

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217686Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Division of Cardiology and Nephrology**

NDA/BLA #s:	217686
PRODUCT:	Tryvio (aprocitentan) tablets
APPLICANT:	Idorsia
FROM:	Selena DeConti
DATE:	March 19, 2024

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Tryvio (aprocitentan) to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity. In reaching this determination, we considered the following:

- A. Tryvio (aprocitentan), in combination with other antihypertensive drugs, will be indicated for the treatment of hypertension, to lower blood pressure (BP) in adult patients who are not adequately controlled on other drugs. The estimated number of patients with uncontrolled BP while taking ≥ 3 classes of antihypertensive medications or taking ≥ 4 classes of antihypertensive medication regardless of BP level is 10.3 million.¹ Female adults of reproductive potential (FRP; ages 18-49 years) are included in the target population for Tryvio (aprocitentan) and represented 5% of the PRECISION study population. Given the number of alternative antihypertensive agents without embryofetal toxicity available, Tryvio (aprocitentan) use in patients who can become pregnant is anticipated to be low.
- B. Hypertension (HTN) is defined as elevated BP ($>130/80$) based on an average of ≥ 2 readings obtained on ≥ 2 occasions. Observational studies have demonstrated graded associations between higher BP and risk of death from stroke, heart disease, and other

¹ Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of Apparent Treatment-Resistant Hypertension in the United States. Hypertension. 2019;73(2):424-431. doi:10.1161/HYPERTENSIONAHA.118.12191

vascular disease. Trials of anti-HTN drugs have shown that lowering BP reduces the risk of fatal and non-fatal cardiovascular events.

- C. Tryvio (aprocitentan) has demonstrated an effect in reducing systolic BP, a validated surrogate endpoint for reduction in cardiovascular morbidity and mortality, in adults taking standardized background antihypertensives (valsartan 160mg, amlodipine 5 or 10 mg, and hydrochlorothiazide 25 mg daily).
- D. Tryvio (aprocitentan) will be used chronically.
- E. Tryvio (aprocitentan) may cause embryo-fetal toxicity (based on animal studies with macitentan for which aprocitentan is an active metabolite). It is contraindicated in pregnancy. The background incidence of adverse pregnancy outcomes in patients with uncontrolled BP while taking ≥ 3 classes of antihypertensive medications is unknown; however, such patients are generally taking commonly prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors which are associated with adverse pregnancy outcomes and contraindicated during pregnancy because of the risk. Chronic hypertension in general carries significant risk of maternal and neonatal morbidity and mortality.² The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20%, respectively.
- F. Tryvio (aprocitentan) is a new molecular entity.

The elements of the REMS will be elements to assure safe use, including that healthcare providers who prescribe Tryvio (aprocitentan) are specially certified, and pharmacies and practitioners that dispense Tryvio (aprocitentan) are specially certified, implementation system, and a timetable for submission of assessments of the REMS.

² Mammaro A, Carrara S, Cavaliere A, et al. Hypertensive disorders of pregnancy. J Prenat Med. 2009;3(1):1-5.
Reference ID: 5349285

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Office of Medication Error Prevention and Risk Management (OMEPRM)
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Application Type	NDA
Application Number	217686
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Review Completion Date	March 19, 2024
Subject	Evaluation of Need for a REMS
Established Name	aprocitentan
Trade Name	Tryvio
Name of Applicant	Idorsia Pharmaceuticals Ltd
Therapeutic Class	Endothelin Receptor Antagonist (ERA)
Formulation	12.5 mg oral tablets
Dosing Regimen	12.5 mg orally once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tryvio (aprocitentan) is necessary to ensure the benefits outweigh its risks. This review also provides the DRM and Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluation of the Applicant's proposed REMS and assessment plan. Idorsia Pharmaceuticals Ltd (Idorsia) submitted a New Drug Application (NDA) 217686 for Tryvio with the proposed indication in combination with other antihypertensive drugs, for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs. The risk associated with Tryvio under review for a REMS is embryo-fetal toxicity.

Tryvio is an orally active endothelin receptor antagonist (ERA). The benefits of Tryvio for the treatment of hypertension were demonstrated in a phase 3 study, PRECISION. In the PRECISION trial, both the 12.5 mg and 25 mg daily doses met the primary endpoint (change from baseline to Week 4 of double-blind treatment in mean trough sitting systolic blood pressure, recorded via unattended automated office blood pressure measurement). The PRECISION trial also met the key secondary endpoint, demonstrating a persistence of the blood pressure lowering effect at Week 40. (b) (4)

(b) (4) the 12.5 mg dose will be approved.

Tryvio is an active metabolite of macitentan, an ERA approved for treating pulmonary arterial hypertension. Non-clinical data associated with macitentan suggest a teratogenic effect of Tryvio on the developing fetus when administered to a pregnant woman. Based on data from macitentan and data from embryo-fetal development studies with Tryvio, the review team concluded that there is insufficient evidence to support that the embryo-fetal toxicity risk for Tryvio is different than macitentan or that it is not a risk for humans. The embryo-fetal toxicity risk can be mitigated by patient selection, preventing pregnancy from occurring by using acceptable contraception, and minimizing exposure by discontinuing the drug as soon as pregnancy is detected.

DRM and the Division of Cardiology and Nephrology (DCN) agree that a REMS with ETASU is necessary to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity. Idorsia initially proposed a (b) (4) REMS to mitigate the risk of embryo-fetal toxicity associated with Tryvio, however, during the application review, DRM and DCN determined that a (b) (4) REMS will not be sufficient to mitigate the risk. DRM and DCN determined that a REMS with elements to assure safe use (ETASU) is necessary to ensure that healthcare providers are aware of the risk and how it differs from other antihypertensives, and the need to counsel patients who can become pregnant to use acceptable contraception while they are treated with Tryvio.

The goal of the Tryvio REMS is to mitigate the risk of embryo-fetal toxicity associated with Tryvio.

Objective: Ensure that prescribers are aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant on the actions necessary to prevent pregnancy and minimize exposure to a fetus.

The Tryvio REMS includes the following REMS elements: ETASU A (healthcare providers who prescribe Tryvio are specially certified), ETASU B (pharmacies that dispense Tryvio are specially certified), an implementation system, and a timetable for submission of assessments. Prescriber certification can ensure that prescribers are informed of the risk of embryo-fetal toxicity associated with Tryvio, that the risk is different from other products that are used for treating hypertension, and the need to counsel patients who can become pregnant on the risk and recommendations for acceptable contraception and pregnancy testing. Pharmacy certification is necessary to confirm the prescriber is certified in the REMS prior to dispensing Tryvio to patients.

All ERA products are approved with a REMS with ETASU to mitigate the risk of embryo-fetal toxicity. The Tryvio REMS differs from other ERA REMS as it does not require patient monitoring or dispensing dependent on documented pregnancy tests. In determining the required elements of the Tryvio REMS, DRM and DCN considered several factors including the indication, available alternate treatment options that do not have an embryo-fetal toxicity risk, baseline stakeholder knowledge, and the medication use process including burden associated with enrolling a potentially large number of patients in the Tryvio target population. DCN believes that healthcare providers who understand the risk will choose alternative therapies in patients who may become pregnant and therefore expects the at-risk population exposed to Tryvio will be limited. DRM notes the limitations of this strategy as it does not directly affect safe use behaviors and will not ensure that patients are counseled or monitored before and during treatment.

DCN recommends approval of Tryvio in combination with other antihypertensive drugs, for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs with a REMS to mitigate the risk of embryo-fetal toxicity. DRM and DMAMES reviewed the Applicant's proposed REMS and find the REMS received on March 15, 2024 acceptable.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tryvio (aprocitentan) is necessary to ensure the benefits outweigh its risks. Idorsia Pharmaceuticals Ltd (Idorsia) submitted a New Drug Application (NDA) 271686 for aprocitentan with the proposed indication for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of aprocitentan outweigh the risk of embryo-fetal toxicity.

2. Background

2.1. Product Information

Tryvio (aprocitentan), a new molecular entity^a, is an orally active endothelin receptor antagonist (ERA), proposed for the treatment of hypertension, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. Tryvio inhibits the binding of endothelin (ET)-1 to ETA and ETB receptors. (ET)-1 binding to its receptors mediates a variety of effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 is upregulated and can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation and increased aldosterone synthesis.

Tryvio is proposed to be available as 12.5 mg (b) (4) tablets taken by mouth. The proposed (b) (4) dose of Tryvio is 12.5 mg orally once daily (b) (4). Tryvio is expected to be administered in the outpatient setting for long term therapy.^b Tryvio is not currently approved in any jurisdiction.

Tryvio has the same chemical structure as the active metabolite of macitentan, another ERA. Other ERA products are approved for pulmonary arterial hypertension (PAH) including bosentan, ambrisentan, and macitentan, or immunoglobulin A nephropathy (IgAN) including sparsentan. These products have a Boxed Warning for embryo-fetal toxicity, a Contraindication for pregnancy, and a REMS with Elements to Assure Safe Use (ETASU) to mitigate the risk of embryo-fetal toxicity. Bosentan and sparsentan also require a REMS to mitigate the risk of hepatotoxicity. The REMS for ERA products includes prescriber certification, pharmacy certification, documentation of safe use conditions including patient enrollment, counseling, and documentation that pregnancy and/or liver testing occurred, monitoring (pregnancy and/or liver tests), an implementation system, and a timetable for submission of assessments.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217686 relevant to this review:

- 3/9/2022: In response to a Type B Pre-NDA Meeting for IND 122772 on March 14, 2022, the Agency informed the Applicant there is insufficient information to determine whether a REMS will be necessary for aprocitentan. Since other products within the class (endothelin receptor antagonist; ERA) have REMS to mitigate the risk of embryo-fetal toxicity, the Agency encouraged the Applicant to submit a REMS with the NDA or rationale for why the Applicant believes a REMS is not needed for aprocitentan.¹
- 3/11/2022: The Applicant canceled the planned March 14, 2022 Pre-NDA Type B meeting and requested a meeting to discuss their planned REMS proposal for the NDA.
- 5/25/2022: The Agency informed the Applicant in response to a Type C Pre-NDA Meeting that aprocitentan, as a metabolite of macitentan, is expected to have the same teratogenic risk as

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

macitentan; therefore, labeling and other risk mitigation would be similar to macitentan. Other products within the ERA drug class have REMS with elements to assure safe use (ETASU) to mitigate the risk of embryo-fetal toxicity; and based on the information provided, a REMS will be necessary to ensure benefits outweigh risks of aprocitentan.²

- 6/2/2022: A Type C Pre-NDA teleconference for IND 122772 was held between the Agency and Applicant for aprocitentan to discuss the Applicant's planned (b) (4) REMS proposal. The Agency reiterated to the Applicant that the Agency believes a REMS with ETASU will be necessary to ensure the benefits outweigh the risks.³
- 12/19/2022: NDA 217686 submitted for the treatment of hypertension with a proposed (b) (4) REMS for the risk of embryo-fetal toxicity.
- 3/3/2023: A Filing Communication Letter was issued to the Applicant to inform them that no filing issues were identified. However, potential review issues were identified which include whether a REMS is needed for aprocitentan to mitigate the potential risk of hepatotoxicity and whether a (b) (4) REMS is sufficient to mitigate the risk of embryo-fetal toxicity.⁴
- 8/23/2023: Applicant informed via teleconference that a REMS with elements to assure safe use (ETASU) was necessary for the risk of embryo-fetal toxicity associated with aprocitentan to ensure the benefits outweigh the risks.
- 9/6/2023: Applicant submitted a REMS with ETASU for the risk of embryo-fetal toxicity which constitutes a major amendment.
- 9/22/2023: Information Request issued to Applicant to clarify aspects of REMS operations.⁵
- 9/24/2023: Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months.⁶
- 9/28/2023: Applicant submitted a response to the Information Request to specify anticipated outpatient pharmacy settings that will dispense Tryvio and to clarify proposed REMS operations for inpatient pharmacies and for stakeholder enrollment in the REMS.
- 10/27/2023: Applicant inquired via email about the feasibility of dispensing samples in the postmarket setting.
- 10/31/2023: Agency informed the Applicant that samples may be dispensed if the processes and procedures for dispensing are included in the REMS requirements.
- 11/3/2023: Agency sent interim comments (ICs) and redlined Tryvio REMS materials to the Applicant in response to their REMS amendment, dated September 6, 2023. Edits included revising the REMS goal, incorporating gender-neutral language, revising REMS requirements, and creating a *Patient Information Sheet* (renamed to *Birth Defects with Tryvio*) and *Prescriber Knowledge Assessment*.⁷
- 11/16/2023: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated November 3, 2023. In addition to responding to the Agency's requested revisions, the Applicant proposed to revise the language describing the outpatient and inpatient pharmacy requirement to verify the prescriber is certified before dispensing Tryvio, removed the requirement for (b) (4), added a requirement for inpatient pharmacies to report pregnancies to the REMS, and proposed inpatient pharmacies (b) (4).

- 11/28/2023: Applicant submitted REMS Website screenshots.
- 1/19/2024: Agency sent ICs to the Applicant in response to their REMS amendments, dated November 16 and November 28, 2023. Edits included revising the REMS requirements and aligning materials to the revised requirements, suggested language for accommodating the dispensing of Tryvio samples by prescribers, proposing Key Risk Messages (KRM)s and a Key Performance Indicator (KPI) with target threshold, and revising the REMS Assessment Plan.⁸
- 2/2/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated January 18, 2024. In addition to responding to the Agency's requested revisions, the Applicant proposed to change the pregnancy reporting contact from the REMS to (b) (4) .
- 2/9/2024: Agency requested information on rationale for changing the pregnancy reporting contact from the REMS Coordinating Center to (b) (4) .⁹
- 2/13/2024: Applicant responded to Agency request for information sent February 9, 2024, proposing to reinstate the REMS Coordinating Center as the contact for pregnancy reporting.
- 2/27/2024: Agency sent ICs to the Applicant in response to their REMS amendment, dated February 2, 2024 and REMS correspondence dated February 13, 2024. Edits included revising the REMS requirements, revising materials to align with proposed label and include all proposed KRM)s, reinstating the REMS as the pregnancy reporting contact, revising audit language and the REMS Assessment Plan.¹⁰
- 3/5/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated February 27, 2024.
- 3/8/2024: Agency sent ICs to the Applicant in response to their REMS amendment, dated March 5, 2024. Edits included aligning the REMS materials to the Prescribing Information and Medication Guide, formatting the materials intended for patients to clarify and align with other REMS materials, and clarifying details of the REMS Website.
- 3/13/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated March 8, 2024.
- 3/14/2024: Agency requested a revision to the REMS Website Screenshots to align with the Prescriber Knowledge Assessment amended March 13, 2024.
- 3/15/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's information request dated March 14, 2024.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hypertension (HTN) is defined as elevated BP (>130/80 mmHg) based on an average of ≥ 2 readings obtained on ≥ 2 occasions.¹¹ Observational studies have demonstrated graded associations between

higher BP and risk of death from stroke, heart disease, and other vascular disease^{c,11}. Trials of anti-HTN drugs have shown that lowering BP reduces the risk of fatal and non-fatal cardiovascular events. The prevalence of HTN is 46% in the U.S. adult population¹¹ and there were approximately 10.3 million patients^d in 2018 with apparent resistant hypertension, defined as uncontrolled BP while taking ≥ 3 classes of antihypertensive medications or taking ≥ 4 classes of antihypertensive medication regardless of BP level.¹² Hypertension is common in the United States and is a serious disease associated with significant morbidity and mortality.

3.2. Description of Current Treatment Options

Control of high BP with medications is part of comprehensive cardiovascular risk management. Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action are available and have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality. Primary agents for treatment include thiazide diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB). Secondary agents include loop diuretics, potassium sparing diuretics, aldosterone antagonists, beta-blockers, direct renin inhibitors, alpha-1 blockers, centrally acting drugs, and direct vasodilators¹¹. Many patients require more than one drug to achieve BP goals.

See Appendix *Table 3: Summary of Treatment Options Relevant to Proposed Indication of Resistant Hypertension* in the appendix for an overview of current treatment options.¹¹

4. Benefit Assessment

The pivotal trial (PRECISION: PaRallel-group study with aproCItentan in Subjects with resistant HypertensiON; NCT03541174) supporting this application consisted of a prospective, multi-part, multi-center, blinded, randomized, parallel-group, phase 3 study in adults with SBP ≥ 140 millimeters of mercury (mmHg) (n=730) comparing Tryvio 12.5 mg daily (n=243), Tryvio 25 mg daily (n=243), and placebo (n=244) while on standardized background antihypertensives (valsartan 160 mg, amlodipine 5 or 10 mg, and hydrochlorothiazide 25 mg daily). The trial included a 4-week double-blind, placebo-controlled treatment period (Part 1), 32-week single blind treatment period (Part 2), and a 12-week placebo-controlled, double-blind withdrawal (DB-WD) period (Part 3). The primary efficacy endpoint was the change from baseline to Week 4 of double-blind treatment in mean trough sitting systolic blood pressure (SiSBP), recorded via unattended automated office blood pressure measurement (uAOBPM). The key secondary endpoint was the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP, recorded via uAOBPM.

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

The study demonstrated that Tryvio was effective in reducing systolic blood pressure, a validated surrogate endpoint for reduction in cardiovascular morbidity and mortality. In the PRECISION trial, both the 12.5 mg and 25 mg doses met the primary endpoint. The least squares mean (LSM) difference in blood pressure at Week 4 compared to baseline was -3.8 mmHg (97.5% CI: -6.8, -0.8; p-value=0.0043) for 12.5 mg compared to placebo, and was -3.7 mmHg (97.5% CI: -6.5, -0.7; p-value=0.0054) for 25 mg compared to placebo.¹³ The PRECISION trial also met the key secondary endpoint, demonstrating a persistence of the BP lowering effect at Week 40. The clinical review team concluded that the Applicant provided substantial evidence of Tryvio's effectiveness in lowering blood pressure when administered in combination with other antihypertensive medications in patients who are not adequately controlled on other therapies.^e

The clinical review team also concluded that data from Part 1 of the PRECISION study indicate that in the study population as a whole, the 25 mg dose of Tryvio does not provide greater efficacy than the 12.5 mg dose, and (b) (4)

the 12.5 mg dose will be approved.¹³

5. Risk Assessment & Safe-Use Conditions

The safety of Tryvio was evaluated in the PRECISION trial which included three treatment periods (Part 1, 2, and 3). The three treatment periods had differing designs and durations, so the treatment periods were analyzed separately. Adverse events were collected up through the safety follow-up period, which started on the day after the last dose of study treatment and ended with a safety follow-up visit 30–33 days later. In the PRECISION safety population, 724 subjects received at least one dose of apocitinatan, and the mean duration of exposure was 36.6 weeks.¹³ Adverse events of special interest (AESIs) for Tryvio include anemia, edema/fluid retention, decompensation/aggravation of heart failure, and hepatic injury.^f Table 1 summarizes data regarding these AESIs, except for hepatic injury, which is described in section 5.3 of this review.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Table 1: Adverse Events of Special Interest, PRECISION Study¹³

	aprocitentan 12.5 mg %	aprocitentan 25 mg %	placebo %
Anemia			
Part 1	4	1	0
Part 2	--	9	--
Edema/Fluid Retention			
Part 1	9	18	2
Part 2	--	17	--
Decompensation/Aggravation of heart failure or heart failure event with hospitalization			
Part 1	0	0.8	0
Part 2	--	0.9	--

The clinical reviewer concluded the risks of anemia, edema/fluid retention, decompensation/aggravation of heart failure and hepatic injury can be managed and adequately addressed through labeling.

The risks of embryo-fetal toxicity and hepatotoxicity are of interest with Tryvio as these are serious risks associated with the ERA class. Embryo-fetal toxicity and hepatotoxicity risks for Tryvio are further described below.

5.1. Deaths

There were 11 treatment-emergent deaths (1.3%) during the PRECISION trial, all reported in aprocitentan-treated patients. Five of the deaths were attributed to COVID-19 (Part 1, n=1; Part 2, n=3; Part 3, n=1), one death was attributed to a colon perforation from a colonoscopy (Part 2), and one death was attributed to invasive breast carcinoma (primary cause of death), with concurrent subdural hemorrhage and brain edema (Part 2). The remaining four deaths were adjudicated as major adverse cardiac events (MACE), all reported in Part 2 with no comparator arm. The clinical review team concluded based on a review of the cases as well as what is known about the pharmacologic class, it seems unlikely that Tryvio played a role in these deaths.¹³

5.2. Embryo-fetal Toxicity

Embryo-fetal toxicity is recognized as a class-wide risk for ERAs based on animal data and due to the mechanism of action of ERAs impacting the endothelin receptor signaling pathway in neural crest development. Tryvio is an active metabolite of macitentan, and therefore expected to have a similar risk of embryo-fetal toxicity. In embryo-fetal developmental (EFD) studies with Tryvio, while no embryo-fetal toxicity, including teratogenic effects, was observed at 5-fold and 29-fold the human exposure at maximum recommended human dose (MRHD) in rats and rabbits, respectively, the highest doses of

Tryvio tested in the rat EFD studies was too low to fully characterize reproductive risk.¹⁴ The Review Team concluded that there is insufficient evidence from non-clinical studies to support that the embryo-fetal toxicity risk for Tryvio is different than macitentan or that it is not a risk for humans.

Clinical data of pregnancy exposure of Tryvio is limited. The PRECISION trial excluded pregnant patients and required monthly pregnancy tests and contraception use. There was one unplanned pregnancy reported during Part 2 of PRECISION (Study Day 139), in which a patient was taking 25 mg daily for approximately 6 weeks (first trimester exposure) prior to discontinuation due to the pregnancy. The outcome was reported as a normal baby born at 38 weeks gestation.

Based on data from EFD studies and the known embryo-fetal toxicity associated with the mechanism of action of Tryvio, the review team concluded that Tryvio may cause fetal harm when administered to pregnant patients. Tryvio labeling will consist of a Boxed Warning, warnings and precautions for embryo-fetal toxicity, medication guide, and a contraindication for pregnancy. In addition, Idorsia proposed a REMS to mitigate the risk of embryo-fetal toxicity. The REMS is discussed in Section 7 below.

5.3. Hepatotoxicity

There was no imbalance in elevations of aminotransferases between Tryvio and placebo exposure in the PRECISION trial.¹³ There were no cases of jaundice or Hy's Law across all study periods. The review team consulted the Division of Hepatology and Nutrition (DHN) to conduct a case level analysis of the PRECISION safety data. In Part 1 of PRECISION, 0% of patients on 12.5 mg dose and 0.4% on 25 mg experienced hepatic injury, elevations in alanine transaminase (ALT) or aspartate transferase (AST) $\geq 3\times$ upper limit of normal (ULN) compared with 1% for placebo. In Part 2, 1% of patients on the 25 mg dose experienced transaminase elevations $\geq 3\times$ with 2 patients experiencing $\geq 5\times$ ULN, with positive rechallenge. The 2 subjects with liver enzyme elevations $\geq 5\times$ ULN were assessed as highly likely related to the use of Tryvio. However, the enzyme elevations were considered modest without hyperbilirubinemia and were resolved or nearly resolved at the last follow-up visit after Tryvio discontinuation.¹³

The review team concluded that the data indicate that Tryvio can cause liver injury. Labeling will include a warning and precaution for hepatotoxicity and recommendations for monitoring of serum aminotransferase levels and total bilirubin prior to initiation and periodically during treatment. Tryvio will not be recommended for use in patients with decompensated cirrhosis or acute liver disease.

6. Expected Postmarket Use

6.1. Healthcare Setting

Tryvio is intended to be dispensed from retail and specialty pharmacies for chronic daily administration by the patient in an outpatient setting, but may also be utilized in an inpatient setting. Expected prescribers of Tryvio include internists, cardiologists and nephrologists. Prescribers should be familiar with the risk for embryo-fetal toxicity as this risk is well established in standard of care

ensure the benefits outweigh the risk of embryo-fetal toxicity. The Applicant was informed on August 23, 2023 that a REMS with ETASU is necessary for Tryvio. The Applicant submitted an updated REMS proposal on September 6, 2023, last amended on March 15, 2024. The Tryvio REMS consists of ETASU including prescriber certification (A), pharmacy certification (B), an implementation system, and a timetable for submission of assessments of the REMS.

7.1.1. REMS Goals

The goal of the Tryvio REMS is to mitigate the risk of embryo-fetal toxicity associated with Tryvio.

Objective: Ensure prescribers are aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant on the actions necessary to prevent pregnancy and minimize exposure to a fetus.

Reviewer's Comments: *DRM concurs with the proposed goal of the REMS. The Applicant updated the proposed goal based on comments from the Agency.*

When determining the goal for the REMS, DRM evaluated how Tryvio will move through the medication use process, potential care gaps, burden on the healthcare system, and how the REMS would align with public health prevention aims. DRM identified potential care gaps in prescriber and patient knowledge of the risk of embryo-fetal toxicity risk associated with Tryvio. Stakeholders are likely knowledgeable of the embryo-fetal toxicity risk among other antihypertensives, however the risk with ERAs occurs earlier in pregnancy compared to antihypertensives that work on the RAAS system. Additionally, the patient population at risk with Tryvio is estimated to be relatively large compared to those of other ERAs indicated for PAH and IgAN.

The Applicant's original proposed goals of ensuring prescribers, pharmacies, and appropriate patients are informed about the risk of embryo-fetal toxicity was incorporated into the current proposed goal, but the goal required adjustments as the REMS evolved (b) (4) to a REMS with ETASU with a risk mitigation strategy to directly affect knowledge. The Applicant's other proposals including ensuring (b) (4) have been removed from the overall goal and objective of the REMS but will be incorporated into the requirements of the REMS to support the goal and objective.

7.1.2. Elements to Assure Safe Use (ETASU)

ETASU A: Prescriber certification

The Applicant proposed that a prescriber must certify in the Tryvio REMS prior to prescribing Tryvio. To become certified, prescribers must review the Prescribing Information, *Prescriber and Pharmacy Guide*, successfully complete the *Prescriber Knowledge Assessment*, and enroll in the REMS by completing and submitting the *Prescriber Enrollment Form* to the REMS. Prior to initiating treatment with Tryvio, prescribers must assess the patient's reproductive status using the definitions in the *Prescriber and Pharmacy Guide*, and counsel patients who can become pregnant on the risk, to use acceptable

contraception, pregnancy testing recommendations before initiating treatment, monthly during treatment, and one month after discontinuing treatment, and about the use of emergency contraception. Prescribers must use the *Patient Guide* to counsel and provide a copy of the material to the patient. At all times, prescribers must report pregnancies to the REMS.

Reviewer's Comments: *We agree with the requirement for prescriber certification (ETASU A). The prescriber certification requirement is similar to the REMS for other approved ERA products. Prescriber training and certification can ensure that prescribers are informed of the risk of embryo-fetal toxicity associated with Tryvio and that the risk is different from the risk of embryo-fetal toxicity associated with other products that are used for treating hypertension. Prescribers will also be educated on the need to counsel patients on the risk of embryo-fetal toxicity and the actions patients should take to prevent fetal exposure and minimize exposure to a fetus during pregnancy. We agree with the inclusion of the Prescriber Enrollment Form, Prescriber and Pharmacy Guide, Prescriber Knowledge Assessment, and Patient Guide to support prescriber education and patient counseling; and find these materials acceptable.*

ETASU B: Pharmacy certification

The Applicant proposed that Tryvio be dispensed by certified pharmacies with separate requirements for outpatient and inpatient pharmacies to accommodate their distinct workflows. Outpatient and inpatient pharmacies must become certified by designating an authorized representative on their respective Pharmacy Enrollment Forms. The authorized representative is responsible for coordinating REMS activities on behalf of the pharmacy, reviewing the Prescribing Information and *Prescriber and Pharmacy Guide*, enrolling in the REMS, ensuring all relevant staff are trained in the REMS, and are responsible for establishing processes and procedures to meet the REMS requirements. If the authorized representative changes, the new authorized representative must re-enroll in the REMS in order to maintain certification. Before dispensing, outpatient pharmacies are required to obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified. Inpatient pharmacies must verify the prescriber is certified or the patient is under the supervision and care of a certified prescriber in order to dispense Tryvio. Pharmacies must also provide the patient with the *Risk of Birth Defects with Tryvio* prior to dispensing Tryvio. Prescribers who dispense Tryvio samples attest on the *Prescriber Enrollment Form* to provide the patient with the *Risk of Birth Defects with Tryvio* and to report dispenses to the REMS. At all times, pharmacies must report pregnancies to the REMS.

Reviewer's Comments: *We agree with the requirement for pharmacy certification (ETASU B). Pharmacy certification is necessary to confirm that the prescriber is certified in the REMS prior to dispensing Tryvio. The pharmacy certification requirement is similar to the pharmacy requirements of REMS for approved ERA products. Pharmacies will also dispense the Risk of Birth Defects with Tryvio to further reinforce risk education and management for patients. We agree with the inclusion of the Outpatient Pharmacy Enrollment Form, Inpatient Pharmacy Enrollment Form, Prescriber and Pharmacy Guide, and Risk of Birth Defects with Tryvio; and find these materials acceptable.*

7.1.3. Implementation System

Elements of the implementation system proposed by the Applicant to support REMS operations are listed in the REMS Supporting Document and include:

- **REMS Website:** The Applicant proposes to maintain a REMS Website to support prescriber and pharmacy ability to interface with the REMS and provide the option to complete prescriber and pharmacy certification online and for pharmacies to obtain a REMS Dispense Authorization (RDA) for a prescription online. REMS materials will be made available electronically by the Applicant through the website.
- **REMS Coordinating Center:** The Applicant proposes a REMS Coordinating Center to provide REMS support to stakeholders. The staff will receive inbound calls from stakeholders and provide support for questions regarding REMS requirements; provide educational materials to stakeholders upon request; receive and process enrollment forms for prescribers and pharmacies; maintain the database of REMS participants who are certified; authorize dispensing based on verifying the prescriber is certified; receive inbound calls for pregnancy reporting; receive dispensing and distribution data from pharmacies and wholesaler-distributors to confirm REMS requirements are met; and provide RDAs via phone.
- **REMS Database:** The Applicant proposes to maintain a validated, secure database of all REMS participants who are certified in the REMS.

***Reviewer's Comments:** The proposed implementation system is similar to other ERA REMS. The Applicant provided adequate detail in the REMS Supporting Document on how pharmacies will utilize an RDA to verify the prescriber is certified in the REMS prior to dispensing Tryvio. We agree with the Applicant's proposal for an implementation system and find it acceptable.*

7.1.4. Compliance

To ensure REMS participants compliance with the REMS, the Applicant must maintain adequate records to demonstrate that the REMS requirements have been met, establish and maintain a plan for addressing non-compliance with REMS requirements, monitor stakeholders on an ongoing basis to ensure the REMS requirements are being met and take corrective action if non-compliance is identified, and take reasonable steps to improve operations and compliance with the REMS requirements based on monitoring and evaluation of the REMS. As part of the requirements to ensure compliance with the REMS, the Applicant must conduct audits of pharmacies and wholesaler-distributors as follows:

1. Audit all certified outpatient specialty pharmacies, a representative sample of certified outpatient retail pharmacies (10% or at least 10, whichever is greater yet not to exceed 100), and a representative sample of certified inpatient pharmacies (10% or at least 10, whichever is greater yet not to exceed 100) within 180 days after their first shipment receipt of TRYVIO to ensure that all the REMS processes and procedures are in place, functioning, and support the REMS requirements. Audit a representative sample (10% or at least 10, whichever is greater yet not to exceed 100) of each annually: certified outpatient specialty pharmacies, outpatient retail

pharmacies, and inpatient pharmacies, to ensure that all the REMS processes and procedures are in place, functioning, and support the REMS requirements.

2. Audit all wholesaler-distributors within 180 days after they become authorized and audit all wholesaler-distributors annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

Reviewer's Comment: *The audit language is acceptable. If the NDA is approved, the Applicant will be asked in the approval letter to submit their audit plan and non-compliance plan methodologies for Agency review. These methodologies were not formally reviewed during the current review cycle.*

7.1.5. Timetable for Submission of Assessments

The Applicant proposed to submit REMS assessments annually from the date of the initial REMS approval.

Reviewer's Comments: *The proposed timetable is acceptable. DRM/DMAMES previously reviewed the proposed timetable. The review dated February 27, 2024 contains details on the proposed timetable.*

7.1.6. REMS Key Risk Messages and Materials

The Applicant proposed the following Key Risk Messages (KRM)s for the Tryvio REMS on March 5, 2024:

Key Risk Messages for Prescribers

- Embryo-fetal toxicity can occur in patients taking Tryvio. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
- Counsel patients who can become pregnant on the recommendations for pregnancy testing monthly during treatment, and for one month after treatment. Instruct patients who can become pregnant to use acceptable contraception.

Key Risk Messages for Patients

- There is a risk of birth defects (embryo-fetal toxicity)
- If you are a patient who can become pregnant:
 - Confirm that you are not pregnant by taking a pregnancy test before starting Tryvio, monthly during treatment, and for one month after discontinuing treatment.
 - Use acceptable contraceptives and avoid pregnancy.

Reviewer's Comments: *The Applicant initially proposed KRM)s in response to the Agency's comments sent on January 19, 2024 and added a section to the Supporting Document. The Applicant revised the KRM)s in response to the Agency's comments on February 27, 2024 to align the description of recommended contraceptives to Tryvio labeling. The KRM)s as submitted on March 5, 2024 are acceptable.*

The Applicant included the following materials in the proposed REMS:

- Prescriber Enrollment Form: serves to enroll prescribers in the REMS and for prescribers to attest they understand the requirements of the REMS as part of the process to become certified to prescriber Tryvio.
- Outpatient Pharmacy Enrollment Form: completed by the outpatient pharmacy's authorized representative on behalf of the outpatient pharmacy to enroll in the REMS. The authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense, will train staff on the REMS requirements, and will develop processes and procedures to meet the REMS requirements.
- Inpatient Pharmacy Enrollment Form: completed by the inpatient pharmacy's authorized representative on behalf of the inpatient pharmacy to enroll in the REMS. The authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense, will train staff on the REMS requirements, and will develop processes and procedures to meet the REMS requirements.
- Prescriber and Pharmacy Guide: serves to inform prescribers and pharmacy authorized representatives of the serious risk of embryo-fetal toxicity associated with Tryvio, the REMS requirements, and the responsibilities of prescribers and certified pharmacies.
- Prescriber Knowledge Assessment: assesses whether KRMs were communicated to prescribers. Prescribers are required to score 100% correct on the assessment before they are able to enroll in the Tryvio REMS.
- Patient Guide (revised from (b) (4) Patient Guide): serves to be used by prescribers when counseling patients who can become pregnant and inform patients about the risk of embryo-fetal toxicity associated with Tryvio therapy, recommendations for preventing pregnancy and monitoring for pregnancy while on Tryvio, and what to do if a patient becomes pregnant while on Tryvio.
- Risk of Birth Defects with TRYVIO: serves to inform patients of the risk of Tryvio for patients who can become pregnant. The material is provided by pharmacies and prescribers that dispense Tryvio to each patient with each dispense of Tryvio. The material reinforces the KRMs to patients during the course of Tryvio therapy.
- REMS Website: serves as a source of information and portal for stakeholders. It allows prescribers and pharmacies to enroll in the REMS online. Prescribers can also complete and submit the *Prescriber Knowledge Assessment* on the website. Outpatient pharmacies will have the option to use the website to obtain a REMS Dispense Authorization required for each dispense. The REMS materials will be available on the website and downloadable in an electronic format. The database of certified REMS stakeholders will also be available on the website.

Reviewer's Comments: The applicant originally included (b) (4) materials as part of their (b) (4) REMS proposal.

(b) (4)

We determined a (b) (4) REMS would not be adequate to mitigate the risk of embryo-fetal toxicity associated with Tryvio. The Applicant made changes to the stakeholder training materials and website and added new materials including stakeholder enrollment forms, a prescriber knowledge assessment, and an additional patient directed material, Risk of Birth Defects with Tryvio, to support the ETASU requirements. The (b) (4) and (b) (4) were removed from the proposed REMS as they were determined to be redundant. We determined the Prescriber Knowledge Assessment was necessary to help ensure certified prescribers are aware of the risk of embryo-fetal toxicity and the need to counsel patients who can become pregnant on actions to take to avoid pregnancy as part of the prescriber certification requirement. We determined an additional patient directed material, the Risk of Birth Defects with Tryvio, was necessary as the REMS does not include patient enrollment. This material is used to reinforce the KRMs for patients as there is expected to be more touchpoints between the patient and the pharmacy throughout the treatment course.

7.1.7.Supporting Document

The REMS Supporting Document includes the background and the Applicant's rationale for the REMS currently under review, information on stakeholders' responsibility in the REMS, how they carry out responsibilities, and how the REMS will be implemented. The Supporting Document also includes the REMS Assessment Plan discussed in Section 7.1.8 below.

In the REMS Supporting Document, the Applicant included the following key performance indicator (KPI) and threshold: "The TRYVIO REMS will assess the percentage of prescribers who are knowledgeable about: 1.) The risk of embryo-fetal toxicity associated with TRYVIO. 2.) The need to counsel patients who can become pregnant. The knowledge performance threshold for the Tryvio REMS KPI is the lower bound of the 95% confidence interval with the targeted knowledge rate of 80% or higher for each REMS key message domain."

Reviewer's Comments: DRM requested additional information in the Supporting Document on November 3, 2023, January 19, 2024, and February 27, 2024, including updates to align sections of the Supporting Document with the REMS Document and REMS materials. The Applicant made all requested edits and provided further details on linking verification of prescriber certification to dispensing of Tryvio

via a REMS Dispense Authorization (RDA) generated by the REMS, submitted REMS KRMs for prescribers and patients, and submitted a KPI and target threshold.

The Applicant outlined verification processes that certified pharmacies must undertake to ensure prescribers are certified prior to dispensing. The outpatient pharmacy must obtain an RDA from the REMS website or by contacting the REMS Coordinating Center by phone. An RDA signifies that the pharmacy is authorized to dispense Tryvio by confirming that the prescriber is certified. The RDA number that is generated must be documented and available for audit. Inpatient pharmacies must either verify the prescriber is certified in the REMS or the patient is under the supervision and care of a certified prescriber. Patients are most likely initiated on Tryvio in the outpatient setting by an outpatient certified prescriber and may continue treatment while in a hospital or other inpatient setting. To reduce burden on the healthcare system and to maintain treatment without interruption, the review team found it acceptable for inpatients to receive Tryvio in the inpatient setting as long as inpatient pharmacies confirm the patient is under the supervision and care of a certified prescriber prior to dispensing, instead of being required to obtain an RDA. Inpatient pharmacies may use an RDA to satisfy their REMS requirement. In the expectedly rare circumstance that an inpatient is initiated on Tryvio, the certified inpatient pharmacy is able to facilitate inpatient prescriber enrollment in the REMS so the REMS requirements are satisfied and Tryvio may be dispensed.

The KPI has been defined and agreed upon for the Tryvio REMS and includes a corresponding target knowledge threshold that indicates if the REMS is functioning as designed or may help determine if modifications to the REMS are necessary.

7.1.8. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document submitted on March 5, 2023 and will be included in the REMS Approval letter. The REMS Assessment Plan includes metrics related to Implementation and Operations (REMS website, Implementation, Infrastructure and Performance, Certification and Enrollment), REMS Utilization, REMS Compliance, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes. Certification and Enrollment metrics capture stakeholder participation including prescribers, pharmacies, and wholesaler/distributors. The REMS compliance section includes a request for the audit plan and non-compliance plan; and methodologies to be submitted with each assessment report. The Knowledge metrics capture post-training knowledge assessment from prescribers, surveys of healthcare providers to assess the education based REMS goal, and a qualitative evaluation of patient comprehension of the “Risk of Embryo-Fetal Toxicity with TRYVIO” guide. The Health Outcomes and/or Surrogates of Health Outcomes metrics do not include adverse event reporting because these data will be captured by a Post-Marketing Requirement study. However, the Health Outcomes and/or Surrogates of Health Outcomes metrics include an estimation of the pregnancy rate, so that the pregnancy rate among Tryvio-exposed patients could potentially be compared to the age-matched general population to help inform understanding of how well the REMS is functioning to mitigate the risk of embryo-fetal toxicity by preventing exposure during pregnancy.

Reviewer’s Comments: *DMAMES previously reviewed and provided comments to the Applicant for the REMS Assessment Plan. The Applicant submitted on March 5, 2024, the revised proposed REMS*

Assessment Plan incorporating the Agency's comments. The revised REMS Assessment Plan is acceptable. If the NDA is approved, the Applicant will be asked in the approval letter to submit their survey methodologies and methodologies for qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with TRYVIO" for Agency review. These methodologies were not formally reviewed during the current review cycle.

7.1.9. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on February 9, 2024, to provide feedback on the content of the REMS materials. The OPDP review was completed by Tierra Butler on February 26, 2024.

OPDP recommended to align the language in the REMS materials with the final approved Prescribing Information (PI) and Medication Guide (MG) to accurately reflect the risk information and minimize promotional content. DRM incorporated these recommendations into the REMS materials. The OPDP recommendations that DRM is not in agreement with are summarized below.

In reference to the material, *Risk of Birth Defects with TRYVIO*:

OPDP comment: Page two of this REMS piece omits REMS related risk information concerning the role of a physician or gynecologist in counseling patients on acceptable birth control options while taking TRYVIO, as well as instructions on the appropriate way to change the form of birth control used. Specifically, the draft TRYVIO MG states:

- "Talk with your (b) (4) or gynecologist (a (b) (4) who specializes in female reproduction) to find out about options for acceptable birth control that you may use to prevent pregnancy during treatment with TRYVIO."
- "If you decide that you want to change the form of birth control that you use, talk with your (b) (4) or gynecologist to be sure that you choose another acceptable form of birth control."

Reviewer's Comments: *We do not agree with the OPDP's recommendation. The bottom of the material reads: "Please read the accompanying TRYVIO™ Medication Guide as it contains additional important safety information about your treatment. This information does not take the place of talking to your healthcare provider about your medical condition or treatment." DRM believes that directing patients to the Medication Guide and to their provider is adequate in this case. This material is meant to be a shortened version of the Patient Guide. By keeping the messages brief and avoiding redundancy across other materials (Patient Guide and Medication Guide), this material will be more effective at communicating the most important risk information. DRM also believes that this information will be covered when the health care provider counsels the patient.*

The HCA communicated DRM's stance on the inclusion of the recommended risk information via email to Tierra Butler on March 15, 2024.

7.2. Other Proposed Risk Management Activities

The Applicant proposed a worldwide descriptive study that collects prospective and retrospective data in women exposed to Tryvio during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

Postmarketing surveillance will also include enhanced pharmacovigilance for a period of 5 years with required submission of all serious cases of liver injury as 15-day alert reports and summary analyses provided in the periodic safety reports.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to the Division of Pediatric and Maternal Health, Division of Pharmacovigilance, and the Division of Hepatology and Nutrition for review and input.*

8. Discussion

Discussion of Need for a REMS

In the ongoing clinical review, the Clinical Reviewer recommends approval of Tryvio on the basis of the efficacy and safety information currently available. Tryvio was determined to be effective in lowering blood pressure when administered in combination with other antihypertensive medications in patients not adequately controlled on other therapies. In the PRECISION study population as a whole, the review team concluded the 25 mg dose of Tryvio did not provide greater efficacy than the 12.5 mg dose.

In general, the safety profile of Tryvio appears consistent with the ERA pharmacologic class. As noted earlier, all ERA products are approved with a REMS with ETASU for embryo-fetal toxicity; however there are uncertainties about the risk. Data regarding pregnancy outcomes in the first trimester exposure of ERAs are limited and the risk in humans remains unclear. The nonclinical data for Tryvio is supported in part by macitentan studies, which showed adverse effects on fertility and development of offspring at higher than recommended human doses. Being a major active metabolite of macitentan, Tryvio is considered to have contributed to the observed effects.

The review team carefully weighed the burden on stakeholders with the benefit-risk profile of Tryvio to determine the appropriate risk management strategy for embryo-fetal toxicity. DRM and DCN agreed that a REMS with ETASU, rather than the Applicant's proposed (b) (4) REMS, was necessary to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity associated with Tryvio. Given the lack of sufficient evidence to support that the embryo-fetal toxicity risk for Tryvio is different than macitentan or that it is not a risk for humans, the review team initially recommended a REMS consistent with the REMS required for the approved ERA products.

Tryvio was discussed at the REMS Oversight Committee (ROC)^g on May 16, 2023. At that time, OND and OSE proposed a REMS with ETASU which included a primary strategy to directly affect safe use behavior. The REMS would require prescriber, pharmacy, and patient enrollment, dispensing of Tryvio only with documentation of safe use conditions including documentation of pregnancy tests and patient counseling, and patient monitoring for pregnancy before treatment initiation and throughout the Tryvio treatment course.¹⁶ Patient enrollment is necessary to ensure patients are counseled and monitored prior to initiating and during treatment and Tryvio is only dispensed when safe conditions are met. Documentation that pregnancy testing occurred and patients are counseled is dependent on patient enrollment in the REMS. This REMS proposal aligned with the REMS for other ERA products which have strategies to directly affect behavior.

OND and OSE recognized that implementation of a REMS with documentation of safe use conditions including patient enrollment that is tied to dispensing may be challenging due to the potentially large treatment population compared to the smaller size of the treatment population for other ERAs (i.e. indicated for PAH or IgAN) and the associated potential burden on the healthcare system.¹⁷ The review team presented four different enrollment strategies discussed at the ROC meeting.

Table 2: DRM and DCN Proposed Patient Enrollment Strategies for Tryvio REMS

Strategy	Use in other ERA REMS	Advantage	Disadvantage
1 Enroll all female patients	Ambrisentan, Macitentan	- Approximately 50% of patients enroll - Used in other REMS	- May miss some patients who can become pregnant - Not gender neutral
2 Enroll all patients	Bosentan, Sparsentan	- Gender neutral - Ensures all patients are counseled - Ensures safe use conditions for at risk patients - Used in other REMS	- Increased burden for patients who cannot become pregnant - Increased burden on prescribers and pharmacies
3 Enroll patients who can become pregnant at the prescriber's discretion	None	- Gender neutral - Less burdensome for patients; estimated 4.5% of patients enroll	- May circumvent safe use conditions - Implementation challenges and stakeholder confusion - Increased burden on pharmacies
4 Enroll all patients under a certain age cut-off	None	- Gender neutral - Less burdensome for patients; estimated 14% of patients enroll	Unclear appropriate age cut-off

^g As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

	• Ensures safe use conditions for at risk patients	• Increased burden for patients who cannot become pregnant
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Two of the enrollment strategies are used in REMS for approved ERA products, which include enrolling all female patients or enrolling all patients. The other two were novel strategies to attempt to reduce burden on the healthcare system. DCN recommended Strategy 3 based on the prescriber enrolling only the patients they determined to be at risk of embryo-fetal toxicity.¹⁶ In the proposed strategy, the pharmacy would not verify patient enrollment, but patients who were enrolled would be required to take pregnancy tests upon treatment initiation and monthly during treatment. DRM expressed concerns with implementation of Strategy 3, including the ability of stakeholders to circumvent safe use conditions, the inability to assess REMS compliance, the possibility of mis-categorization of reproductive risk of patients as evidenced in other REMS, and the dilemma and burden for pharmacies that would need to confirm pregnancy testing completion for enrolled patients prior to dispensing without having all the information to determine if a patient should be enrolled in the REMS. DRM formulated and recommended a different novel strategy (Strategy 4) in which only patients under a certain age (i.e. patients most likely to have reproductive potential based on age) would be enrolled in the REMS.¹⁶ The proposed strategy would utilize gender neutral language while reducing the burden of patient enrollment in the REMS, maintain pharmacy verification of patient enrollment and monitoring, and otherwise align with other REMS for approved ERAs.

A second ROC meeting was held on May 31, 2023 to continue discussions about potential enrollment strategies for the proposed Tryvio REMS. Given DRM's concerns with Strategy 3, the discussion evolved to reconsider if a (b) (4) may be sufficient to educate prescribers about the risk as the Applicant originally proposed. DCN suggested that the care gap they were most concerned about was prescriber knowledge about the difference in the risk between Tryvio and other antihypertensives. However, there was still concern that a (b) (4) REMS may not be sufficient to mitigate the risk and could provide the impression the Agency was not applying a consistent approach to risk mitigation in the same drug class.¹⁶ At the conclusion of the second ROC discussion, the review team was tasked to provide rationale to support a (b) (4) REMS for Tryvio that includes a clear explanation as to why an ETASU REMS is not considered necessary for the ROC to consider.

DRM and DCN re-evaluated the risk mitigation approach for Tryvio taking into consideration the indication, available alternative treatment options, baseline stakeholder knowledge, and the medication use process. The team concluded a (b) (4) REMS would not be sufficient to ensure prescribers are knowledgeable about the risk of embryo-fetal toxicity associated with Tryvio.¹⁸ A (b) (4) would not ensure that healthcare providers received, read, or understood the risk messaging. Prescribers need to understand the difference in the embryo-fetal toxicity risk between Tryvio and other products for hypertension they may be more familiar with. Other than renin-angiotensin aldosterone system (RAAS) inhibitors, most antihypertensive therapies do not describe teratogenic risks in labeling or require particular risk mitigation for pregnancy. The RAAS inhibitors (ACEi and ARBs) are commonly used for the treatment of hypertension and are labeled for embryo-fetal toxicity when used in the second and third

trimester. For Tryvio, the risk of embryo-fetal toxicity occurs earlier in gestation, during the first trimester.

During the discussions, DRM and DCN also continued to consider the medication use process and increased burden on the REMS stakeholders associated with a proposed REMS that includes patient enrollment. DCN articulated that they do not believe documentation of pregnancy testing linked to dispensing is necessary to ensure safe use of Tryvio.¹⁸ DCN believes the at-risk population for Tryvio will be limited. Unlike PAH and IgAN, a number of well-known treatment alternatives without the risk of embryo-fetal toxicity are available to treat HTN. DCN expects that prescribers who understand the embryo-fetal toxicity risk with Tryvio will likely choose alternative therapies for patients who may become pregnant.¹⁸ DCN believes the target patient population will likely already be counseled and knowledgeable about embryo-fetal toxicity risk of other treatments they are on and note that current hypertension guidelines include recommendations for treatment during pregnancy and alternatives for patients planning to become pregnant.¹⁸ Therefore, DCN suggested that alternative risk mitigation strategies should be considered based on the underlying risk in the patient population expected to be prescribed Tryvio.¹⁸

DRM and DCN aligned on a REMS to directly affect knowledge. The REMS includes prescriber training and certification (ETASU A) to ensure that prescribers are informed of the risk of embryo-fetal toxicity associated with Tryvio and that it is different from the risk of embryo-fetal toxicity associated with other products that are used for treating hypertension. Prescribers will also be educated on the need to counsel patients who can become pregnant on the risk of embryo-fetal toxicity and the actions these patients are recommended to take to prevent fetal exposure and minimize exposure to a fetus during pregnancy. To further ensure prescribers are aware of the risk and risk mitigation strategies, the REMS requires prescribers to complete a knowledge assessment to be certified in the REMS. Pharmacy certification (ETASU B) is necessary to confirm that the prescriber is certified in the REMS prior to dispensing. Pharmacies will also dispense a patient-directed REMS material (*Risk of Birth Defects with Tryvio*) to all patients to further reinforce risk education and management for patients. The review team's revised recommendation for a REMS with ETASU A and B was communicated to the ROC via email and the ROC concurred that a REMS with ETASU A and ETASU B is necessary to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity.¹⁸

DRM and DCN recognize the limitations of this strategy that may not result in changes in behavior. This REMS is not designed to ensure safe use conditions, including that patients are counseled and are not pregnant prior to starting or continuing Tryvio, occur. The risk period for embryo-fetal toxicity associated with Tryvio is during the first trimester, often before patients know they are pregnant. Therefore, treatment with Tryvio should only occur after a pregnancy is ruled out (i.e. negative pregnancy test is confirmed). Pregnancy testing repeated monthly during treatment to detect a pregnancy could minimize exposure to a fetus and aligns with the clinical trial protocol which included monthly pregnancy testing for women of childbearing potential. DRM maintains that patient enrollment and documentation of counseling and monthly pregnancy testing linked to dispensing of Tryvio would likely have a more substantial impact on stakeholder behavior. Confirmation that patients are not pregnant prior to starting treatment and minimizing embryo-fetal exposure during Tryvio treatment can

be achieved by enrolling patients in the REMS, documenting negative pregnancy status on the patient enrollment form, and documentation of monthly pregnancy testing linked to dispensing. Other REMS for approved ERAs use similar strategies and have been found to be successful. This approach which has been used in other REMS for ERAs aligns with a primary prevention public health approach which aims to prevent an event from ever occurring. However, we recognized there is burden associated with patient enrollment, documentation of patient counseling and monitoring, and dispensing Tryvio only with documentation of safe use conditions.

Assessment of the REMS and Key Performance Indicator

A Key Performance Indicator (KPI) is a measure that is essential in determining if the REMS is functioning as designed and helps to assess whether the Tryvio REMS is achieving its goal of mitigating the risk of embryo-fetal toxicity. The Agency considered multiple potential KPIs including process oriented KPIs as well as outcome (knowledge) focused KPIs. Because the REMS uses a strategy to directly affect knowledge, DRM and DMAMES aligned on a KPI to evaluate prescribers' knowledge of the risk of embryo-fetal toxicity associated and the need to counsel patients which aligns with the REMS objective.

The KPI and threshold are defined as: The TRYVIO REMS will assess the percentage of prescribers who are knowledgeable about: 1.) The risk of embryo-fetal toxicity associated with TRYVIO. 2.) The need to counsel patients who can become pregnant. The knowledge performance threshold for Tryvio REMS KPI is the lower bound of the 95% confidence interval with the targeted knowledge rate of 80% or higher for each REMS key message domain.

Collectively, analysis of the REMS assessment plan data and the KPI will inform the assessment of how the Tryvio REMS is functioning. Operationally, the Tryvio REMS requires prescriber and pharmacy certification, and prescriptions must be authorized by the REMS prior to dispensing. The assessment plan will include metrics regarding the number of REMS Dispense Authorization requests that were not authorized because the prescriber is not certified as an indicator of the REMS functioning as designed. In addition, because the Tryvio REMS does not require patient enrollment or documentation of safe use behaviors such as pregnancy testing reported to the REMS, the Agency did not pursue pregnancy test result related KPIs. The assessment plan includes metrics related to the estimated pregnancy rate in the Tryvio-exposed population, but metrics related to pregnancy outcomes were not included because these data will be captured as part of a Post-Marketing Requirement study.

DRM concludes that based on the review of the proposed REMS received on March 15, 2024, the REMS will support actions that will mitigate the risk of embryo-fetal toxicity associated with Tryvio. The REMS will ensure that prescribers are trained on the risk and support safe use of the product. The expectation is that prescribers who understand the risk will choose alternative therapies for patients who may become pregnant, or if Tryvio will be used in patients who can become pregnant, the prescribers will appropriately counsel patients. The assessment plan includes an estimation of pregnancy rates and there is a planned pregnancy PMR that collects prospective and retrospective data in women exposed to Tryvio during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the

developing fetus and neonate, and adverse effects on the infant. Upon review of this data, we may re-evaluate the requirements of the Tryvio REMS in the future.

9. Conclusion & Recommendations

The risk of embryo-fetal toxicity associated with Tryvio is serious, and it is necessary for prescribers to understand this risk and how it differs from other antihypertensives, the importance of assessing pregnancy status before initiation and during treatment with Tryvio, and appropriate patient selection. Based on the magnitude and severity of the risk of embryo-fetal toxicity, we agree that requiring a REMS consisting of prescriber education and certification and pharmacy certification is necessary to ensure that the benefits outweigh the risk. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's proposed REMS received on March 15, 2024, to be acceptable and is appended to this review.

10. Appendices

10.1. Summary of FDA-approved Therapies for Resistant HTN

Table 3: Summary of Treatment Options Relevant to Proposed Indication of Resistant Hypertension¹¹

Class of Oral Antihyper-tensive agents	Products	Important Safety and Tolerability Issues	Embryo-Fetal Toxicity Risk Management Approaches/ Boxed Warning, Medication Guide
FDA Approved – Primary Agents			
Thiazide or thiazide-type diuretics	Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	- Hyponatremia, hypokalemia, uric acid, calcium levels - Caution with history of acute gout	Pregnancy Category B
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	Avoid in Pregnancy - Do not use in combination with ARBs or direct renin inhibitor - Hyperkalemia - Acute renal failure - Do not use if history of angioedema with ACE inhibitors	Boxed Warning: Avoid use in pregnancy

Table 3 (continued)

Class of Oral Antihyper-tensive agents	Products	Important Safety and Tolerability Issues	Embryo-Fetal Toxicity Risk Management Approaches/ Boxed Warning, Medication Guide
Angiotensin Receptor Blockers (ARB)	Azilartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telimsartan Valsartan	• Avoid in Pregnancy • Do not use in combination with ACEi or direct renin inhibitor • Hyperkalemia • Acute renal failure • Do not use if history of angioedema with ARBs	• Boxed Warning: Fetal toxicity
Calcium Channel Blockers (CCB) (dihydropyridines)	Amlodipine Felodipine Isradipine Nicardipine SR Nifedipine LA Nisoldipine	• Avoid use in HFrEF • Dose related pedal edema more common in women than men	• Pregnancy Category C
CCB (nondihydropyridines)	Diltiazem ER Verapamil IR Verapamil SR Verapamil-delayed onset ER	• Avoid routine use with beta blockers • Do not use in HFrEF • Drug interactions with diltiazem and verapamil	• Pregnancy Category C
FDA Approved – Secondary Agents			
Diuretics (loop)	Bumetanide Furosemide Torsemide	• Preferred diuretics in patients with symptomatic HF • Preferred over thiazides in patients with mild-to-severe chronic kidney disease (CKD)	• Pregnancy Category C
Diuretics (potassium sparing)	Amiloride Triamterene	• Monotherapy agents and minimally effective hypertensive agents • Avoid in patients with significant CKD	• Warnings and Precautions: teratogenic effects
Diuretics (aldosterone antagonists)	Eplerenone Spironolactone	• Preferred agents in primary aldosteronism and resistant hypertension • Spironolactone with greater risk of gynecomastia and impotence as compared with eplerenone • Avoid use with K+ supplements, other K+ sparing diuretics, or significant renal dysfunction	• Pregnancy discussed in Section 8, Use in Specific Populations
Beta blockers (cardioselective)	Atenolol Betaxolol Bisoprolol Metoprolol tartrate Metoprolol succinate	• Preferred in patients with bronchospastic airway disease requiring a beta blocker • Bisoprolol and metoprolol succinate are preferred in patients with HFrEF • Avoid abrupt cessation	• Pregnancy discussed in Section 8, Use in Specific Populations

Table 3 (continued)

Class of Oral Antihypertensive agents	Products	Important Safety and Tolerability Issues	Embryo-Fetal Toxicity Risk Management Approaches/ Boxed Warning, Medication Guide
Beta blockers (cardioselective and vasodilatory)	Nebivolol	- Nebivolol induces nitric oxide-induced vasodilation - Avoid abrupt cessation	- Pregnancy discussed in Section 8, Use in Specific Populations - Pregnancy Category C
Beta blockers (noncardioselective)	Nadolol Propranolol IR Propranolol LA	- Avoid in patients with reactive airways disease - Avoid abrupt cessation	Pregnancy Category C
Beta blockers (intrinsic sympathomimetic activity)	Acebutolol Penbutolol Pindolol	- Generally avoid, especially in patients with IHD or HF - Avoid abrupt cessation	Pregnancy Category B
Beta blockers (combined alpha- and beta-receptor)	Carvedilol Carvedilol phosphate Labetalol	- Carvedilol is preferred in patients with HFrEF - Avoid abrupt cessation	Pregnancy Category C
Direct renin inhibitor	Aliskiren	- Do not use in combination with ACE inhibitors or ARBs - Increased risk of hyperkalemia in CKD or in those on K⁺ supplements or K⁺-sparing drugs Avoid in pregnancy.	Boxed Warning: Fetal toxicity
Alpha-1 blockers	Doxazosin Prazosin Terazosin	Associated with orthostatic hypotension, especially in older adults	Pregnancy Category C
Central alpha2-agonist and other centrally acting drugs	Clonidine oral Methyldopa Guanfacine	- Generally reserved as last-line because of significant CNS adverse effects, especially in older adults - Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis	Pregnancy Category B
Direct vasodilators	Hydralazine Minoxidil	- Associated with sodium and water retention and reflex tachycardia; use with a diuretic and beta blocker - Hydralazine is associated with drug-induced lupus-like syndrome at higher doses - Minoxidil is associated with hirsutism and requires a loop diuretic. Minoxidil can induce pericardial effusion.	Pregnancy Category C

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; CVD, cardiovascular disease; ER, extended release; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; IR, immediate release; LA, long-acting; and SR, sustained release.

10.1. Tryvio REMS Assessment Plan^h

The REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

REMS Implementation and Operations:

1. REMS Website
 - a. Date REMS Website went live (first assessment report only)
 - b. Number of total visits and number of unique visits to the REMS Website
 - c. Number and type of REMS materials downloaded or printed for each material
 - d. Summary of outages or problems with the operation of the REMS Website

2. REMS Implementation (first assessment report only)
 - a. Date of first commercial availability of TRYVIO
 - b. Date of TRYVIO REMS launch
 - c. Date that each stakeholder (e.g., healthcare providers, pharmacies, wholesaler/distributors) could become certified/authorized
 - d. Date when the REMS Coordinating Center was established and fully operational

3. REMS Infrastructure and Performance
 - a. REMS Coordinating Center
 - i. Number of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacies, wholesaler/distributors, other)
 - ii. Summary of reasons for calls (e.g., authorization to dispense, enrollment question, location of a pharmacy) and by stakeholder type (e.g., healthcare providers, pharmacies, wholesaler/distributors, patients, authorized representative, other). Limit the summary to the top five reasons for calls by each stakeholder group.
 - iii. If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues, and how these issues were resolved
 - iv. Summary of frequently asked questions (FAQs) by stakeholder type

^h The REMS Assessment Plan submitted on March 5, 2023 available in EDR at:

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4. REMS Certification and Enrollment

a. Certified Pharmacies

- i. Number and percentage of newly certified pharmacies, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
- ii. Method of pharmacy certification (i.e., online, fax)
- iii. Total number of certified pharmacies at the end of the reporting period, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
- iv. Number and percentage of active certified pharmacies (i.e., have dispensed TRYVIO), stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)

b. Certified Healthcare Providers

- i. Number and percentage of newly certified healthcare providers, stratified by medical specialty (e.g., cardiology, internal medicine, etc.)
- ii. Method of healthcare provider certification (i.e., online, fax)
- iii. Total number of certified healthcare providers at the end of the reporting period
- iv. Number and percentage of active certified healthcare providers (i.e., have prescribed TRYVIO)

c. Authorized Wholesaler/Distributors

- i. Number of newly contracted wholesaler/distributors
- ii. Number of active (i.e., have shipped TRYVIO) wholesaler/distributors

5. REMS Utilization

- a. Number of tablets sent to certified prescribers, certified pharmacies, stratified by type of pharmacy

6. REMS Compliance

- a. Audits: Provide a report of audit findings for each stakeholder (i.e., certified inpatient pharmacies; certified outpatient pharmacies; authorized wholesalers/distributors) including but not limited to:
 - i. A copy of the audit plan for each stakeholder
 - ii. The number of audits expected, and the number of audits conducted
 - iii. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for group of audited stakeholders
 - iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
 - v. For any that did not complete the CAPA within the timeframe specified

- in the audit plan, describe actions taken
- vi. Confirm documentation of completion of training for relevant staff
- vii. Verify the existence of documented processes and procedures for complying with the REMS
- viii. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. Non-Compliance: Provide a summary of the non-compliance identified, including but not limited to:

- i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
- ii. The number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
 - 1. The unique identifier (ID(s)) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
 - 2. The source of the non-compliance data
 - 3. The results of the root cause analysis
 - 4. What action(s) were taken in response and whether any follow up is planned
- iii. Number and percentage of certified healthcare providers that were non-compliant with the REMS requirements
 - 1. Number of certified healthcare providers that had certification suspended or revoked. Include the reasons for the action.
- iv. Number and percentage of authorized wholesaler/distributors that were non-compliant with the REMS requirements
 - 1. Number of shipments sent to non-certified pharmacies. Include the source of the report, corrective actions taken to prevent future occurrences, and the outcome of such actions
- v. Number and percentage of certified pharmacies that were non-compliant with the REMS requirements, stratified by setting (e.g., inpatient, outpatient)
 - 1. Number of certified pharmacies that had certification suspended or revoked. Include the reasons for the action
- vi. Outpatient pharmacy-related REMS Dispense Authorizations (RDAs) compliance
 - 1. The number of RDAs issued
 - 2. The number of RDA requests that were not authorized because the prescriber is not certified
 - 3. Summary of RDA compliance issues (e.g., pharmacy did not request RDA, pharmacy dispensed without RDA, etc.) identified in audits, corrective actions, and resolution.

- vii. For certified inpatient and outpatient pharmacies that are audited: the number and percentage of patients who received the patient material, Risk of Birth Defects with TRYVIO, stratified by pharmacy type (inpatient, outpatient specialty, outpatient retail)
- viii. For all other non-compliance with the REMS requirements, provide source of non-compliance report, and the corrective action taken

Knowledge

7. Post-training Knowledge Assessment

- a. Number of healthcare providers who completed post-training knowledge assessment. Include method of completion and number of attempts needed to complete.
- b. Number of healthcare providers who did not pass the knowledge assessment.
- c. A summary of the most frequently missed questions.
- d. A summary of potential comprehension or perception issues identified with the knowledge assessment (first assessment report only)

8. Evaluation of Knowledge of the TRYVIO REMS and Risks of TRYVIO

- a. An evaluation of certified healthcare providers' knowledge, attitudes, and behaviors (to be conducted annually from the date of REMS approval) related to:
 - i. The risks of embryo-fetal toxicity associated with TRYVIO
 - ii. The need to counsel patients who can become pregnant about:
 - 1. The risks of embryo-fetal toxicity associated with TRYVIO
 - 2. The recommendation for pregnancy testing prior to initiating treatment, monthly during treatment, and for one month after discontinuing treatment
 - 3. The need for patients who can become pregnant to use acceptable contraception
- b. Qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with TRYVIO" (to be conducted once initially).

Health Outcomes and/or Surrogates of Health Outcomes

- 9. An estimation of the percent pregnancy rate per reporting period and cumulatively, reported as:
 - a. Percentage pregnancy rate, calculated as the number of pregnancies reported divided by the number of women of reproductive age who were exposed to TRYVIO
 - b. Pregnancy incidence rate (in person-years), calculated as the number of pregnancies reported divided by the amount of person-time that women of reproductive age were exposed to TRYVIO

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

10.2. REMS

- REMS Document
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Prescriber and Pharmacy Guide
- Prescriber Knowledge Assessment
- Patient Guide
- Risk of Birth Defects with TRYVIO
- REMS Website

10.3. References

¹ Soukehal, S. DCN. Meeting Preliminary Comments for Tryvio (aprocitentan) IND 122772, September 9, 2022.

² Soukehal, S. DCN. Meeting Preliminary Comments for Tryvio (aprocitentan) IND 122772, May 25, 2022.

³ Soukehal, S. DCN. Meeting Minutes for June 2, 2022 Teleconference for Tryvio (aprocitentan) IND 122772, July 1, 2022.

⁴ Soukehal, S. DCN. Filing Review Issues Identified for Tryvio (aprocitentan) NDA 217686, March 3, 2023.

⁵ Soukehal, S. DCN. REMS Information Request for Tryvio (aprocitentan) NDA 217686, September 22, 2023 (in DARRTs September 27, 2023).

⁶ Soukehal, S. DCN. Review Extension – Major Amendment Letter for Tryvio (aprocitentan) NDA 217686, September 24, 2023.

⁷ Lambert, C. DRM. Interim Comments on the Proposed Tryvio (NDA 217686) REMS, November 3, 2023.

⁸ Lambert, C. DRM. Interim Comments on the Proposed Tryvio (NDA 217686) REMS, January 18, 2024.

⁹ Soukehal, S. DCN. REMS Information Request (email) for Tryvio (aprocitentan) NDA 217686, February 9, 2024.

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- ¹⁰ Lambert, C. DRM. Interim Comments on the Proposed Tryvio (NDA 217686) REMS, February 27, 2024.
- ¹¹ ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-e248
- ¹² Carey RM et al. Hypertension. 2019;73(3):424-431.
- ¹³ Division of Cardiology and Nephrology (DCN). Draft Integrated Review for Tryvio (aprocitentan) BLA 217686. February 22, 2024.
- ¹⁴ Division of Cardiology and Nephrology (DCN). Integrated Review for Tryvio (aprocitentan) BLA 217686. March 15, 2024.
- ¹⁵ Idorsia. Risk Evaluation and Mitigation Strategy Justification Document for aprocitentan NDA 217686, December 19, 2022.
- ¹⁶ Minutes from the May 16 and May 31, 2023 Tryvio (aprocitentan) REMS Oversight Committee (ROC) Meeting.
- ¹⁷ Tryvio REMS, REMS Oversight Committee (ROC) Meeting Executive Summary Document May 16, 2023.
- ¹⁸ REMS Oversight Committee (ROC) Updates on the Tryvio (NDA 217686) REMS via email July 20, 2023.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217686
PDUFA Goal Date	March 19, 2024
Nexus TTT#	2022-3102 and 2022-3104
Reviewer Names	Cristen Lambert, PharmD Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Laura Zendel, PharmD
Review Completion Date	March 8, 2024
Subject	Interim Review of proposed REMS
Established Name	aprocitentan
Trade Name	Tryvio
Name of Applicant	Idorsia Pharmaceuticals Ltd
Therapeutic Class	Endothelin Receptor Antagonist (ERA)
Formulation(s)	12.5 mg (b) (4) oral tablets
Dosing Regimen	12.5 mg orally once daily (b) (4)

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Tryvio (aprocitentan), New Drug Application (NDA) 217686 submitted by Idorsia on December 19, 2022 and amended on September 6, 2023, November 16, 2023, November 28, 2023, February 2, 2024, and March 5, 2024.

Tryvio is an endothelin receptor antagonist (ERA) proposed for the treatment of hypertension (HTN), to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity.

This interim review discusses DRM's comments on the amendment to the proposed REMS submitted in response to the Agency's February 27, 2024 information request¹ to:

1. Revise REMS requirements
2. Revise REMS materials to align with the revised REMS Requirements and proposed label
3. Incorporate all Key Risk Messages (KRM) into the REMS materials
4. Reinstate the REMS as the pregnancy reporting contact
5. Revise the REMS audit language and Assessment Plan

The Applicant's REMS proposal is not acceptable as further edits are needed to align the REMS materials with the proposed Tryvio label and medication guide.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 2/27/2024: Agency sent Interim Comments (IC) to the Applicant in response to their REMS amendment, dated February 2, 2024 and REMS correspondence dated February 13, 2024.
- 3/5/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated February 27, 2024.

3. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on March 5, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comment

- Additional proposed changes to the REMS requirements may result in delay of approval of your proposed REMS since we are in proximity of the PDUFA date. Redlined REMS materials are attached. Please see the edits for content and clarity. Please address all edits and comments from the Agency in your redlined materials and cover letter if necessary.

REMS Supporting Document

- Align the REMS Supporting Document to the revisions in the REMS materials.

Prescriber and Pharmacy Guide

- Revise statements on page one to specify that TRYVIO can cause embryo-fetal toxicity to align with the proposed Tryvio label.
- Revise the second bullet point of the Important Information box on page two to clarify reminding patients about pregnancy testing “monthly” during treatment to align with the proposed Tryvio label.
- Ensure page numbers are accurate.
- See the redlined material for details on these edits.

Patient Guide

- Move the chart for birth control options up to be directly underneath the section that starts with “If you are a patient who can become pregnant, you should:”
- See the redlined material for details on these edits.

Prescriber Knowledge Assessment

- Revise Question 6, Answer choice B to align with the proposed Tryvio medication guide and clarify that patients who can become pregnant should report not only a missing, but also a delayed menstrual period to their doctor.
- See the redlined material for details on this edit.

Risk of Birth Defects with TRYVIO

- Revise page one to read “TRYVIO can cause serious birth defects if taken during pregnancy” to align with the proposed Tryvio medication guide.
- Revise the last section of the table on page one to read “You should continue to use acceptable birth control and get a pregnancy test one month after stopping treatment with TRYVIO because the medicine may still be in your body.” to clarify and align with the proposed Tryvio medication guide.
- Add the following statement to page two above the chart of birth control options: “Choose one option below for birth control.” to clarify and align with the Prescriber and Pharmacy Guide.
- See the redlined material for details on these edits.

REMS Website

- Align the REMS Website to the revisions in the REMS materials and all attestations.
- Confirm hyperlinks on the REMS website direct users to the Medication Guide or Prescribing Information (b) (4).
- Ensure the REMS email address is inserted in all placeholders for email contact information on the REMS website (e.g. bottom of page 12)

Submit a REMS amendment that includes the following revised REMS materials by close of business March 13, 2024. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. **Revisions to REMS materials in addition to those requested in these comments may impact the review timeline for the REMS.** Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment Form	PDF version
4	Outpatient Pharmacy Enrollment Form	PDF version
5	Inpatient Pharmacy Enrollment Form	PDF version
6	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF version
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
9	Risk of Birth Defects with TRYVIO	Tracked MS Word, Clean MS Word, PDF version
10	REMS Website	Tracked MS Word, Clean MS Word, PDF version
11	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	PDF Version

4. Appendix

1. Prescriber and Pharmacy Guide
2. Prescriber Knowledge Assessment
3. Patient Guide
4. Risk of Birth Defects with TRYVIO

5. References

¹ Soukehal, S. DCN. Information Request for NDA 217686, February 27, 2024.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
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Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217686
PDUFA Goal Date	March 19, 2024
Nexus TTT#	2022-3102 and 2022-3104
Reviewer Names	Cristen Lambert, PharmD Katherine Hyatt Hawkins Shaw, PhD Page Crew, PharmD, MPH, BCPS (DMAMES)
Team Leader	Yasmeen Abou-Sayed, PharmD CDR Zachary Oleszczuk, PharmD, MSPH, BCGP (DMAMES)
DMAMES Division Director	Sevan Kolejian, PharmD, MBA, BCPPS
Deputy Division Director	Laura Zendel, PharmD
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Dosing Regimen	12.5 mg orally once daily

(b) (4)

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Tryvio (aprocitentan), New Drug Application (NDA) 217686 submitted by Idorsia on December 19, 2022 and amended on September 6, 2023, November 16, 2023, November 28, 2023, and February 2, 2024.

DRM collaborated with the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) to revise the Applicant's proposed REMS evaluation plan.

Tryvio is an endothelin receptor antagonist (ERA) proposed for the treatment of hypertension (HTN), to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity.

This interim review discusses DRM's comments on the amendment to the proposed REMS submitted in response to the Agency's January 19, 2024 information request¹ to:

1. Revise REMS requirements
2. Revise REMS materials to align with the revised REMS Requirements
3. Propose Key Risk Messages (KRMs) to incorporate into the REMS materials
4. Propose a Key Performance Indicator (KPI) and target threshold
5. Revise the REMS Assessment Plan

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 9/6/2023: Applicant submitted a REMS with ETASU for the risk of embryo-fetal toxicity which constitutes a major amendment
- 1/19/2024: Agency sent interim comments (ICs) to the Applicant in response to their REMS amendment, dated November 16 and November 28, 2023.
- 2/2/2024: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated January 19, 2024.
- 2/9/2024: Agency requested information on rationale for changing the pregnancy reporting contact from the REMS Coordinating Center to (b) (4).
- 2/13/24: Applicant responded to Agency request for information sent February 9, 2024, proposing to reinstate the REMS Coordinating Center as the contact for pregnancy reporting.

3. Review of Applicant's Proposed REMS

3.1. REMS Requirements

3.1.1. REMS Participant Requirements

3.1.1.1. Healthcare Provider

Prescriber Knowledge Assessment

In response to DRM's January 19, 2024 comments, Idorsia proposed revisions to the content and format of the *Prescriber Knowledge Assessment* Questions. Three true/false questions assess prescriber knowledge on prescriber requirements in the REMS. Two true/false questions assess prescriber knowledge on actions a patient should take if they suspect they are pregnant and actions a patient should take to monitor for pregnancy after treatment ends. One multiple choice question assesses prescriber knowledge on Tryvio indication, risk of embryo-fetal toxicity associated with Tryvio, and contraindications. Another multiple choice question assesses prescriber knowledge on when, during pregnancy, the risk of embryo-fetal toxicity could occur. The last multiple choice question assesses prescriber knowledge of the information to include when prescribers counsel patients who can become pregnant.

Reviewer Comment: *The Prescriber Knowledge Assessment requires revisions to be acceptable. Idorsia must provide the intended answers to the questions to assess whether the true/false questions are worded appropriately. Idorsia will be advised to submit an Answer Key within the Supporting Document. Question 6 must be revised to align with the REMS requirements for prescribers. If the answers to questions 7 and 8 are "True", then the questions must align with the REMS requirements for prescribers and utilize the word "must" in the questions. The redlined Prescriber Knowledge Assessment contains details on these edits. With these revisions, the proposed Prescriber Knowledge Assessment is expected to accurately assess that the KRMs for prescribers were communicated.*

Patient Guide

In response to DRM's January 19, 2024 comments, Idorsia proposed to rename the (b) (4) to the *Patient Guide*. Idorsia revised the material to improve usability and readability. In response to DRM's comments Idorsia also added a chart which clearly communicates (b) (4) contraception options to patients who can become pregnant. Idorsia proposed to include the proposed KRMs for patients within the content of the *Patient Guide* by describing the risk of birth defects associated with Tryvio and by including the reliable contraceptives chart. In the *Patient Guide* Idorsia proposed if the patient can become pregnant, they should confirm they are not pregnant by taking a pregnancy test before treatment begins, monthly during treatment, and for one month after treatment.

Reviewer Comment: *We agree with the proposed title revision and revisions to improve useability and readability. Additional revisions to the Patient Guide are needed to be acceptable. The guide should be revised to include the definitions of patients who can and who cannot become pregnant and the definition of menopause that are aligned with the definitions included in the Pharmacy and Prescriber Guide. We provided revisions using plain language definitions in the redlined Patient Guide. The section directed to patients who can become pregnant regarding recommendations to prevent pregnancy while on Tryvio treatment should be reorganized to clearly convey important information to patients. The Patient Guide should be contained to two pages for improved utility of the material. The redlined "Patient Guide" contains details on these edits.*

3.1.1.2. Patients

Risk of Birth Defects with TRYVIO

In response to DRM's January 19, 2024 comments, Idorsia revised the name of the *Patient Information Sheet* material to *Risk of Birth Defects with TRYVIO*. Idorsia changed the font color of the main text from

(b) (4) to black, simplified some of the statements within the number sections of the material, and included a table which communicates reliable birth control options.

Reviewer Comment: Additional revisions are required for the Risk of Birth Defects with TRYVIO to be acceptable. The material should be reformatted to move the risk information to the top and highlight it in a box for emphasis. The definition of a patient who can become pregnant should be revised to align with the definition used in the Patient Guide. The KRMs for patients should be reformatted into a table which succinctly explains what a patient who can become pregnant should do before starting Tryvio, during treatment, and one month after treatment. The redlined “Risk of Birth Defects with TRYVIO” contains details on these edits.

3.1.1.3. Pharmacy/Prescriber/Healthcare Setting that Dispenses

Idorsia generally responded appropriately to DRM’s January 19, 2024 comments regarding requirements for pharmacies and prescribers that dispense and respective enrollment forms.

Reviewer Comment: The inpatient and outpatient pharmacy enrollment forms require additional changes to align the attestations with the requirements as described in the REMS document. Idorsia should also clarify the requirements in the REMS document for prescribers who dispense to state they do not need to obtain authorization from the REMS prior to dispensing. See discussion section for additional details.

3.1.2. REMS Applicant Requirements

3.1.2.1. Training

Prescriber and Pharmacy Guide

In response to DRM’s January 19, 2024 comments, Idorsia reformatted and revised the *Prescriber and Pharmacy Guide* to align with the updated REMS requirements and to remove information on (b) (4), revised the patient definitions, included a table for birth control options, and communicated several of the KRMs to prescribers. The KRMs in the proposed material include embryo-fetal toxicity can occur in patients taking Tryvio, prescribers must counsel patients who can become pregnant on recommendations for pregnancy testing monthly during treatment and for one month after treatment, and prescribers should instruct patients who can become pregnant to use (b) (4) contraception. In response to DRM’s January 19, 2024 comments, Idorsia revised the definitions of patient categories relevant to the REMS to not include the term “(b) (4)”. Also in response to DRM’s January 19, 2024 comments, Idorsia revised the prescriber and pharmacy requirements sections to include steps for each stakeholder in the REMS

Reviewer Comment: We agree with Idorsia’s proposed revisions; however further revisions are required. The *Prescriber and Pharmacy Guide* should be revised to align with the updated REMS requirements. The material should also be revised to include the proposed KRM related to the recommendation that prescribers should confirm that patients who can become pregnant are not pregnant before initiating treatment. The guide should encourage prescribers to continue to check-in with patients regularly during treatment. We agree with Idorsia’s revisions of definitions of patient categories used in the *Prescriber and Pharmacy Guide*. The definitions of patient categories in the *Patient Guide* and the *Risk of Birth Defects with Tryvio* require revisions to align with those in the *Prescriber and Pharmacy Guide* to be acceptable. The *Prescriber and Pharmacy Guide* should also recommend “acceptable contraception”

rather than “(b) (4)” to align with the Tryvio label and the revisions to the KRM in this review. The redlined Prescriber and Pharmacy Guide includes more detail on these changes.

3.1.2.2. Operations

In response to DRM’s January 19, 2024 comments, Idorsia proposed that a REMS Dispense Authorization (RDA) to dispense each prescription is required for outpatient pharmacies and must be obtained by contacting the REMS. Idorsia proposed that inpatient pharmacies are not required to obtain an RDA to dispense, but must establish processes and procedures to verify the prescriber is certified or the patient is under the supervision and care of a certified prescriber. Inpatient pharmacies may contact the REMS for an RDA to satisfy their REMS requirements for dispensing. Also, in response to DRM’s January 19, 2024 comments, Idorsia proposed the REMS Website be fully operational and all REMS materials available at the time Tryvio first becomes commercially available. Idorsia independently proposed prescribers and pharmacies report pregnancies to (b) (4) by phone (b) (4) instead of the previous contact which was proposed as the REMS Coordinating Center (Phone: 1-866-429-8964; Fax: 1-800-465-0391). In response to DRM’s Information Request sent on February 9, 2024 regarding rationale for the change in the pregnancy reporting contact, on February 13, 2024, Idorsia proposed to reinstate the REMS Coordinating Center phone number for pregnancy reporting. Idorsia proposed the REMS Coordinating Center as the pregnancy contact to align with the pregnancy reporting contact for the proposed pregnancy surveillance program, to reduce burden on healthcare providers by providing a single phone number for REMS questions, enrollment, and pregnancy reporting, and to streamline reporting of pregnancies.

Reviewer Comment: We agree with Idorsia’s proposal that outpatient pharmacies are required to obtain an RDA to dispense prescriptions and we agree that inpatient pharmacies are not required to obtain an RDA to dispense. We agree with Idorsia’s proposal for the timeline of the availability of the fully operational REMS Website and REMS materials. We require further revisions to REMS operations to be acceptable. To support the REMS Operations, Idorsia must ensure prescribers are able to report dispensing Tryvio. Idorsia should clarify how prescribers are able to report dispensing Tryvio (i.e. by fax and online or online only or by phone only, etc). Idorsia must ensure outpatient pharmacies are able to obtain authorization to dispense by phone and online. Idorsia must ensure that prescribers and pharmacies are able to report pregnancies and Idorsia should clarify how prescribers and pharmacies are able to report pregnancies (i.e. by phone only or by phone and online). The redlined REMS Document contains more details on these edits. We agree with Idorsia’s proposal to reinstate the REMS Coordinating Center as the pregnancy reporting contact.

Tryvio REMS Website

In response to DRM’s January 19, 2024 comments, Idorsia revised the website to reflect all the proposed revisions made within the REMS Document, updated all the proposed REMS materials, and clearly labeled which web pages are available only after login. Idorsia clarified their proposal for how prescribers and authorized representatives for pharmacies can login to the website to complete certification without requiring the creation of a password. Idorsia also revised the proposed description of an RDA on the website.

Reviewer Comment: We agree with Idorsia’s proposed revisions to the website. Website pages that are only available after login may be removed from the website screenshots and made available in the Supporting Document. The website should be updated to reflect all revisions made within the REMS Document and all materials.

3.1.2.3. Compliance

The Applicant proposed the following audit requirements for certified pharmacies and authorized wholesaler/distributors in their submission dated February 2, 2024:

4.

5.

(b) (4)

The Applicant accepted the recommended annual audit language, but proposed changes to the initial audit requirement for pharmacies, to include outpatient specialty pharmacies only. The Applicant noted that “Regarding auditing of pharmacies, Idorsia plans to (b) (4) distribute TRYVIO via outpatient specialty pharmacies and commits to audit all certified outpatient specialty pharmacies within 180 days after their first shipment receipt of TRYVIO. (b) (4) outpatient retail and inpatient pharmacies, we propose to audit a sample percentage of outpatient and inpatient pharmacies via annual auditing per the audit plan. Given the large potential number of outpatient retail and inpatient pharmacy sites, it is impractical to audit all pharmacies within 180 days after their first shipment of TRYVIO.”

Reviewer Comment:

- *The audit requirement for wholesaler/distributors is acceptable.*
- *The audit requirement for certified pharmacies requires revision.*
 - (b) (4) *should be removed from the annual audit requirement language in the REMS document.*
 - *Given the anticipated open distribution among outpatient specialty pharmacies, outpatient retail pharmacies, and inpatient pharmacies, all outpatient specialty pharmacies, a representative sample of certified outpatient retail pharmacies (10% or at least 10, whichever is greater yet not to exceed 100), and a representative sample of certified inpatient pharmacies (10% or at least 10, whichever is greater yet not to exceed 100) will be audited initially within 180 days of Tryvio shipment receipt. A representative sample (10% or at least 10, whichever is greater yet not to exceed 100) of certified outpatient specialty pharmacies, outpatient retail pharmacies, and inpatient pharmacies will be audited annually.*

3.1.3. Key Risk Messages (KRM) for REMS

In response to DRM’s January 19, 2024 comments, Idorsia submitted KRMs within the Supporting Document as follows:

- For healthcare providers:
 - Embryo-fetal toxicity can occur in patients taking Tryvio. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
 - Counsel patients who can become pregnant on the recommendation for pregnancy testing prior to initiating treatment, monthly during treatment, and

for one month after discontinuing treatment. Instruct patients who can become pregnant to use (b) (4) contraception.

- For patients:
 - There is a risk of birth defects (embryo-fetal toxicity)
 - If you are a patient who can become pregnant:
 - Confirm that you are not pregnant by taking a pregnancy test before starting Tryvio, monthly during treatment, and for one month after discontinuing treatment.
 - Use (b) (4) contraceptives and avoid pregnancy

Reviewer Comment:

We agree with the proposed KRMs and with Idorsia's clarification that prescribers counsel patients on the recommendation, not the "need," for pregnancy testing. We also agree with Idorsia's clarification that pregnancy testing recommendations are for patients who can become pregnant to take a pregnancy test prior to starting treatment, monthly during treatment, and for one month after discontinuing treatment. To align with the Tryvio label, "acceptable" contraception should be used instead of "(b) (4)" or "(b) (4)" when describing birth control options in the REMS.

We determined that surveys will be used to evaluate the healthcare providers' understanding of risks associated with, and safe use of, Tryvio to assess the REMS knowledge goal. The survey's objective would be relating to assessing the REMS goal and objective and may cover several related KRMs for REMS. The Applicant will need to develop survey specific key risk messages based on the REMS goals and objectives and other relevant REMS materials. The Applicant will be recommended in the approval letter to submit a well-designed survey(s) methodology that informs the REMS evaluation for Agency's review. Qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with TRYVIO" will also be conducted once initially.

4. Supporting Document

The REMS Supporting Document includes the background of the REMS currently under review. In response to DRM's January 19, 2024 comments, Idorsia described the proposed REMS Dispense Authorization (RDA) process.

Reviewer Comment: *We agree with the description of the RDA and find the mechanism acceptable. The REMS Supporting Document must be revised to align with the revised REMS Document, operations, and requirements as discussed in this review.*

Key Performance Indicators (KPI)

In response to DRM's January 19, 2024 comments, Idorsia proposed KPI within the Supporting Document as follows:

The TRYVIO REMS will assess the percentage of prescribers who are knowledgeable about:

1. The risk of embryo-fetal toxicity associated with Tryvio.
2. The need to counsel patients who can become pregnant.

The targeted threshold for this KPI is 80%.

Reviewer Comment: *We agree with the proposed KPI since it aligns with the REMS goal and objective. The KPI is expected to reflect measurable outcomes so we may determine if the REMS is functioning as designed to achieve the goal of mitigating the risk of embryo-fetal toxicity associated with Tryvio.*

The knowledge performance threshold for this KPI is the lower bound of the 95% confidence interval with the targeted knowledge rate of 80% or higher for each REMS key message domain.

4.1. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be addressed in the REMS Approval letter. The Applicant submitted a revised REMS Supporting Document containing the REMS Assessment Plan, on February 2, 2024^a.

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the revised REMS Assessment Plan. The Applicant accepted the Agency's changes and then proposed several additional changes, which are summarized below:

- Edits to metric 4.c.i to change the word (b) (4) to contracted when referring to wholesaler/distributors
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

Reviewer Comments:

- The Applicant's proposal to (b) (4) is not acceptable. DMAMES will propose revised metrics to the Applicant. See Section 7 below, Comments to the Applicant, for details.
- Metric 8.a.ii (b) (4) will be removed because it does not inform the goal.
- The edits to metric 8.a to align with the REMS Document are acceptable.
- Metric 8b will be revised to remove the requirement for (b) (4) would not inform the REMS

^a Submission is available in EDR at: <\\CDSESUB1\evsprod\NDA217686\0045\m1>

goal, and since the design of the REMS focuses on prescriber knowledge of the risk and (b) (4)

- Metrics 9.a and 9.b will be (b) (4).
- In Section 7 below, Comments to the Applicant, DMAMES provides comments regarding the REMS Assessment Plan. The comments include requests for changes to the utilization metrics, compliance metrics, and knowledge surveys.

5. Discussion

The Applicant's proposed REMS Goal and Objective were previously aligned with the principles of the REMS Logic Model and Public Health Prevention Aims^{2,3}. The Applicant proposed REMS Goal and Objective now also align with a primary KPI and goal knowledge threshold (80%). The Applicant proposed KRMs for prescribers and patients are acceptable, but further revisions to REMS materials are required to ensure the KRMs are conveyed in all the applicable REMS materials.

DRM's January 19, 2024, comments directed the Applicant to align requirements between outpatient and inpatient pharmacies such that pregnancies are reported to the REMS and to remove the requirement for outpatient pharmacies to (b) (4). In their February 2, 2024 submission, the Applicant proposed for prescribers and pharmacies to report pregnancies to a singular contact as DRM directed; however, the Applicant changed the contact from the REMS to (b) (4). The Review Team discussed the Applicant's proposal to change the contact for reporting pregnancies from the REMS to (b) (4) and requested the Applicant's rationale for the change in pregnancy reporting contact to decide whether this change was acceptable. In their response to the Agency's request for information⁴, the Applicant proposed to reinstate the REMS Coordinating Center phone as the pregnancy reporting contact since it aligns with the proposed pregnancy surveillance program and is expected to ease burden on healthcare providers by providing a single contact for REMS questions, enrollment, and pregnancy reporting. The Review Team was informed via email of the proposed reinstatement of the REMS Coordinating Center for pregnancy reporting and agreed the REMS as a pregnancy reporting contact is acceptable.

The Applicant and the Agency are aligned with the proposed REMS that requires outpatient pharmacies to contact the REMS to obtain authorization to dispense each prescription whereas inpatient pharmacies must verify the prescriber is certified or the patient is under the supervision and care of a prescriber, but are not required to obtain authorization to dispense. The proposed REMS does not require prescribers that dispense samples to obtain authorization prior to dispensing. Wholesalers-distributors only distribute Tryvio to certified prescribers who complete the additional section of the prescriber enrollment form, so non-certified prescribers are not expected to have access to the product to dispense.

Revisions to the proposed Tryvio REMS are required to be acceptable. The REMS Document requires administrative revisions as well as revisions to align with the further revised REMS requirements and audit language. The enrollment forms require revisions to the attestation section to be acceptable. The *Prescriber and Pharmacy Guide*, *Patient Guide*, and *Risk of Birth Defects with Tryvio*, and must be revised to convey all KRMs, improve useability and readability, and include acceptable patient definitions.

The REMS Assessment Plan requires revisions to clarify utilization metrics, compliance metrics, and to remove knowledge metrics for (b) (4).

6. Conclusions and Recommendations

DRM does not find the proposed REMS for Tryvio (aprocitentan) as submitted on December 19, 2022 and last amended on February 2, 2024, to be acceptable, as described in this review. Send the comments in Section 7 to Idorsia in an Information Request and instruct the Applicant to submit a REMS amendment within 5 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on February 2, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comment

- Additional proposed changes to the REMS requirements may result in delay of approval of your proposed REMS since we are in proximity of the PDUFA date. A redlined REMS Document is attached. Redlined REMS materials are also attached. Please see the edits for content and clarity. Please address all edits and comments from the Agency in your redlined materials and cover letter if necessary.
- Revise Key Risk Messages (KRMs) for REMS within your REMS Supporting Document and throughout REMS materials to use “acceptable contraception” rather than “(b) (4)” or “(b) (4)” contraception to align with the proposed Tryvio label.
 - For healthcare providers:
 - Embryo-fetal toxicity can occur in patients taking Tryvio. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
 - Counsel patients who can become pregnant on the recommendation for pregnancy testing prior to initiating treatment, monthly during treatment, and for one month after discontinuing treatment. Instruct patients who can become pregnant to use acceptable contraception.
 - For patients:
 - There is a risk of birth defects (embryo-fetal toxicity)
 - If you are a patient who can become pregnant:
 - Confirm that you are not pregnant by taking a pregnancy test before starting Tryvio, monthly during treatment, and for one month after discontinuing treatment.
 - Use acceptable contraceptives and avoid pregnancy
- Revise the REMS Document, Supporting Document, and applicable REMS materials to reinstate the REMS as the contact for pregnancy reporting as proposed in your correspondence on February 13, 2024.
- Submit the email address for the REMS Coordinating Center and include in all applicable materials.
- Key Performance Indicator: The knowledge performance threshold for Tryvio REMS KPI is the lower bound of the 95% confidence interval with the targeted knowledge rate of 80% or higher for each REMS key message domain.

REMS Document

- REMS Administrative Information

- Revise “Section VI. Statutory Elements” to remove the (b) (4) as an element of the Tryvio REMS.
- The full regulatory authority under which this REMS is required must be added to the REMS Document as indicated in the redline REMS Document.
- Incorporate “Idorsia Pharmaceuticals Ltd” throughout the document.
- REMS Requirements
 - Add the requirement that healthcare providers who prescribe Tryvio must provide a copy of the *Patient Guide* to patients who can become pregnant.
 - Clarify that only outpatient pharmacies (not prescribers that dispense samples) must obtain authorization to dispense each prescription.
 - In section III. REMS Requirements for patients, clarify that prescriber counseling of patients who can become pregnant includes pregnancy testing recommendations before treatment initiation, monthly during treatment, and one month after discontinuing treatment.
 - To support REMS operations, ensure prescribers are able to report dispensing Tryvio and clarify how prescribers are able to report dispensing (i.e. by fax and online, by phone only, etc.).
 - To support REMS operations, ensure outpatient pharmacies are able to obtain authorization to dispense and how pharmacies may obtain authorization (i.e. by phone and online, by phone only, etc).
 - To support REMS operations, ensure prescribers and pharmacies are able to report pregnancies by phone.
 - Incorporate these changes through all REMS materials.
- The audit language in the REMS Document should be revised to include the following:

18. Audit all certified outpatient specialty pharmacies, a representative sample of certified outpatient retail pharmacies (10% or at least 10, whichever is greater yet not to exceed 100), and a representative sample of certified inpatient pharmacies (10% or at least 10, whichever is greater yet not to exceed 100) within 180 days after their first shipment receipt of TRYVIO to ensure that all the REMS processes and procedures are in place, functioning, and support the REMS requirements. Audit a representative sample (10% or at least 10, whichever is greater yet not to exceed 100) of each annually: certified outpatient specialty pharmacies, outpatient retail pharmacies, and inpatient pharmacies, to ensure that all the REMS processes and procedures are in place, functioning, and support the REMS requirements.

19. Audit all wholesaler-distributors within 180 days after they become authorized and audit all wholesaler-distributors annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

REMS Supporting Document

- Align the REMS Supporting Document to the revisions in the REMS requirements and REMS Document.
- Revise the wording of section 3.1.2. to the following, in order to remove the concept that (b) (4) :

3.1.2. Tryvio prescribers must counsel patients who can become pregnant

Prescribers of Tryvio must assess the reproductive status of patients and counsel patients who can become pregnant using the Patient Guide.

REMS Assessment Plan

We have the following comments regarding the Tryvio REMS Assessment Plan included in the REMS Supporting Document. The Agency requires further revisions to the REMS Assessment Plan to inform REMS evaluation. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in strikethrough.

- Edits throughout the document to align non-compliance with hyphen for consistency, and to align numbering.
- Metric 5 REMS utilization should be revised to include the number of tablets sent to certified prescribers, certified pharmacies, stratified by type of pharmacy.
- Metric 6.b.iv. pharmacy-related compliance metrics should be revised to include outpatient pharmacy-related REMS Dispense Authorization (RDAs) compliance metrics (the number of RDAs issued; the number of REMS dispense requests that were not authorized because the prescriber is not certified; summary of RDA compliance issues (e.g., pharmacy did not request RDA, pharmacy dispensed without RDA, etc.) identified in audits, corrective actions, and resolution). We also added a metric to capture the number and percentage of patients who received the patient material, Risk of Birth Defects with TRYVIO, stratified by pharmacy type (inpatient, outpatient specialty, outpatient retail), only for certified pharmacies that are audited.
- Metric 8.a.ii ((b) (4)) was removed since it does not inform the goal.
- Metric 8.a.iii.3 was edited to replace (b) (4) with acceptable (i.e., the need for patients who can become pregnant to use acceptable contraception)
- Metric 8.b. (b) (4) has been removed (b) (4)
- Metrics 9a. and 9.b were removed (b) (4)

Prescriber Enrollment Form

- Revise the wording of the Prescriber agreement statement.
- For all prescribers, before treatment initiation, include the requirement to provide a copy of the *Patient Guide* to the patient.
- For prescribers who dispense TRYVIO samples, include requirements to the agreement section regarding training relevant staff involved in dispensing on the REMS, establishing processes and procedures for providing the *Risk of Birth Defects with TRYVIO* to each patient, and providing the patient with the *Risk of Birth Defects with Tryvio* with each dispense.
- See edits in the redlined *Prescriber Enrollment Form* for details regarding these changes.

Outpatient Pharmacy Enrollment Form

- Add an “outpatient pharmacy type” selection section to capture whether the pharmacy is retail or specialty which is necessary for audits.
- Revise the wording of the outpatient pharmacy authorized representative agreement statement and section titles to attest from the point of view of the authorized representative. See edits in the redlined *Outpatient Pharmacy Enrollment Form* for details regarding these changes.

Inpatient Pharmacy Enrollment Form

- Revise the wording of the inpatient pharmacy authorized representative agreement statement and section titles to attest from the point of view of the authorized representative. See edits in the redlined *Inpatient Pharmacy Enrollment Form* for details regarding these changes.

Prescriber and Pharmacy Guide

- Communicate to prescribers the proposed KRM related to the recommendation that prescribers should confirm patients who can become pregnant are not pregnant before initiating treatment.
- Revise to encourage prescribers to check-in with patients regularly during treatment.
- See edits in the redlined *Prescriber and Pharmacy Guide* for details regarding these changes.

Prescriber Knowledge Assessment

- Provide the answers to the knowledge assessment questions within the *Supporting Document*.
- Question 6 must be revised to state the prescribers “must” inform patients who can become pregnant of the key risk messages to align with the REMS requirement for prescribers.
- If the intended answers to questions 7 and 8 are ‘True’, assessment questions 7 and 8 must be revised to align with the REMS requirements for prescribers (i.e. “must” will be used rather than “(b) (4)”).
- See edits in the redlined *Prescriber Knowledge Assessment* for details regarding these changes.

Patient Guide

- Revise the definitions of patients who can and who cannot become pregnant and the definition of menopause to align with the definitions in the *Pharmacy and Prescriber Guide* and use patient-friendly language.
- Reorganize the section with recommendations for pregnancy prevention to clearly convey the important information.
- Once all edits are made, reformat the *Patient Guide* so content is limited to no more than two pages, if possible, for improved utility of the material. See edits in the redlined *Patient Guide* for details regarding these changes

Risk of Birth Defects with TRYVIO

- Reformat to move the risk information to the top and highlight it in a box for emphasis.
- Revise the definition of a patient who can become pregnant to align with the definition used in the *Patient Guide* (based on the definitions in the *Pharmacy and Prescriber Guide*)
- Reformat the key risk messages into a table which succinctly explains recommendations for patients who can become pregnant before starting Tryvio, during treatment, and one month after treatment.
- See edits in the redlined *Risk of Birth Defects with TRYVIO* for details regarding these changes

REMS Website

- Align the REMS Website to the revisions in the REMS requirements, REMS Document, and REMS materials.

- Screenshots of website pages that are only accessible after login may be removed from the website screenshots and added as an appendix to the *Supporting Document*.
- Revise the wording of the “Patients” information box on the home page (page 2) as follows:
Prescribers must counsel patients who can become pregnant on the risk of birth defects associated with TRYVIO and actions patients should take to prevent pregnancy and minimize exposure to a developing baby before birth.
Patients who can become pregnant will receive a Patient Guide.
- On page 8, clarify that prescribers have the option to certify by submitting the form online or by filling out the form online and then printing and faxing. Change the “(b) (4)” button name to “Certify by Fax” and move the button closer in proximity to the “Certify Online Now” button.
- Revise page 9 to clarify the same as above, but for pharmacies.
- Revise page 11 to align with the *Patient Guide* and *Risk of Birth Defects with Tryvio*. Include the definition of a patient who can become pregnant and clarify that the *Patient Guide* is for patients who can become pregnant provided by the prescriber and a *Risk of Birth Defects* is for all patients provided by pharmacies.
- Revise page 14 to clarify the instructions for the Prescriber Knowledge Assessment.
 - Step 2: Successfully complete and submit this Prescriber Knowledge Assessment.
 - Step 3: You must answer ALL eight questions of this Prescriber Knowledge Assessment correctly in order to pass the assessment. You have 3 attempts to answer all questions correctly. After passing the Prescriber Knowledge Assessment, you may proceed to completing and submitting the Prescriber Enrollment Form.
- Revise pages 23 and 26 to replace “(b) (4)” with “wish to dispense TRYVIO”.

Submit a REMS amendment that includes the following revised REMS materials within 5 business days. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. **Revisions to REMS materials in addition to those requested in these comments may impact the review timeline for the REMS.** Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). For the REMS Assessment Plan edits, include in your response an updated REMS Supporting Document including the REMS Assessment Plan in Word tracked changes, Word clean, and a clean PDF version. The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	Tracked MS Word, Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
4	Outpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version

5	Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
6	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF version
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
9	Risk of Birth Defects with TRYVIO	Tracked MS Word, Clean MS Word, PDF version
10	REMS Website	Tracked MS Word, Clean MS Word, PDF version
11	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	PDF Version

8. Appendix

1. REMS Document
2. REMS Assessment Plan
3. Prescriber Enrollment Form
4. Outpatient Pharmacy Enrollment Form
5. Inpatient Pharmacy Enrollment Form
6. Prescriber and Pharmacy Guide
7. Prescriber Knowledge Assessment
8. Patient Guide
9. Risk of Birth Defects with TRYVIO
10. Website Screenshots

9. References

¹ Soukehal, S. DCN. Information Request for NDA 217686, January 19, 2024.

² World Health Organization (WHO), Eastern Mediterranean Region, Disease Prevention, accessed October 13, 2023 from: <https://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html>.

³ Center for Disease Control (CDC), Picture of America – Prevention, accessed October 13, 2023 from: https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf

⁴ Idorsia. REMS Correspondence, February 13, 2024.

79 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217686
PDUFA Goal Date	March 19, 2024
Nexus TTT#	2022-3102 and 2022-3104
Reviewer Names	Cristen Lambert, PharmD Katherine Hyatt Hawkins Shaw, PhD Page Crew, PharmD, MPH, BCPS (DMAMES)
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Review Completion Date	January 18, 2024
Subject	Interim Review of proposed REMS
Established Name	aprocitentan
Trade Name	Tryvio
Name of Applicant	Idorsia Pharmaceuticals Ltd
Therapeutic Class	Endothelin Receptor Antagonist (ERA)
Formulation(s)	12.5 mg oral tablet
Dosing Regimen	12.5 mg orally once daily

(b) (4)

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Tryvio (aprocitentan), New Drug Application (NDA) 217686 submitted by Idorsia on December 19, 2022 and amended on September 6, 2023, November 16, 2023, and November 28, 2023.

Tryvio is an endothelin receptor antagonist (ERA) proposed for the treatment of hypertension (HTN), to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity.

This interim review discusses DRM's comments on the amendment to the proposed REMS submitted in response to the Agency's November 3, 2023 information request¹ to:

1. Revise the REMS goal based on Public Health Preventative Aims
2. Incorporate gender-neutral language in the REMS Document and REMS Materials
3. Revise REMS requirements
4. Revise REMS materials to align with the revised REMS Requirements
5. Create a Patient Information Sheet and Prescriber Knowledge Assessment

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 9/6/2023: Applicant submitted a REMS with ETASU for the risk of embryo-fetal toxicity which constitutes a major amendment
- 10/27/2023: Applicant inquired via email about the feasibility of dispensing samples in the postmarket setting
- 11/3/2023: Agency sent interim comments (ICs) to the Applicant in response to their REMS amendment, dated September 6, 2023.
- 11/16/2023: Applicant submitted a REMS amendment to NDA 217686 in response to the Agency's IC dated November 3, 2023.
- 11/28/2023: Applicant submitted REMS Website screenshots.

3. Review of Applicant's Proposed REMS

3.1. REMS Goals

In response to DRM's November 3, 2023 comments, Idorsia proposed the goal of the Tryvio REMS is to mitigate the risk of embryo-fetal toxicity associated with Tryvio (aprocitentan)^{(b) (4)}

Objective: Ensure that prescribers are aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant on the actions necessary to prevent pregnancy and minimize exposure to a fetus.

Reviewer Comment: We agree with Idorsia’s proposed REMS goal, but require a grammar edit. The goal should be revised to:

The goal of the Tryvio REMS is to mitigate the risk of embryo-fetal toxicity associated with Tryvio (aprocitantan).

Objective: Ensure that prescribers are aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant on the actions necessary to prevent pregnancy and minimize exposure to a fetus.

3.2. REMS Requirements

In response to DRM’s November 3, 2023 comments, Idorsia revised the REMS Document, Supporting Document, and REMS materials to use gender neutral patient categories and use gender neutral language (i.e. “Patients who can become pregnant”) throughout.

Reviewer Comment: We agree with Idorsia’s revisions of gender-neutral language throughout the REMS materials; however more edits are required to be acceptable. Definitions of patient categories relevant to the REMS should not include the term (b) (4).” Acceptable definitions of patient categories are stated below and are consistent with those used in other REMS programs that use gender neutral language. Revisions to make language in the REMS gender-neutral should align with the Tryvio Prescribing Information.

Patients Who Cannot Become Pregnant:

- Patients with a uterus who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Patients with a uterus who have passed through Menopause (as defined below)
- Patients with other medical reasons for permanent, irreversible infertility
- Patients without a uterus (including patients who were born male)

Patients Who Can Become Pregnant:

- Patients with a uterus who have entered puberty and all patients with a uterus that have not passed through Menopause (as defined below)
- For the purpose of the TRYVIO REMS, puberty includes those patients with a uterus who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)
- For the purposes of the TRYVIO REMS, patients who have undergone tubal sterilization are classified as patients who can become pregnant

Definition of Menopause:

- Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition (b) (4) medical therapy) or post-surgical from bilateral oophorectomy

3.2.1. REMS Document

In response to DRM’s November 3, 2023 comments, Idorsia revised the proposed REMS Document to add the risk the REMS addresses, revised the REMS goal based on the Public Health Preventative Aims, incorporated gender-neutral language, and revised the REMS requirements to only include requirements within the scope of a REMS with ETASU A and B.

Reviewer Comment: We agree with the proposed revisions to the REMS Document, but additional revisions are required to be acceptable. A ‘Statutory Elements’ section should be added to the REMS

Document, as described in the January 2023 Format and Content of a REMS Document Guidance for Industry and REMS Document Technical Conformance Guide. The Statutory Elements section should list the elements of the Tryvio REMS (i.e. ETASU A and B, Implementation System, and Timetable for Submission of Assessments). A redlined REMS Document with these edits will be sent to Idorsia. The REMS Document should also be revised to align with the proposed revisions to the REMS requirements in this review.

3.2.2. REMS Participant Requirements

3.2.2.1. Healthcare Provider

In response to DRM's November 3, 2023 comments, Idorsia removed the requirement for prescribers to

(b) (4)

Reviewer Comment: We agree with removing this prescriber requirement.

(b) (4)

A drug sample is a unit of a drug which is not intended to be sold, but is intended to promote sale of the drug. Depending on the design of the REMS, dispensing of samples may be accommodated within the REMS requirements. Further revisions to the proposed prescriber REMS requirements are needed if Idorsia incorporates dispensing of Tryvio samples in the REMS. The redlined REMS Document includes suggested language for prescribers who dispense samples for Idorsia's consideration. If Idorsia chooses to proceed with incorporating dispensing of samples in the REMS, corresponding changes related to prescriber dispensing of samples should be made to other REMS materials as applicable.

Prescriber Enrollment Form

In response to DRM's November 3, 2023 comments, Idorsia proposed a revised *Prescriber Enrollment Form* which includes a section noting successful completion of a Prescriber Knowledge Assessment as part of the enrollment process. The Prescriber Enrollment Form was also revised to include gender neutral language.

Reviewer Comment: We agree with the proposed revisions to the Prescriber Enrollment Form. If Idorsia chooses to dispense Tryvio samples, the Prescriber Enrollment Form should be updated to include requirements for prescribers who dispense samples. The redlined Prescriber Enrollment Form includes suggested language for including Tryvio samples similar to the Riociguat REMS Prescriber Enrollment and Agreement Form. If Idorsia chooses to not include samples, this language does not need to be included in the Prescriber Enrollment Form or REMS Document.

Prescriber Knowledge Assessment

In response to DRM's November 3, 2023 comments, Idorsia proposed a Prescriber Knowledge Assessment to be completed successfully by the prescriber in order to enroll in the REMS. The Prescriber Knowledge Assessment consists of

(b) (4)

. All eight questions must be answered correctly to certify in the REMS.

Reviewer Comment: We do not agree with the proposed Prescriber Knowledge Assessment. The assessment does not convey that the prescriber is competent in their knowledge of the risk of embryo-

fetal toxicity associated with Tryvio, the need to counsel patients who can become pregnant on actions to take to avoid becoming pregnant, monitoring for pregnancy, and steps to take if a patient becomes pregnant while taking Tryvio. The assessment should be revised to be more rigorous to more accurately assess whether Key Risk Messages (KRM)s for prescribers were communicated. The Applicant will be referred to the knowledge assessment of the Tecvayli and Talvey REMS as an example for guidance on revising the Tryvio REMS prescriber knowledge assessment.

(b) (4) ^a

In response to DRM's November 3, 2023 comments, Idorsia proposed a revised patient guide which includes gender neutral language. The proposed (b) (4) aligns with the revised prescriber requirements and the revised requirements for patients who can become pregnant in the REMS Document.

Reviewer Comment: We agree with the proposed revisions to the (b) (4) to use gender neutral language and the alignment with the revised requirements for patients in the REMS Document. Additional revisions to the (b) (4) are needed to be acceptable. The guide should be renamed to "Patient Guide" for consistency across REMS and to indicate the material's intended stakeholder in the first word of the title. The guide requires edits to improve usability and readability of the material and to align with the KRM)s for patients described in section 3.2.4 of this review. The redlined "Patient Guide" contains details on these edits.

3.2.2.2. Patients

In response to DRM's November 3, 2023 comments, Idorsia proposed several revisions to patient requirements and REMS materials for patients. Idorsia proposed to change the name of a stakeholder in the REMS from "(b) (4)" to "Patients who are prescribed Tryvio." Idorsia proposed to remove the REMS requirements (b) (4). Idorsia proposed that patients who can become pregnant must review the (b) (4) and receive counseling from a prescriber prior to treatment initiation. Idorsia proposed that all patients must receive a *Patient Information Sheet* from the dispensing pharmacy during treatment. Idorsia included a requirement for patients who can become pregnant to inform a prescriber immediately if they miss a menstrual period or suspect a pregnancy.

Reviewer Comment: We agree with the proposed revisions to the REMS requirements for patients who are prescribed Tryvio as described in the REMS Document.

Patient Information Sheet

In response to DRM's November 3, 2023 comments, Idorsia proposed a *Patient Information Sheet* to be dispensed with apocritentan to all patients to reinforce education for the Tryvio REMS. The sheet contains (b) (4) information for patients: the definition of a patient who can become pregnant, to not start Tryvio if pregnant or stop Tryvio if you become pregnant while taking Tryvio due to the risk of serious birth defects associated with Tryvio; and the recommendation to use (b) (4) birth control while on Tryvio therapy.

Reviewer Comment: Additional revisions are required for the *Patient Information Sheet* to be acceptable. Idorsia should revise the name of the material to "Risk of Birth Defects with TRYVIO" to align with the content of similar materials for other REMS. The "Risk of Birth Defects with TRYVIO" material

^a Renamed from (b) (4) *Patient Guide* in previous REMS submissions.

should be revised to inform on the Key Risk Messages for patients. Idorsia should add information about when and how often patients should test for pregnancy. Idorsia may use the Qysmia REMS “Risk of Birth Defects with Qsymia” REMS material for content guidance. Idorsia should revise for brevity and incorporate graphics and/or charts as well as section headings to communicate the Key Risk Messages to patients.

The REMS Assessment Plan will include a metric related to the “Risk of Birth Defects with TRYVIO”: Qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the “(b) (4)” (to be conducted once initially).

3.2.2.3. Pharmacy/Prescriber/Healthcare Setting that Dispenses

Outpatient Pharmacies

In response to DRM’s November 3, 2023 comments, Idorsia proposed to remove the requirement for (b) (4) and proposed to add the requirement for pharmacies to dispense a *Patient Information Sheet* to each patient each time Tryvio is dispensed. Idorsia independently proposed to require outpatient pharmacies to establish processes and procedures (b) (4) if a patient becomes pregnant and report the pregnancy to the Tryvio REMS. Idorsia independently proposed to revise the language of the requirement before dispensing from “(b) (4)” to “Obtain authorization to dispense each prescription (b) (4)”

Reviewer Comment: We agree with the removal of requirements for (b) (4). We also agree with the added requirement for pharmacies to dispense a “Patient Information Sheet”, but as mentioned in section 2.2.2.2., the name of the material should be changed to “Risk of Birth Defects with TRYVIO”. We agree that outpatient pharmacies should obtain authorization to dispense each prescription, but we do not agree that (b) (4). On page 17 of their website screenshots submitted on November 28, 2023, Idorsia proposed that pharmacies must obtain authorization to dispense Tryvio through a REMS Dispense Authorization (RDA) process. Therefore, Idorsia should remove the requirement for (b) (4). The redlined REMS Document includes this change. In order to align requirements between outpatient pharmacies and inpatient pharmacies, all pharmacies are required to report pregnancies to the REMS. (b) (4).

Outpatient Pharmacy Enrollment Form

In response to DRM’s November 3, 2023 comments, Idorsia proposed a revised *Outpatient Pharmacy Enrollment Form* which aligns with the revised outpatient pharmacy requirements as described in the REMS Document and which is able to be submitted online or via fax.

Reviewer Comment: We agree with the revisions to the *Outpatient Pharmacy Enrollment Form*. The *Outpatient Pharmacy Enrollment Form* should be further revised to align with the revisions to the outpatient pharmacy requirements for obtaining authorization to dispense Tryvio.

Inpatient Pharmacies

In response to DRM's November 3, 2023 comments, Idorsia proposed several revisions to the requirements for inpatient pharmacies. Idorsia proposed to remove the requirements that involve inpatient pharmacies (b) (4)

(b) (4) Idorsia proposed inpatient pharmacies must verify all inpatients on Tryvio therapy are under the supervision and care of a certified prescriber. Idorsia proposed inpatient pharmacies must dispense a *Patient Information Sheet*^b to patients on Tryvio therapy at discharge. Independent of DRM's November 3, 2023 comments, Idorsia removed the requirement for (b) (4) and to instead require inpatient pharmacies to report pregnancies to the Tryvio REMS. Idorsia also proposed to revise the language of the requirement before dispensing from " (b) (4) " to " (b) (4) " Idorsia proposed inpatient pharmacies (b) (4) .

Reviewer Comment: We agree with the proposed removal of certain requirements for inpatient pharmacies. We agree with the requirement for inpatient pharmacies to dispense a "Risk of Birth Defects with TRYVIO" (revised name for Patient Information Sheet) upon discharge. We agree that pregnancies should be reported directly to the REMS. We do not agree that inpatient pharmacies must (b) (4) . Instead, inpatient pharmacies must establish processes and procedures to verify the prescriber is certified or the patient is under the supervision and care of a certified prescriber. Before dispensing, inpatient pharmacies must verify the prescriber is certified or the patient is under the supervision and care of a certified prescriber, through their established processes and procedures. Inpatient pharmacies may utilize an RDA or the prescriber look-up function to verify prescriber certification. We do not agree with (b) (4) . (b) (4) may cause unnecessary burden on the healthcare system since (b) (4) is not linked to any patient activity requirements. The (b) (4) restriction should be removed. The redlined REMS Document includes these changes.

Inpatient Pharmacy Enrollment Form

In response to DRM's November 3, 2023 comments, Idorsia proposed a revised *Inpatient Pharmacy Enrollment Form* to align with the revised inpatient pharmacy requirements.

Reviewer Comment: We agree with the revisions to the *Inpatient Pharmacy Enrollment Form* to align with the revised inpatient pharmacy requirements. The *Inpatient Pharmacy Enrollment Form* should be further revised to align with the revisions to the inpatient pharmacy requirements for verifying the prescriber is certified or the patient is under the supervision and care of a certified prescriber.

Prescribers That Dispense

Idorsia inquired about the feasibility of dispensing Tryvio samples in the postmarketing setting under a REMS.²

Reviewer Comment: Requirements can be added to the REMS to accommodate prescriber dispensing of Tryvio samples. As mentioned in Section 3.2.2.1, if Idorsia chooses to dispense Tryvio samples, the Prescriber Enrollment Form and REMS Document should be updated to include requirements for

^b To be renamed *Risk of Birth Defects with TRYVIO*.

prescribers who dispense samples. If Idorsia chooses to not include samples, this language should be removed from the redlined REMS Document.

3.2.3. REMS Applicant Requirements

3.2.3.1. Training

Prescriber and Pharmacy Guide

In response to DRM's November 3, 2023 comments, Idorsia revised the *Prescriber and Pharmacy Guide* to align with the updated REMS requirements, REMS operations and REMS Document. The *Prescriber and Pharmacy Guide* includes definitions of patients (b) (4) who can and cannot become pregnant.

Reviewer Comment: *The Prescriber and Pharmacy Guide should be revised to align with the updated REMS requirements, which include pharmacies reporting pregnancies to the REMS. The Prescriber and Pharmacy Guide should be revised to ensure the proposed KRMs are conveyed to prescribers and should emphasize the need for prescribers to counsel patients and encourage prescribers to continue to check-in with patients regularly during treatment. The definitions of patients who can become pregnant should be revised to include gender-neutral language. The table containing birth control options should be reformatted to a reader-friendly chart. The guide should be reformatted for readability and to refrain from copying directly from the attestations on the enrollment forms for prescribers and pharmacies. The redlined Prescriber and Pharmacy Guide includes more detail on these changes and example REMS materials are referenced for Idorsia.*

3.2.3.2. Operations

In response to DRM's November 3, 2023 comments, Idorsia proposed that all stakeholders are able to enroll in the REMS via fax and/or online and updated all materials accordingly. Idorsia updated the Applicant REMS requirements to provide pharmacies that are not yet certified with materials from Idorsia when they receive their first prescription or inquire about how to become certified. Idorsia proposed (b) (4) must obtain a REMS Dispense Authorization (RDA) to dispense each prescription through processes and procedures established as a requirement of the REMS. Idorsia proposed that pharmacies may request an RDA online using the prescriber National Provider Identifier (NPI) or using the prescriber name and state and may also request an RDA via phone by calling the REMS Coordinating Center. Idorsia proposed the REMS Website be fully operational and all REMS materials available through the REMS website or coordinating center (b) (4).

Reviewer Comment: *We agree with Idorsia's proposed revisions to allow all stakeholders to enroll in the REMS via fax and/or online and the updated materials. We also agree with the proposed revisions for Idorsia to provide REMS materials to pharmacies when they receive their first prescription or when they inquire about enrollment. We agree with Idorsia's proposal for outpatient pharmacies to obtain authorization prior to dispensing each Tryvio prescription via an RDA. Idorsia will need to update the REMS Document and materials to indicate that the RDA must be obtained for each prescription dispensed by a certified outpatient pharmacy. We do not agree that (b) (4). Inpatient pharmacies must establish processes and procedures to verify the prescriber is certified or the patient is under the supervision and care of a certified prescriber and verify certification of the prescriber before dispensing. (b) (4)*

The REMS Website must be fully operational and REMS materials available at the time Tryvio first becomes commercially available. The redlined REMS Document includes this revision.

Tryvio REMS Website

The REMS website screenshots include the home page, site menu, log in screen, pages for each stakeholder, printable materials on a resources page, and a contact page. The prescriber and the pharmacy pages include information on REMS requirements and a link to certify online or print and fax the enrollment form for certification. The Prescriber Knowledge Assessment is available to submit online as part of prescriber certification, or can be filled out and faxed to the REMS. The website also contains a page describing the REMS Dispense Authorization process for pharmacies and includes options to request an RDA using the Prescriber NPI or using the Prescriber name and state. A certified participant page allows stakeholders to look up certified pharmacies and certified prescribers. The REMS contact page includes options for live chat, email, phone or fax communication with call center hours Monday to Friday from 8 am to 8 pm.

Reviewer Comment: *The website should be updated to reflect all revisions made within the REMS Document and all materials. Idorsia will need to clarify if users create a password using an NPI number/mobile number as a username or if the NPI number is the username and the mobile number entered serves as the password. The REMS Dispense Authorization website contains language which begins, “(b) (4) (b) (4)” Revised language to remove the word (b) (4) is included in the redlined Website Screenshots which will be sent to Idorsia. Idorsia should confirm which web pages are available only under login.*

3.2.3.3. Compliance

The Applicant proposed the following audit requirements for certified pharmacies and authorized wholesaler/distributors:



Reviewer Comment:

- *The audit timeline for wholesaler/distributors, which includes initial audits within 180 days of authorization and annual audits thereafter, are acceptable. The Applicant will be asked to use the term “authorization” instead of “(b) (4)” in reference to wholesaler/distributors, since (b) (4) according to the REMS.*
- *The audit timeline for certified pharmacies requires revision. Initial audits of pharmacies were not proposed. In addition, the sample size for annual certified pharmacy audits should be addressed in the audit plan instead of the REMS Document, so that it can be adjusted depending on the scale of distribution and the scale of compliance findings.*

3.2.4. Key Risk Messages (KRM)

KRMs are based on the proposed REMS goal and objectives. KRMs guide the messaging throughout the REMS materials. Idorsia did not propose KRMs for the Tryvio REMS.

Reviewer Comment: Idorsia will need to submit KRMs. We will refer Idorsia to the Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge and to our suggested KRMs:

- For healthcare providers:
 - Embryo-fetal toxicity can occur in patients taking Tryvio. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
 - Counsel patients who can become pregnant on the need for pregnancy testing monthly during treatment, and for one month after treatment. Instruct patients who can become pregnant to use (b) (4) contraception.
- For patients:
 - There is a risk of birth defects (embryo-fetal toxicity)
 - If you are a patient who can become pregnant:
 - Confirm that you are not pregnant by taking a pregnancy test before starting Tryvio and monthly during treatment.
 - Use (b) (4) contraceptives and avoid pregnancy

3.3. REMS Assessment Timetable

The Applicant proposed to submit REMS assessments annually from the date of the initial REMS approval.

Reviewer Comment:

- The proposed timetable is acceptable. The REMS goal is education based and the awareness of the healthcare providers about the risk of embryo-fetal toxicity associated with Tryvio and counseling patients will be assessed through prescribers' knowledge, attitudes and behaviors (KAB) surveys. The Applicant will need to develop, conduct, and submit the prescriber KAB survey results which will not be available at the (b) (4) month timepoint. A 12-month assessment report should provide a more complete picture of how the REMS is functioning, and will have more data to inform an assessment of whether the REMS is meeting the goal.
- The Agency will also be monitoring adverse event reports as they are submitted to the FDA Adverse Event Reporting System (FAERS).

4. Supporting Document

The REMS Supporting Document includes the background of the REMS currently under review.

Reviewer Comment: The REMS Supporting Document must be revised to align with the revised REMS Document, operations, and requirements as discussed in this review. Further description of the RDA process should be included in the Supporting Document.

Key Performance Indicators (KPI)

Idorsia did not propose Key Performance Indicators (KPIs) for the Tryvio REMS.

Reviewer Comment: To align with the REMS objective, the suggested KPI will rely on surveys of healthcare providers to assess knowledge of KRMs. Our suggested KPI is the percentage of prescribers who are knowledgeable about (a) the risk of embryo-fetal toxicity associated with Tryvio and (b) the need to counsel patients who can become pregnant. The KPI will be calculated as:

Numerator = Number of prescribers who achieve a satisfactory score on the knowledge survey

Denominator = # of prescribers who completed the knowledge survey

The targeted knowledge threshold for this KPI is suggested to be 80%. A targeted knowledge performance threshold of 80% is in accordance with the FDA Draft Guidance for Industry Survey Methodologies to Assess REMS Goals That Relate to Knowledge (January 2019). Regarding the targeted knowledge threshold, 80% represents the lower bound of a 95% confidence interval with a 5% margin of error for knowledge related to KRMs. Performance above this threshold will support that prescribers are aware of the KRMs, and performance below this threshold will have to be assessed to determine causal factors such as inadequate knowledge levels, insufficient sample size, survey methodology issues, or multifactorial contributing issues.

The suggested KPI and associated target knowledge threshold will be communicated to Idorsia.

4.1. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be addressed in the REMS Approval letter. The Applicant submitted a revised REMS Supporting Document, containing the REMS Assessment Plan, on September 6, 2023. The REMS Assessment Plan metrics are necessary to evaluate if the REMS is operating as intended and meeting its goal of mitigating the risk embryo-fetal toxicity associated with Tryvio by meeting its stated objective.

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the REMS Assessment Plan, which included metrics under the following categories: Program Implementation and Operations, Health Outcomes and/or Surrogates of Health Outcomes, and Knowledge. The Program Implementation and Operations section contains metrics related to REMS Certification and Enrollment regarding pharmacies, prescribers, and wholesaler/distributors. There are also metrics related to the REMS Coordinating Center and the REMS website. The Health Outcomes and/or Surrogates of Health Outcomes section contains metrics related to reported pregnancy cases, including root cause analysis and estimation of the percent pregnancy rate per reporting period. The Knowledge section contains metrics related to surveys of certified prescribers (b) (4)

regarding the REMS goal, risk, and program. The Knowledge section also proposes that surveys of healthcare providers be conducted at (b) (4).

Reviewer Comments:

- *In Section 7 below, Comments to the Applicant, DMAMES provides comments regarding the REMS Assessment Plan. The comments include requests for editorial changes, additional metrics, revisions to existing metrics, and changes to the knowledge survey timeline. Significant changes were made to metrics in each category to capture more comprehensive data; however, the Health Outcomes section was streamlined in anticipation of capturing key safety related data through a requirement^c outside of the REMS assessment plan that will focus on evaluating embryo-fetal toxicity.*

^c Proposed postmarketing requirement

5. Discussion

The Applicant proposed REMS Goal and Objective now align with the principles of the REMS Logic Model and Public Health Prevention Aims^{3,4}. In addition, the proposed prescriber knowledge assessment supports confirmation that prescribers of Tryvio have knowledge of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients on the actions patients should take to prevent pregnancy and minimize exposure of a fetus to Tryvio.

The REMS goal and objectives should be aligned with key performance indicators (KPIs) to better reflect measurable outcomes so we may determine if the REMS is functioning as designed to achieve the goal of mitigating the risk of embryo-fetal toxicity associated with Tryvio. The targeted thresholds for the KPIs are based on the Agency's experience with REMS designed to mitigate similar risks and REMS which have education based strategies. DRM and DMAMES agreed to recommend one primary KPI related to education as measured by healthcare provider KAB surveys. The goal knowledge threshold (80%) is consistent with the *FDA Draft Guidance for Industry Survey Methodologies to Assess REMS Goals That Relate to Knowledge (January 2019)* and represents the lower bound of a 95% confidence interval with a 5% margin of error for knowledge related to KRMs.⁵ The Review Team discussed the proposed KPI for Tryvio and a target knowledge threshold which will be communicated to the Applicant.

DRM proposed KRMs for prescribers and patients to be conveyed in the REMS materials and to guide revisions of the materials for conciseness. These KRMs will be communicated to the Applicant. The Review Team discussed the requirement for pharmacies to report pregnancies (b) (4) to the REMS. The Review Team agreed to keep pregnancy reporting the same between outpatient and inpatient pharmacies to avoid confusion in REMS requirements; thus outpatient and inpatient pharmacies are required to report pregnancies to the REMS. During discussions, it was noted that standard of practice for pharmacists is to report pregnancies to the prescriber for a pregnant patient discovered to be on a drug with a contraindication for pregnancy.

Revisions to the Tryvio REMS are required to be acceptable. The REMS Document requires administrative revisions as well as revisions to align with the further revised REMS requirements and audit language. KRMs for prescribers and patients must be submitted and materials revised to convey the KRMs. The REMS materials must be revised to improve useability and readability and include gender-neutral patient definitions. The REMS website requires revisions to reflect changes in REMS requirements and materials, requires clarification for website access by stakeholders, and revision of language describing the RDA process. The REMS Assessment Plan requires revisions to clarify and add metrics as part of REMS assessments. A KPI and target threshold must also be submitted so the Agency can determine during future assessments if the REMS is functioning as designed to achieve the REMS goal.

6. Conclusions and Recommendations

DRM does not find the proposed REMS for Tryvio (aproциттан) as submitted on December 19, 2022 and last amended on November 16 2023, to be acceptable, as described in this review. Send the comments in Section 7 to Idorsia in an Information Request and instruct the Applicant to submit a REMS amendment within 10 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on November 16 and November 28, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comment

- Revise all materials so that the font size and style is consistent to improve material usability. It is appropriate to use one larger sized font for headings and one smaller sized font for main text.
- Remove all instances of (b) (4) and instead include the content in main text of the materials (Also indicated in redlined versions of materials).
- Revise the definitions for categories of patients included throughout the REMS materials to use gender-neutral language. Find acceptable definitions below. You may refer to the Filspari REMS for examples of gender neutral patient category definitions.

Patients Who Cannot Become Pregnant:

- Patients with a uterus who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Patients with a uterus who have passed through Menopause (as defined below)
- Patients with other medical reasons for permanent, irreversible infertility
- Patients without a uterus (including patients who were born male)

Patients Who Can Become Pregnant:

- Patients with a uterus who have entered puberty and all patients with a uterus that have not passed through Menopause (as defined below)
- For the purpose of the TRYVIO REMS, puberty includes those patients with a uterus who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)
- For the purposes of the TRYVIO REMS, patients who have undergone tubal sterilization are classified as patients who can become pregnant

Definition of Menopause:

- Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy
- Rename the “(b) (4)” to “Patient Guide” to align with consistency across REMS programs and to indicate the material’s intended stakeholder in the first word of the title. Apply this change to all instances within all materials and REMS Document where the original naming, “(b) (4)” appears.
- Rename the “Patient Information Sheet” to “Risk of Birth Defects with TRYVIO” Apply this change to all instances within all materials and REMS Document where the original naming, “Patient Information Sheet” appears.
- Submit Key Risk Messages (KRM)s within your REMS Supporting Document. KRM)s should identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risk of embryo-fetal toxicity. The KRM)s should be based on the proposed REMS goals and objectives and should guide the messaging throughout the REMS materials. For more information on KRM)s, refer to the Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge. We are providing the following suggested KRM)s:

- For healthcare providers:
 - Embryo-fetal toxicity can occur in patients taking Tryvio. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
 - Counsel patients who can become pregnant on the need for pregnancy testing monthly during treatment, and for one month after treatment. Instruct patients who can become pregnant to use (b) (4) contraception.
- For patients:
 - There is a risk of birth defects (embryo-fetal toxicity)
 - If you are a patient who can become pregnant:
 - Confirm that you are not pregnant by taking a pregnancy test before starting Tryvio and monthly during treatment.
 - Use (b) (4) contraceptives and avoid pregnancy.

REMS Document

Redlined edits and comments are provided. Update and align all REMS materials and website with the changes in the REMS Document.

- REMS Administrative Information
 - Add “Section VI. Statutory Elements” as described in the January 2023 *Format and Content of a REMS Document Guidance for Industry and REMS Document Technical Conformance Guide*. The Statutory Elements section should list the elements of the Tryvio REMS (i.e. ETASU A and B, Implementation System, and Timetable for Submission of Assessments).
- REMS Goal
 - Revise the grammar of the REMS goal statement as indicated in the redlined REMS Document
- REMS Requirements
 - Remove the requirement for outpatient pharmacies to (b) (4), since a REMS Dispense Authorization mechanism will be used.
 - Revise the requirement so inpatient pharmacies must verify the prescriber is certified or verify the patient is under the supervision and care of a certified prescriber.
 - Remove (b) (4).
 - If you choose to incorporate dispensing of Tryvio samples in the REMS, we have included suggested additions to the outpatient dispensing requirements in the redlined REMS Document for your consideration. If you choose not to include samples at this time, remove the suggested edits from the REMS Document before your next submission.
 - Revise the Applicant requirements for the REMS Website. The website must be fully operational and REMS materials available at the time Tryvio first becomes commercially available.
 - See edits in the redlined REMS Document for details regarding these changes.
- The audit language in the REMS Document should be revised to include the following:
 - 4. Audit all certified pharmacies within 180 days after their first shipment receipt of TRYVIO and audit all wholesaler-distributors within 180 days after they become authorized to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
 - 5. Audit annually according to the audit plan which includes: 1) a sample of certified outpatient and inpatient pharmacies, 2) all wholesaler-distributors to ensure that all the

REMS processes and procedures are in place, functioning, and support the TRYVIO REMS requirements.

- Proposed changes to the above audit requirements should include a rationale for the change, and supporting information regarding the anticipated scale of distribution.

REMS Supporting Document

- Align all revisions to the REMS requirements and REMS Document to the REMS Supporting Document, including the REMS Assessment Plan.
- Submit a Key Performance Indicator (KPI) and target threshold with a rationale within your Supporting Document. The KPI should align with the REMS goal and objective to reflect a measurable outcome so we may determine if the REMS is functioning as designed to achieve the REMS goal. We are providing the following suggested KPI and threshold:
 - KPI: Percentage of prescribers who are knowledgeable about (a) the risk of embryo-fetal toxicity associated with Tryvio and (b) the need to counsel patients who can become pregnant.
 - Target knowledge threshold: 80%.
- Describe the REMS Dispense Authorization (RDA) process as mentioned in the website screenshots submitted on November 28, 2023.

REMS Assessment Plan

We have the following comments regarding the Tryvio REMS Assessment Plan included in the REMS Supporting Document. The Agency requires further revisions to the REMS Assessment Plan. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in strikethrough.

1. Editorial changes were made to clarify requirements for reporting of each metric for the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.
2. Implementation metrics were added to capture additional data related to the REMS website, and to measure key implementation data for the first assessment report
3. REMS Coordinating Center (CC) metrics were added to capture more granular data about the nature of contacts to the REMS CC
4. REMS Certification and Enrollment metrics were added to distinguish between newly certified/authorized, total certified/authorized, and active stakeholders
5. REMS utilization metrics were added to capture dispensing data
6. REMS compliance metrics were added to capture audit and non-compliance procedures, and to capture indicators to help assess if the REMS is functioning as intended. The edits include descriptions of processes to assess identification of non-compliance of stakeholders, resolution of non-compliance, and tracking non-compliance over time, and indicators related to non-compliance by stakeholders (healthcare providers and pharmacies).
7. Metrics were added to measure data related to the post-training knowledge assessment
8.  (b) (4)
9. Comprehension study to test patients' comprehension of the Patient Information Sheet's major communications messages that detail the safe and effective use was added.
10. Health outcomes data were streamlined to avoid redundant capture of individual cases  (b) (4). A descriptive summary will be included in the REMS assessment, and the pregnancy rate will be captured so it can be compared to the general population pregnancy rate.

11. The heading “Overall Assessment of REMS Effectiveness” was added to the last metric in the assessment plan

Prescriber Enrollment Form

- If you choose to incorporate dispensing of Tryvio samples in the REMS, we have included suggested additions to the Prescriber Enrollment Form in the redlined version. You may also refer to the Riociguat REMS *Prescriber Enrollment and Agreement Form* as an example of a REMS that supports samples. If you choose not to include samples at this time, the suggested edits should be removed from the *Prescriber Enrollment Form* before your next submission.

Outpatient Pharmacy Enrollment Form

- Revise to align with the revisions to the outpatient pharmacy requirements for obtaining authorization to dispense Tryvio. See the redlined version for suggested edits.
- Remove the requirement for outpatient pharmacies to (b) (4).

Inpatient Pharmacy Enrollment Form

- Revise to align with the revised inpatient pharmacy requirements for verifying the prescriber is certified or that the patient is under the supervision and care of a certified prescriber. See the redlined version for suggested edits.

Prescriber and Pharmacy Guide

- Revise to align with the revised REMS requirements and ensure the proposed KRMs are conveyed to prescribers. Emphasize the need to counsel patients and to check-in with patients regularly during treatment.
- Format into a comprehensive checklist and refrain from copying directly from the attestations on the enrollment forms. See the redlined version for suggested edits.

Prescriber Knowledge Assessment

- Revise to be more rigorous in order to more accurately assess that KRMs for prescribers were communicated. You may refer to the knowledge assessment of the Tecvayli and Talvey REMS as an example.

Patient Guide

- Revise to improve useability and readability and incorporate the KRMs. The redlined *Patient Guide* contains details on these edits.
- Once all edits are made, reformat the *Patient Guide* so content is limited to no more than three pages, if possible. Materials that are short yet still comprehensive are more effective. See redlined version for additional edits.

Risk of Birth Defects with TRYVIO

- Revise content and formatting. We suggest you review the following FDA-approved Qsymia REMS in the public domain (found at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>) to give you a better understanding of what the Agency is asking for in your re-submission. Use the Qsymia “Risk of Birth Defects with Qsymia” REMS material as a guide for content.
- Revise for brevity and incorporate graphics and/or charts as well as section headers to communicate the KRMs clearly to patients.

REMS Website

- Update website to reflect all changes made within and across materials.
- Clarify whether users create a password using an NPI/mobile number as a username or if the NPI number is the username and the mobile number entered serves as the password.

- Page 17 of the website screenshots contain language which begins, “ (b) (4) ”. This language should be revised to remove the word (b) (4). Suggested language is included on the redlined Website Screenshots.
- Submit all website screenshots, including post-login screenshots. Clarify which webpages are only available after login to the website.

Submit a REMS amendment that includes the following revised REMS materials within 10 business days. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). For the REMS Assessment Plan edits, include in your response an updated REMS Supporting Document including the REMS Assessment Plan in Word tracked changes, Word clean, and a clean PDF version. The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	Tracked MS Word, Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
4	Outpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
5	Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
6	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber Knowledge Assessment	Tracked MS Word, Clean MS Word, PDF version
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
9	Risk of Birth Defects with TRYVIO	Tracked MS Word, Clean MS Word, PDF version
10	REMS Website	Tracked MS Word, Clean MS Word, PDF version
11	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	PDF Version

8. Appendix

1. REMS Document
2. REMS Assessment Plan
3. Prescriber Enrollment Form
4. Outpatient Pharmacy Enrollment Form
5. Inpatient Pharmacy Enrollment Form
6. Prescriber and Pharmacy Guide
7. Patient Guide
8. REMS Website Screen Shots

9. References

¹ Soukehal, S. DCN. Information Request for NDA 217686, November 3, 2023.

² Idorsia, Email Correspondence to Agency (Soukehal, S. DCN RPM), October 27, 2023.

³ World Health Organization (WHO), Eastern Mediterranean Region, Disease Prevention, accessed October 13, 2023 from: <https://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html>.

⁴ Center for Disease Control (CDC), Picture of America – Prevention, accessed October 13, 2023 from: https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf

⁵ Crew, P. DMAMES. Email Correspondence, December 20, 2023.

58 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217686
PDUFA Goal Date	March 19, 2024
Nexus TTT#	2022-3102 and 2022-3104
Reviewer Name	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Laura Zendel, PharmD
Review Completion Date	November 3, 2023
Subject	Interim Review of proposed REMS
Established Name	aprocitentan
Trade Name	Tryvio
Name of Applicant	Idorsia Pharmaceuticals Ltd
Therapeutic Class	Endothelin Receptor Antagonist (ERA)
Formulation(s)	12.5 mg oral tablet
Dosing Regimen	12.5 mg orally once daily

(b) (4)

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Tryvio (aprocitentan), New Drug Application (NDA) 217686 submitted by Idorsia on December 19, 2022 and amended on September 6, 2023.

Tryvio is an endothelin receptor antagonist (ERA) proposed for the treatment of hypertension (HTN), to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. This application is under review in the Division of Cardiology and Nephrology (DCN).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Tryvio outweigh the risk of embryo-fetal toxicity.

This interim review discusses DRM's initial comments on the REMS proposal.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 3/9/2022: In response to a Type B Pre-NDA Meeting for IND 122772 on March 14, 2022, the Agency informed the Applicant there is insufficient information to determine whether a REMS will be necessary for aprocitentan. The Agency stated other products within the class (endothelin receptor antagonist; ERA) have REMS to mitigate the risk of embryo-fetal toxicity. The Agency encouraged the Applicant to submit a REMS with the NDA or rationale for why the Applicant believes a REMS is not needed for aprocitentan.
- 3/11/2022: The Applicant canceled the planned March 14, 2022 Pre-NDA Type B meeting and requested a meeting to discuss their planned REMS proposal for the NDA.
- 5/25/2022: The Agency informed the Applicant in response to a Type C Pre-NDA Meeting that aprocitentan, as a metabolite of macitentan, is expected to have the same teratogenic risk as macitentan; therefore, labeling and other risk mitigation would be similar to macitentan. The Agency informed the Applicant that other products within the ERA drug class have REMS with elements to assure safe use (ETASU) to mitigate the risk of embryo-fetal toxicity; and based on the information provided, a REMS will be necessary to ensure benefits outweigh risks of aprocitentan.
- 6/2/2022: A Type C teleconference was held between the Agency and Applicant for aprocitentan under IND 122772/NDA 217686, in which the Agency reiterated to the Applicant that the Agency believes a REMS with ETASU will be necessary to ensure the benefits outweigh the risks.
- 12/19/2022: NDA 217686 submitted for the treatment of hypertension with a proposed (b) (4) REMS for the risk of embryo-fetal toxicity
- 3/3/2023: A Filing Communication Letter was issued to the Applicant to inform them that no filing issues were identified. However, potential review issues were identified which include whether a REMS is needed for aprocitentan to mitigate the potential risk of hepatotoxicity and whether a (b) (4) to mitigate the risk of embryo-fetal toxicity.

- 8/23/2023: Applicant informed via teleconference that a REMS with elements to assure safe use (ETASU) was necessary for the risk of embryo-fetal toxicity associated with aprocitentan to ensure the benefits outweigh the risks.
- 9/6/2023: Applicant submitted a REMS with ETASU for the risk of embryo-fetal toxicity which constitutes a major amendment
- 9/22/2023: Information Request issued to Applicant to clarify aspects of REMS operations
- 9/28/2023: Applicant submitted response to Information Request

3. Review of Applicant's Proposed REMS

3.1. REMS Goals

Idorsia proposed the goal of the Tryvio REMS is to mitigate the risk of embryo-fetal toxicity associated with Tryvio by:

(b) (4)

Reviewer Comment: We do not agree with Idorsia's proposed REMS goal. When determining the goal and objectives for this REMS, DRM evaluated the risks, potential care gaps, prior experience with products in the ERA class, and how the goals of the REMS align with the Public Health Preventative Aims. Given the broader prescriber population, DRM identified a potential care gap that stakeholders may not be aware of the risk of embryo fetal toxicity associated with Tryvio and actions necessary to mitigate it. We determined the REMS goal should be:

Goal: To mitigate the risk of embryo-fetal toxicity associated with Tryvio (aprocitentan) by

Objective: Ensure that prescribers are aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant on the actions necessary to prevent pregnancy and minimize exposure to a fetus.

3.2. REMS Requirements

Idorsia refers to patients who can become pregnant as “ (b) (4) throughout the REMS Document, Supporting Document, and REMS Materials.

Reviewer Comment: The Agency is incorporating gender-neutral language in newly established REMS for embryo-fetal toxicity to achieve health equality, eliminate disparities, and improve health in all groups as one of the health priorities in the Healthy People 2020 and 2023 initiatives. The REMS Document, Supporting Document, and REMS Materials should all be revised to create gender neutral patient categories and use gender neutral language throughout the materials. Examples of gender-

neutral patient categories may include “patients who can become pregnant,” and “patients who cannot become pregnant.”

3.2.1. ETASU

In response to Agency comments that a REMS with ETASU would be necessary to ensure the benefits of Tryvio outweigh the risks, Idorsia proposed to include prescriber certification and specialized training on the risk of embryo-fetal toxicity (ETASU A) and to include pharmacy certification and pharmacy verification of prescriber certification prior to dispensing Tryvio (ETASU B).

Reviewer Comment: We agree with ETASU A and ETASU B for the Tryvio REMS. Prescriber training and certification (ETASU A) can ensure that all prescribers are informed of the risk of embryo-fetal toxicity and that the risk associated with Tryvio is different from the risk of embryo-fetal toxicity associated with other products that are used for treating hypertension. Prescribers will also be educated on the need to counsel patients on the risk of embryo-fetal toxicity and the actions patients should take to prevent fetal exposure and minimize fetal exposure during pregnancy. Pharmacy certification (ETASU B) is necessary to confirm that the prescriber is certified in the REMS prior to dispensing. Pharmacies can dispense patient-directed REMS materials to reinforce risk education and management for patients.

3.2.2. REMS Participant Requirements

3.2.2.1. Healthcare Provider

Idorsia proposed that to become certified, a healthcare provider who prescribes Tryvio must review the drug's Prescribing Information (PI), review the *Prescriber and Pharmacy Guide*, and enroll in the REMS by completing the *Prescriber Enrollment Form* and submitting it to the REMS. Idorsia proposed before treatment initiation, prescribers are required to assess the reproductive status (b) (4) using the definitions in the *Prescriber and Pharmacy Guide*. For (b) (4) before treatment initiation, Idorsia proposed that prescribers counsel the patient (using the (b) (4) *Patient Guide*) on the risk of embryo-fetal toxicity and the need to use (b) (4) contraception and emergency contraception. Idorsia also proposed that prescribers, before treatment initiation, assess the current pregnancy status of (b) (4) and counsel on the importance of regular pregnancy testing including prior to (within 1 month) of initiating treatment, monthly during treatment, and 1 month after treatment discontinuation. During treatment, Idorsia proposed that prescribers (b) (4)

(b) (4)

. Idorsia proposed that at all times prescribers are required to report pregnancies to the Tryvio REMS via phone.

Reviewer Comment: We agree with the proposed requirements of prescribers to become certified to prescribe. In addition to the proposed requirements for certification, Idorsia must create a prescriber knowledge assessment to be completed successfully by the prescriber in order to enroll in the REMS. The knowledge assessment should convey that the prescriber is competent in their knowledge of the risk of embryo-fetal toxicity associated with Tryvio, the need to counsel patients who can become pregnant on actions to take to avoid becoming pregnant, monitoring for pregnancy, and steps to take if a patient becomes pregnant while taking Tryvio.

We agree with the proposed requirements of prescribers to counsel patients who can become pregnant prior to starting treatment using a patient guide.

We disagree with the prescriber requirement to (b) (4). The REMS as currently designed does not require patient enrollment, monitoring, or documentation of safe use conditions. The REMS should encourage prescribers to continue to counsel patients during treatment and check-in with patients regularly during the treatment course; however, without patient enrollment in the REMS, prescribers cannot be required to (b) (4).

Prescriber Enrollment Form

Idorsia proposed a *Prescriber Enrollment Form* which requires healthcare providers who prescribe Tryvio to fill in personal and administrative information on the form and sign and date their agreement with the obligations of a certified prescriber in the Tryvio REMS.

Reviewer Comment: As mentioned above in comments on prescriber requirements, Idorsia should also require successful completion of a prescriber knowledge assessment as part of the enrollment process. The *Prescriber Enrollment Form* should also be revised to include gender neutral language and to align with the revised prescriber requirements, revised REMS Document and titles of other REMS materials.

(b) (4) Patient Guide

Idorsia proposed a (b) (4) *Patient Guide* for prescribers to review and to utilize when counseling (b) (4) before treatment initiation. The guide includes background information on Tryvio, the serious risk of birth defects associated with use, and description of the Tryvio REMS. The guide also includes REMS requirements for (b) (4), reliable birth control options, how Tryvio is dispensed, and a checklist of responsibilities for (b) (4) when starting Tryvio and during their treatment course.

Reviewer Comment: As mentioned above in comments on prescriber requirements, Idorsia should revise the proposed (b) (4) *Patient Guide* to include gender neutral language in the title (for example: 'Patient Guide' or (b) (4)) and throughout the guide, and align the guide with the revised prescriber requirements, revised requirements for patients who can become pregnant¹, and the REMS Document.

3.2.2.2. (b) (4)

Idorsia proposed that (b) (4) that are prescribed Tryvio must review the (b) (4) *Patient Guide*, (b) (4), and receive counseling from the prescriber before treatment initiation. During treatment, Idorsia proposed that (b) (4)

(b) (4). Idorsia proposed that (b) (4) are required at all times to inform a prescriber immediately if a menstrual period is missed or they suspect a pregnancy.

¹ "Patients who can become pregnant are referred to as (b) (4)" by Idorsia.

Reviewer Comment: We agree that patients who can become pregnant should review the ‘Patient Guide’ (proposed by Idorsia as the (b) (4) Patient Guide” in the current submission) and receive counseling from the prescriber before treatment initiation. We agree that patients who can become pregnant should at all times inform their prescriber immediately if a menstrual period is missed or they suspect a pregnancy.

The REMS as currently designed does not include documentation of safe use conditions, including patient enrollment, or monitoring requirements. Therefore, we do not agree with Idorsia’s proposed requirements for (b) (4)

. These requirements will be removed from the REMS.

(b) (4)
a new requirement will be added for all patients during treatment: receive a patient information hand-out from the dispensing pharmacy each time Tryvio is dispensed to the patient (further described in Section 3.2.2.3 of this review).

3.2.2.3. Pharmacy/Prescriber/Healthcare Setting that Dispenses

Outpatient Pharmacies

Idorsia proposed that to become certified to dispense, outpatient pharmacies must (1) designate an authorized representative (AR) to carry out the certification process and oversee implementation and compliance with the REMS, (2) (b) (4), (3) have the AR enroll in the REMS by completing the *Outpatient Pharmacy Enrollment Form* and submitting it, (4) train all relevant staff, and (5) (b) (4). Before dispensing, Idorsia proposed that outpatient pharmacies must verify the prescriber is certified in the Tryvio REMS, and (b) (4)

(b) (4). In order to maintain certification to dispense, Idorsia proposed that the AR complete and submit an updated *Outpatient Pharmacy Enrollment Form* to the Tryvio REMS immediately if the AR changes. Idorsia proposed at all times the outpatient pharmacy must (1) (b) (4) if a patient becomes pregnant and report the pregnancy to the Tryvio REMS, (2) the outpatient pharmacy must not distribute, transfer, loan, or sell Tryvio except to certified pharmacies, (3) it must maintain records that all processes and procedures are in place and being followed, and (4) comply with audits.

Reviewer Comment: We agree with the proposed requirements of outpatient pharmacies to become certified to dispense, to maintain certification, and to follow at all times.

We also agree outpatient pharmacies must verify the prescriber is certified with the Tryvio REMS before dispensing, but we do not agree they are required to (b) (4)

should be removed and Idorsia should add a requirement for outpatient pharmacies to dispense a patient information hand-out each time Tryvio is dispensed to all patients (also described in Section 3.2.2.2 of this review). Idorsia must create a patient information hand-out with information to reinforce education on the risk of embryo-fetal toxicity, the actions patients who can become pregnant should take to avoid pregnancy while taking Tryvio, and actions to take to minimize drug exposure to a fetus (i.e. contact prescriber immediately if pregnancy is suspected).

Outpatient Pharmacy Enrollment Form

Idorsia proposed an *Outpatient Pharmacy Enrollment Form* which requires authorized representatives for outpatient pharmacies to fill in contact and administrative information on the form and sign and date their agreement with the requirements for an outpatient pharmacy in the Tryvio REMS.

Reviewer Comment:

In response to our Information Request (IR) sent on September 22, 2023, to clarify a discrepancy between the draft REMS document and REMS supporting document, Idorsia clarified that they intend for outpatient pharmacies, inpatient pharmacies, and prescribers to be able to enroll via fax and/or online. Idorsia stated in their response on September 29, 2023 that they will revise REMS Materials to reflect this information and will submit them in response to the Agency's first iteration of comments. The Outpatient Pharmacy Enrollment Form should also be revised to include gender neutral language and to align with the revised outpatient pharmacy requirements as described in the REMS Document and titles of other REMS materials.

Inpatient Pharmacies

Idorsia proposed that to become certified to dispense, inpatient pharmacies must (1) designate an AR to carry out the certification process and oversee implementation and compliance with the REMS, (2) have the AR review the PI and *Prescriber and Pharmacy Guide*, (3) have the AR enroll in the REMS by completing the *Inpatient Pharmacy Enrollment Form* and submitting it, (4) train all relevant staff, and (5)

(b) (4)

Before dispensing, Idorsia proposed that inpatient pharmacies must verify the patient is under the supervision and care of a certified prescriber. For (b) (4), Idorsia proposed that inpatient pharmacies

(b) (4)

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order to maintain certification to dispense, Idorsia proposed that the AR complete and submit an updated *Inpatient Pharmacy Enrollment Form* to the Tryvio REMS immediately if the AR changes. At discharge, Idorsia proposed inpatient pharmacies (b) (4). Idorsia proposed at all times the inpatient pharmacy must (1) report pregnancies to the Tryvio REMS, (2) the inpatient pharmacy must not distribute, transfer, loan, or sell Tryvio except to certified pharmacies, (3) maintain records that all processes and procedures are in place and being followed, and (4) comply with audits.

Reviewer Comment: *We agree with the proposed inpatient pharmacy requirements to maintain certification to dispense, requirements upon discharge of a patient receiving Tryvio, and requirements at all times.*

We do not agree with all of the requirements for inpatient pharmacies to become certified to dispense. We agree inpatient pharmacies must designate an AR, have the AR review PI and Prescriber and Pharmacy Guide, have the AR enroll, and train all relevant staff. We do not agree that inpatient pharmacies

(b) (4)

(b) (4). We do not agree that inpatient pharmacies (b) (4).
(b) (4). This requirement to become certified to dispense should be removed.

We do not agree with all of the requirements for inpatient pharmacies before dispensing. We agree inpatient pharmacies must verify patients are under the supervision and care of a certified prescriber. The proposed requirement should be revised so inpatient pharmacies verify all patients are under the supervision and care of a certified prescriber, (b) (4). The requirement to verify that (b) (4) should be removed. Idorsia should add a requirement for inpatient pharmacies to dispense a patient information hand-out at discharge (also described in Section 3.2.2.2 and the Outpatient Pharmacy REMS Requirements section of this review).

Inpatient Pharmacy Enrollment Form

Idorsia proposed an *Inpatient Pharmacy Enrollment Form* which requires authorized representatives for inpatient pharmacies to fill in contact and administrative information on the form and sign and date their agreement with the requirements of an inpatient pharmacy in the Tryvio REMS.

Reviewer Comment: *The Inpatient Pharmacy Enrollment Form should be revised to include gender neutral language and to align with the revised inpatient pharmacy requirements as described in the REMS Document and titles of other REMS materials.*

3.2.2.4. Wholesaler/Distributor

Idorsia proposed that for wholesalers-distributors to be able to distribute Tryvio they must establish processes and procedures to ensure the drug is distributed only to certified pharmacies and they must train staff involved in distribution on the Tryvio REMS requirements. Idorsia proposed that at all times, wholesalers-distributors must distribute only to certified pharmacies and comply with audits.

Reviewer Comment: *We agree with the proposed requirements of wholesalers-distributors. If a wholesaler-distribution registration form is developed, it should be appended to the REMS supporting document.*

3.2.3. REMS Applicant Requirements

3.2.3.1. Training

Idorsia proposed to provide training to healthcare providers who prescribe Tryvio and pharmacies that dispense Tryvio. The proposed educational materials include the *Prescribing Information* and the *Prescriber and Pharmacy Guide* available online or by calling the Tryvio REMS.

Reviewer Comment: *We agree with the Applicant's proposal to provide training to healthcare providers who prescribe and pharmacies that dispense Tryvio and that it should be available online or by requesting it via phone.*

Prescriber and Pharmacy Guide

The proposed *Prescriber and Pharmacy Guide* contains information on the Tryvio indication, risk of embryo-fetal toxicity, brief summary of the proposed REMS and Goal, prescriber REMS requirements, outpatient pharmacy REMS requirements, and inpatient pharmacy REMS requirements.

Reviewer Comment:

The Prescriber and Pharmacy Guide should be revised to align with the updated REMS requirements, REMS operations, and revised REMS Document and to include gender-neutral language throughout.

3.2.3.2. Operations

Idorsia proposed they will establish and maintain a REMS Website for online enrollment, printing REMS materials, and for querying the database of certified prescribers. Idorsia also proposed they will establish and maintain a REMS coordinating center available by phone to support stakeholders, facilitate enrollment of HCPs and pharmacies, receive and process enrollment forms, provide REMS materials, and verify certified prescribers and pharmacies upon request. Idorsia proposed they will establish and maintain a validated, secure database of enrolled prescribers and pharmacies, confirm prescribers and pharmacies are able to enroll online or by fax, and confirm that pharmacies are able to confirm prescriber certification online or by calling the Tryvio REMS. Idorsia will provide certified prescribers access to the database of certified pharmacies and will provide certified pharmacies access to the database of certified prescribers.

Idorsia proposed they will provide prescribers with the *Prescriber Enrollment Form* and the *Prescriber and Pharmacy Guide* to prescribers who (1) attempt to prescribe Tryvio and are not yet certified or (2) inquire about how to become certified.

Prior to dispensing, pharmacies can query the REMS, by calling the REMS coordinating center or by accessing the online database available through the REMS website, to confirm the prescriber is certified in the REMS.

Reviewer Comment:

In response to our Information Request (IR) sent on September 22, 2023, Idorsia clarified that they intend for outpatient pharmacies (in addition to inpatient pharmacies and prescribers) to be able to enroll via fax and/or online. Idorsia stated in their response on September 29, 2023 that they will revise REMS Materials to reflect this information and will submit them in response to the Agency's first iteration of comments.

We agree Idorsia should provide prescribers with the Prescriber Enrollment Form and REMS Materials when they attempt to prescribe the first time or inquire about how to become certified. Pharmacies who are not yet certified should also be provided materials from Idorsia when they receive their first prescription or inquire about how to become certified.

Idorsia does not explain the process that pharmacies undertake to verify and/or document that the REMS requirements are met prior to dispensing. Idorsia proposed that pharmacies call the REMS or access the REMS electronic database to verify a prescriber is certified in the REMS, but it is unclear how this verification is linked to dispensing of Tryvio. Idorsia will need to clarify whether a REMS Dispense Authorization will be used or another mechanism employed to ensure the REMS requirements are met prior to dispensing.

Tryvio REMS Website

Idorsia proposed to establish and maintain a REMS Website which includes capability to complete prescriber and inpatient pharmacy enrollment online, print the Prescribing Information, Medication Guide, and REMS materials. The REMS Website will also give enrolled pharmacies access to the database of enrolled prescribers to query prior to dispensing Tryvio.

Reviewer Comment: We agree with the proposed functions of the REMS website. The website content will need to be aligned with the revised REMS requirements as described in the REMS Document.

3.2.3.3. Compliance

Idorsia proposed that to ensure participants' compliance with the REMS the Applicant must maintain records to ensure REMS requirements have been met and have the records readily available for inspection. Idorsia proposed the Applicant must also establish a plan for addressing noncompliance with the REMS requirements, monitor participants on an ongoing basis to ensure REMS requirements are being met and take corrective action if noncompliance is identified. Idorsia proposed to audit annually a portion of certified pharmacies and all wholesalers to ensure REMS processes and procedures are in place, functioning, and support the REMS requirements. Idorsia proposed to audit all wholesalers-distributors within 180 days after they become (b) (4). Lastly, Idorsia proposed to take reasonable steps to improve the operation and compliance with the REMS requirements based on monitoring and evaluation of the REMS.

Reviewer Comment: Applicant requirements for compliance will be addressed in a future review.

3.2.4. Key Risk Messages

A detailed discussion of the proposed key risk messages will be included in a forthcoming review.

3.3. REMS Assessment Timetable

Idorsia proposed that the Applicant must submit the REMS Assessments annually from the date of initial REMS approval. The REMS Assessment Timetable will be addressed in a future review.

4. Supporting Document

The REMS Supporting Document includes the background and goal of the REMS currently under review. The REMS Supporting Document provides more information on proposed elements of the REMS described as prescribers being specially certified (Section 3.1.1), (b) (4) (Section 3.1.2), pharmacies that dispense Tryvio will be certified (Section 3.1.3), and wholesaler-distributor requirements (Section 3.1.4). The REMS Supporting Document also includes more details regarding the Implementation System, role of the Coordinating Center, and Audit Plan.

Reviewer Comment: The REMS Supporting Document must be revised to align with the revised REMS Document, operations, and requirements as discussed in this review. The Applicant cannot use language such as “(b) (4)” and “(b) (4)” to describe actions of prescribers and/or pharmacies that are not REMS requirements. For example, section 3.1.2 of the proposed REMS Supporting Document states “(b) (4) This requirement should be eliminated or revised to “(b) (4) since confirmation of patient counseling will not be a requirement of pharmacies in the Tryvio REMS.

4.1. REMS Assessment Plan

A detailed REMS Assessment Plan will be addressed in a future review.

5. Discussion

Following extensive discussions with the REMS Oversight Committee (ROC) on May 16, 2023 and May 31, 2023, and through email on July 20, 2023, DRM and DCN obtained ROC concurrence for a proposed Tryvio REMS with ETASU A and B.¹ The intent of the REMS is to educate prescribers on the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients on the actions necessary to prevent and minimize Tryvio exposure to a fetus. A REMS with ETASU is necessary for Tryvio to ensure prescribers are knowledgeable about the risk and dispensed only when prescribed by a certified prescriber.

DRM and DCN discussed and agreed to incorporate gender-neutral language and patient categories in the Tryvio REMS to align with our current approach that newly established REMS for embryo-fetal toxicity use such language to achieve health equality, eliminate disparities, and improve health in all groups as one of the health priorities in the Healthy People 2020 and 2023 initiatives. This agreement is supported by the ROC who agreed earlier this year that REMS materials may use gender-neutral language, though it may diverge from sex and gender terms used in labeling.¹

The Applicant proposed REMS Goal requires revisions to align with the principles of the REMS Logic Model and Public Health Prevention Aims^{2,3}. The Applicant-proposed REMS requirements require revisions to align with the intended outcome of the REMS, the revised REMS Goal, and a REMS with ETASU A and B only. REMS requirements that (b) (4)

, must be removed since patients will not be enrolled in the Tryvio REMS. A limitation of this REMS design is that the REMS will not ensure patients are not pregnant prior to starting Tryvio or monitored during treatment because pregnancy testing and monitoring is not documented and verified under the REMS requirements. Prescribers are responsible for determining reproductive status of patients, prescribing for appropriate patients, and counseling patients who are prescribed Tryvio. Given the emphasis on prescriber education on the risks, we are adding a requirement for prescribers to successfully complete a prescriber knowledge assessment in order to enroll in the REMS. Successful completion of a prescriber knowledge assessment supports confirmation that prescribers of Tryvio have knowledge of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients on the actions patients should take to prevent pregnancy and minimize exposure of a fetus to Tryvio.

6. Conclusions and Recommendations

DRM does not find the proposed REMS for Tryvio (aprocitentan) as submitted on December 19, 2022 and last amended on September 6, 2023, to be acceptable, as described in this review. Send the comments in Section 7 to Idorsia in an Information Request and instruct the Applicant to submit a REMS amendment within 10 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on September 6, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comment

- The Agency is moving toward establishing REMS goals based on Public Health Preventative Aims (Adopted from: [World Health Organization, Centers for Disease Control](#)). We have provided an updated Tryvio REMS goal based on this. See the redlined REMS Document for the revised goal and update your REMS proposal accordingly.
- The Agency is incorporating gender-neutral language in newly established REMS for embryo-fetal toxicity to achieve health equality, eliminate disparities, and improve health in all groups as one of the health priorities in the Healthy People 2020 and 2023 initiatives. Update the language in the REMS Document and all REMS materials to establish gender neutral patient categories and use gender neutral language throughout. You may refer to other REMS, such as isotretinoin (iPLEDGE), Qsymia, and Filspari for examples.
- Revise the following materials to incorporate changes to the REMS requirements as requested below:
 - *Prescriber Enrollment Form*
 - *Outpatient Pharmacy Enrollment Form*
 - *Inpatient Enrollment Form*
 - *Prescriber and Pharmacy Guide*
 - (b) (4) *Patient Guide*
 - *Website Screenshots*

REMS Document

Redlined edits and comments are provided. Please update and align the REMS materials and website with the changes in the REMS Document.

- REMS Administrative Information
 - Add the risk that the REMS addresses to the Administrative Information (Section I) of the REMS Document in alignment with the January 2023 *Format and Content of a REMS Document Guidance for Industry* and *REMS Document Technical Conformance Guide*.
- REMS Goal
 - Update the REMS goal statement to align with the Public Health Preventative Aims.
- Participant enrollment/certification
 - Update REMS materials to indicate that all participants may enroll by fax and online.
 - Create a prescriber knowledge assessment to be successfully completed by the prescriber after reviewing the training materials in order to enroll in the REMS. The assessment should support confirmation that the prescriber is aware of the risk of embryo-fetal toxicity associated with Tryvio and the need to counsel patients who can become pregnant. The assessment should be made available via all modalities for enrollment (i.e. online, fax, etc.).
- REMS Requirements
 - We do not agree with your proposed requirements (b) (4) REMS design. All requirements related to (b) (4) should be removed.

- REMS materials should still emphasize the importance of ruling out pregnancy before starting treatment and appropriate monitoring during treatment.
- To ensure patients are aware of the risk and actions required to mitigate the risk, develop a patient information sheet that pharmacies will be required to dispense to all patients with every Tryvio prescription. The patient information sheet will reinforce risk information and mitigation to patients during treatment. You may refer to the Qsymia REMS for an example of a REMS that has a similar pharmacy requirement.
- We do not agree that inpatient pharmacies are required to (b) (4).
 (b) (4). Revise the requirement so inpatient pharmacies are required to verify all patients taking Tryvio are under supervision and care of a certified prescriber, (b) (4).
- Add the requirement for the Applicant to provide an enrollment form and REMS materials to pharmacies who receive a Tryvio prescription to fill for the first time and/or when a pharmacy inquires about how to become certified in the REMS.
- See edits in the redlined REMS Document for details regarding these changes

REMS Supporting Document

- Align all revisions to the REMS requirements and REMS Document to the REMS Supporting Document, including the REMS Assessment Plan. Comments on the REMS Assessment Plan will be forthcoming in a future communication.
- You proposed that pharmacies call the REMS or access the REMS electronic database to verify a prescriber is certified in the REMS, but it is unclear how this verification is linked to dispensing of Tryvio. Clarify whether a REMS Dispense Authorization will be used, or provide more detail regarding another mechanism employed to ensure the REMS requirements are met prior to dispensing by pharmacies.

Prescriber Enrollment Form

- Add prescriber knowledge assessment completion as a requirement to become certified to prescribe.

Outpatient Pharmacy Enrollment Form

- As noted in your September 29, 2023 Information Request response, revise the form to reflect outpatient pharmacies may enroll via fax and/or online.

Patient Information Sheet

- Create a brief patient information sheet to be dispensed by pharmacies to all patients who receive Tryvio with each medication dispense. The material should be no longer than one page and should communicate the following:
 - Risk of embryo fetal toxicity to patients who can become pregnant
 - Description of patients who can become pregnant
 - Actions patients who can become pregnant should take to avoid getting pregnant while taking Tryvio
 - Actions patients should take if they become pregnant while on Tryvio treatment

Submit a REMS amendment that includes the following revised REMS materials within 10 business days. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	Tracked MS Word, Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Website Screenshots	Tracked MS Word, Clean MS Word, PDF version
4	Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
5	Outpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
6	Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
8	Prescriber Knowledge Assessment	Clean MS Word, PDF version
9	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
10	Patient Information Sheet	Clean MS Word, PDF version
11	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	PDF Version

8. Appendix

1. REMS Document

9. References

¹ REMS Oversight Committee (ROC) Meeting Minutes, May 11, 2023.

² World Health Organization (WHO), Eastern Mediterranean Region, Disease Prevention, accessed October 13, 2023 from: <https://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html>.

³ Center for Disease Control (CDC), Picture of America – Prevention, accessed October 13, 2023 from: https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf

7 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

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