertility was assessed in a standard fertility/reproductive performance study in which male and female rats were administered oral doses of 8, 30 and 120 mg/kg/day. Four of 20 male rats given 30 mg/kg (240 mg/m^2; 20 times the maximum recommended human dose), and five of 19 male rats given 120 mg/kg (960 mg/m^2; 80 times the maximum recommended human dose), failed to sire a litter. Testicular weights and morphology were unaffected by treatment. Vaginal smears at 30 and 120 mg/kg/day, however, appeared to contain less sperm than smears from control matings and good

correlation was reported between sperm count and subsequent pregnancy.

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

Novitium submitted NDA 218139 for Terazosin Hydrochloride Oral Solution, 1 mg/mL for the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension. This a 505(b)(2) NDA submission where the Applicant references Terazosin Hydrochloride Capsules 10 mg (approved under NDA 020347 and ANDA 075317). The Applicant conducted a 28-day oral toxicity and toxicokinetic study in rats to nonclinically bridge their new formulation to the reference product.

In this 28-day rat study, Terazosin Oral Solution, 1 mg/mL (at 0, 0.5, 2.7, and 20.7 mg/kg) was given to rats for 28 days, with 14-day recovery period. Terazosin Capsules 10 mg (at 20.7 mg/kg) was used as a reference. Both formulations were well tolerated in rats and there was no new safety concern raised with Terazosin Oral Solution, 1 mg/mL. The NOAEL for the Terazosin Oral Solution = 20.7 mg/kg ($AUC_{0\text{-}24h}$ of 6368.29 ng•h/mL in males and 6969.23 ng•h/mL in females on Day 28), 21X and 23X the recommended human starting dose of 1 mg Terazosin Oral Solution (Table 1). When compared to an equivalent dose of the reference product, Terazosin Hydrochloride Oral Solution had lower systemic exposure. Additionally, a sex-related difference in systemic exposure was observed for the reference item but was not observed for the Terazosin Oral Solution. A review of information for other alpha-1 adrenoreceptor antagonists (e.g., tamsulosin, doxazosin, silodosin, alfuzosin) did not show consistent sex-related effects on systemic exposure across the nonclinical species tested. Therefore, this sex-related effect on systemic exposure in the Terazosin Capsules reference item does not appear to be an established class effect.

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 LD allowing the reliance on the Agency's previous nonclinical findings of safety of HYTRIN, Pharm/Tox recommends approval.

Table 1 Safety Margin.

Study	Toxicity	NOAEL (mg/kg)	Safety Margin Based on AUC*
28-day rat with 14-day recovery	No new toxicity was noted when compared to the reference item (Terazosin Oral Capsule 10 mg).	20.7 HED = 3.3 mg/kg $\underline{AUC_{0\text{-}24}}$ (ng•h/mL) 6368.29 (male) 6969.23 (female) $\underline{C_{max}}$ (ng/mL) 472.23 (male) 618.34 (female)	 21X 23X 22X 29X

*$AUC_{0\text{-}t}$ in human: 308.05 ng•hr/mL and C_{max} = 21.3 ng/mL at 1 mg/day Terazosin Oral Solution, obtained from the clinical study, TERA-12-003.

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/s/

MIYUN M TSAI-TURTON
06/17/2024 10:55:22 AM

ANDREA BENEDICT
06/17/2024 11:34:01 AM
I concur with the review and recommendations of Dr. Tsai-Turton.

PHARMACOLOGY/TOXICOLOGY LABELING REVIEW

Date:	06/17/24
NDA #	NDA 218139 (SDN 1, eCTD 0001)
Sponsor:	Novitium Pharma LLC (East Windsor, NJ)
Drug/Indication:	Terazosin Oral Solution, 1 mg/mL for the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension
Reviewer:	Miyun Tsai-Turton, PhD, MS

Background

NDA 218139 is a 505(b)(2) application submitted by Novitium Pharma for Terazosin Oral Solution (proposed tradename TEZRULY) for the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension. Since this is a 505(b)(2) NDA submission, the Applicant relies on NDA 020347 (HYTRIN, Terazosin Capsules, 1 mg, by Abbott Laboratories, which was discontinued in late 2013 not due to reasons of safety or efficacy) as the Listed Drug (LD) and ANDA 075317 (Terazosin Capsules 1 mg, by Jubilant Cadista Pharmaceuticals) as the Reference Standards (RS).

Novitium Pharma is seeking approval of the following dosing regimen:

- For the treatment of BPH: Initiate therapy at 1 mg at bedtime. Titrate the dose upwards stepwise from 2 to 10 mg once daily. Doses of 10 mg once daily are generally required for a clinical response. Data is insufficient to support doses greater than 20 mg once daily.

- For the treatment hypertension: Initiate therapy at 1 mg at bedtime. Usual recommended dose range is 1 mg to 5 mg once daily. If response is substantially diminished at 24 hours, increase the dose, or use twice daily. Dose may be titrated as needed up to 20 mg once daily.

TEZRULY's Prescribing Information is in the required PLLR format. However, the current HYTRIN label is not in PLLR format. The nonclinical review of Terazosin Oral Solution was presented in a separate review. The current document is for labeling only.

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

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MIYUN M TSAI-TURTON
06/17/2024 11:26:46 AM

ANDREA BENEDICT
06/17/2024 11:35:02 AM
I concur with the review and recommendations of Dr. Tsai-Turton.