Category

Best Pharmaceutical Product

General Information

Company Name *

Idorsia Pharmaceuticals Ltd.

Product/Solution Name *

Aprocitentan

Compound/Tech Name*

Aprocitentan

Trade Name *

TRYVIO

Corporate Name *

TRYVIO

Date of Approval *

2024-03-19

Indications *

TRYVIO is a dual endothelin receptor antagonist (ERA) indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure (BP) in adult patients who are not adequately controlled on other drugs. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions.

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Therapeutic Areas *

Hypertension, resistant hypertension, difficult to control hypertension, hypertension in patients with chronic kidney disease, hypertension in African American patients, hypertension in elderly, in high body weight patients, in patients with type 2 diabetes.

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Attached Files:

- Idorsia_Aprocitentan_US FDA Package Insert.pdf

Background information and need for drug / device
(please be as specific as possible in your description; limit 500 words)

Size of the problem: Hypertension, defined by a BP of 130/80 mmHg or higher, affects ≈45% of the US adult population (1.3 billion worldwide) [1]. Hypertension is a major cause of strokes, myocardial infarction, heart failure and chronic kidney disease (CKD). Hypertension is the leading modifiable risk factor for cardiovascular disease and premature death [2]. Control of BP has been shown to improve prognosis and lower risks of cardiovascular, renal, and cerebrovascular complications, including Alzheimer's [3-5]. However, there has been little important innovation in the last 40 years, and TRYVIO is the first anti-hypertensive to act via a new mechanism since captopril.

A major medical need: Despite numerous available therapeutic options for hypertension, >50% of adults do not achieve the BP goals of 130/80. In addition, 10-20% of patients have resistant hypertension (RHT) [6], when BP remains high despite a combination of ≥3 drugs of different classes at their maximum tolerated doses, including a diuretic [7]. Uncontrolled hypertension, particularly RHT, is a critical unmet medical need as the risk of cardiovascular diseases and death is markedly increased compared to well-controlled hypertension (30% increased risk of death, doubled risk of heart failure and CKD) [5]. RHT is frequently associated with CKD, obesity, diabetes, ischemic heart disease and heart failure, which can all be causes and consequences [8-11].

Why endothelin? Starting with our first publication in 1989 [12,13], we hypothesized that an overstimulated endothelin (ET) system plays a central role in hypertension: Endothelin-1 is the most potent vasoconstrictor [14], a potentiator of other vasoconstrictors or growth factors, is pro-fibrotic and pro-inflammatory. Yet none of the available antihypertensive therapies inhibited the detrimental effects of ET. We speculated that the persistence of hypertension in 50% of patients was due to unopposed ET activity, highlighting the need for a novel approach specifically targeting the ET system, especially because drugs frequently used in RHT have limitations.

Blockade of the RAAS system has limitations: Spironolactone is frequently used as a fourth- or fifth-line agent in patients not at treatment goals despite guideline-directed therapy. However, spironolactone is limited by poor tolerance, high discontinuation rate and safety concerns, especially among those with CKD. Spironolactone may cause life-threatening hyperkalemia and worsening of renal function, even in patients with mild or moderate CKD [15]. Intensive blockade of the renin-angiotensin-aldosterone system (RAAS) commonly poses risks of hyperkalemia, hyponatremia and aggravation of renal function [16-18]. Accordingly, the renin inhibitor aliskiren became contraindicated in combination with a second RAAS blocker [19] , and precautions are required when two RAAS blockers are co-administered. TRYVIO (aprocitentan) has a novel mechanism of action, targets the ET system and can be added safely to existing anti-hypertensive drugs, including RAAS blockers [20].

For these reasons there was a need for an innovation like TRYVIO. TRYVIO is the first therapy to target the ET pathway in hypertension. It provides an effective and well-tolerated treatment for patients with uncontrolled and resistant hypertension. As such, the discovery of aprocitentan addresses an extremely important unmet need that can revolutionize the treatment of hypertension.

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Attached Files:

- Idorsia_Aprocitentan_Background 1_Trensz et al 2019.pdf
- Idorsia_Aprocitentan_Background 2_Clozel 2022.pdf
- Idorsia_Aprocitentan_Background 3_AHA Hypertension Presentation.pptx

History of the development of the solution/product *
(please be as specific as possible in your description; 500 words)

Aprocitentan is the result of 35 years of research on endothelin and endothelin receptor antagonists (ERAs).

Our research history: Endothelin was discovered in 1988 [14]. Since then, the research team of now Idorsia has led the research on the role of endothelin and its receptors, the possible therapeutic applications of endothelin blockers, and the discovery of ERAs. This team has published over 200 peer-reviewed manuscripts on this topic. Among those, we published on the discovery of 8 ERAs with different profiles of selectivity [20-27], ETA selective, ETB selective and dual, which served as pharmacological tools to elucidate the role of the endogenous ET system in physiology and pathology. As a result of this research, we discovered that a dual profile was preferred in chronic diseases to maximize efficacy and minimize fluid retention [28-31].

Our drug discovery history: This work initially resulted in two drugs, Tracleer (bosentan) [32] and Opsumit (macitentan) [33], which revolutionized the treatment of pulmonary arterial hypertension (PAH). Tracleer was the first molecule to be studied in a placebo-controlled trial and Opsumit was the first to slow disease progression. Our work opened the way to other important discoveries by other teams, and, twenty-four years after the registration of Tracleer, the prognosis of PAH has dramatically improved. The Idorsia team later registered Tracleer in digital ulcerations of scleroderma. In 2020, a third ERA, Pivlaz (clazosentan) was approved in Japan for the prevention of delayed ischemic neurological deficits in subarachnoidal hemorrhage [21,34].

Arriving at aprocitentan: Aprocitentan, our 4th ERA, results from the learnings of this research. Even though we showed early on that ERAs decrease BP in hypertension [35], it took time to arrive at a perfectly suited drug for the treatment of hypertension, a disease with minimal symptomatology, where ease-of-use and excellent tolerability are paramount. Our first ERAs were not yet suited: Tracleer posed a risk of liver toxicity. Opsumit was devoid of liver liability, but it accumulated in patients with low kidney function and had significant drug-drug interactions, as it was mostly metabolized by cytochrome CYP3A4. TRYVIO is devoid of any increased exposure in patients with renal failure, has no liver toxicity and is not metabolized through any cytochromes.

TRYVIO: Aprocitentan has now been registered in 2024 under the brand name TRYVIO in the US and JERAYGO in EU and UK. After it showed a BP lowering effect superior to that of lisinopril in Phase 2 [28], we proved in a very stringent Phase 3 study called PRECISION, which enrolled confirmed RHT patients, a highly significant and durable BP lowering (-15.4 mmHg), even on top of three or more anti-hypertensives [36,37]. It also caused major reduction in albuminuria (-67% in albuminuric patients on top of valsartan) and metabolic effects (decrease in lipids). It has no relevant drug-drug interactions and is efficacious and safe in difficult-to-treat hypertension: in African-Americans [38], patients with

CKD (no accumulation, no renin nor potassium increase) [39,40] and elderly (no orthostatic hypotension, thus no falls) [37].

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Attached Files:

- Idorsia_Aprocitentan_Evidence 1_Verweij et al 2020.pdf
- Idorsia_Aprocitentan_Evidence 4_Flack et al 2025.pdf
- Idorsia_Aprocitentan_Evidence 3_Schlaich et al 2022.pdf
- Idorsia_Aprocitentan_Evidence 2_Danaietash et al 2022.pdf

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

TRYVIO is a true therapeutic breakthrough and has impressive clinical data. The drug is unique in many aspects:

1) Innovation in hypertension: TRYVIO is the first drug registered by FDA for not adequately controlled hypertension including RHT. TRYVIO showed highly significant, rapid and durable BP lowering effects in RHT patients, and impressive nighttime BP lowering [37]. Lack of sufficient BP dipping at night correlates with poor prognosis. TRYVIO also decreased aldosterone, triglycerides and cholesterol [41].

2) Who will TRYVIO help the most? TRYVIO decreased BP in subgroups of patients notoriously difficult to treat, such as African Americans [38], elderly patients [37], CKD patients [39] and patients with diabetes.

3) Unique benefit in hypertensive CKD patients: Unlike other classes of anti-hypertensives, TRYVIO provides a safe and effective treatment for patients with CKD. In PRECISION, we included patients with eGFR as low as 15 mL/min/1.73 m2. Contrary to RAAS blockers, TRYVIO does not increase the risk of hyperkalemia. Importantly, TRYVIO markedly reduced albuminuria [38,39]. Reducing proteinuria has been shown to slow progression of CKD [42]. TRYVIO was well tolerated and safe and may confer a considerable renoprotective effect [37].

4) Why is blocking endothelin so important? The reduction in BP observed with TRYVIO could lower the risk of major cardiovascular events (MACE) by more than 30% [43]. TRYVIO can provide major end-organ damage protection for additional reasons beyond BP: first, because of the strong nighttime BP lowering, second, because ET, by causing cardiac and vascular hypertrophy, mesangial proliferation, fibrosis and inflammation, certainly contributes to end-organ damage in hypertension [Reviewed in 44], including Alzheimer's disease and atrial fibrillation [45,46]. In Phase 3, two observations already suggest a benefit beyond BP reduction: the major reduction in albuminuria was not correlated with, and surpassed, the BP reduction, and the number of MACE over the 48 weeks of PRECISION were lower than published databases in RHT patients [39,47].

5) An impressive tolerability: Safety and tolerability of TRYVIO are particularly good, with only 7.3% discontinuation over 48 weeks in PRECISION [37]. The only two side effects were mild peripheral edema, which caused less than 1% discontinuation, and decrease in hemoglobin by plasma volume

expansion [37,48]. There were no headaches, tachycardia or orthostatic hypotension. Three main reasons for this tolerability:
- TRYVIO only acts on the up-regulated ET system (it does not decrease BP in healthy subjects, even at 50-fold higher dose than in hypertension) [49].
- Dual ERAs blunt baroreceptor reflexes, explaining the absence of reactive tachycardia, even when BP is markedly reduced [50].
- Aprocitentan does not cause excessive blockade of the RAAS and therefore does not expose to a risk of aggravation of renal function [18].

In conclusion, TRYVIO represents the first major advancement in antihypertensive therapy in over 40 years, introducing a novel mechanism, and may significantly improve cardiovascular outcomes. First evidence after approval confirms exceptional efficacy and tolerability.
Beyond its first indication, TRYVIO may offer benefits in CKD patients undergoing hemodialysis, in pre-eclampsia, the leading medical cause of maternal death, and more.

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Attached Files:

- Idorsia_Aprocitentan_Innovation 3_Press Release 1.pdf
- Idorsia_Aprocitentan_Innovation 4_Press Release 2.pdf
- Idorsia_Aprocitentan_Innovation 6_Press Release 4.pdf
- Idorsia_Aprocitentan_Innovation 5_Press Release 3.pdf
- Idorsia_Aprocitentan_Innovation 2_Markus Schlaich.pdf
- Idorsia_Aprocitentan_Innovation 7_Press Release 5_REMS Removal.pdf
- Idorsia_Aprocitentan_Innovation 1_MACE Abstract 2024.docx
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Please provide appropriate references (PubMed, Abstract, Website) *

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