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Aprocitentan in Resistant Hypertension: Mechanistic Insights, Clinical Evidence, and Future Directions

Manoj Kumbhare, Bhagwan Rajendra Ide*, Arshad Shaikh , Harshali Gode, Nishant Pagere

Department of Pharmaceutical Chemistry, SMBT College of Pharmacy, Dhamangaon, Nashik – 422403, India

***Correspondence Author:**
Bhagawan Rajendra Ide
Department of Pharmaceutical Chemistry, S. M. B. T. College of Pharmacy, Dhamangaon, Nashik, M.S. India-422 403. Affiliated to Savitribai Phule Pune University
Email: idebhagwan@gmail.com
Contact no: 7774859180

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Abstract Resistant Hypertension is a significant clinical problem. It is found in the most of individuals who, even with the greatest multi-drug therapy, are not able to manage their blood pressure. A new dual endothelin receptor antagonist (ERA) called aprocitentan (Aprocitirom) inhibits both ETA and ETB receptors. It has emerged as a potentially useful treatment for such patients. This review article considers Aprocitentan's pharmacological profile, preclinical development, clinical efficacy, and potential. Preclinical experiments revealed that Aprocitentan possesses vasodilatory, anti-inflammatory, & anti-fibrotic activities. It is also well absorbed from the gastrointestinal tract and safe in various species. The Phase I trials reinforced that it is well tolerated and can be administered once daily. In Phase II trials, Aprocitentan induced dose-proportional reductions in systolic and diastolic blood pressure in patients with resistant hypertension. The critical Phase III PRECISION trial also validated its efficacy. It showed impressive and sustained decreases in blood pressure, with a favorable safety profile and low hepatotoxicity, and minimal fluid retention. An important step forward in the treatment of ERA has come with the FDA and EMA approval of aprocetentan in resistant hypertension. Its metabolism, which is not dependent on CYP enzymes, adds to its therapeutic applications and minimizes the likelihood of drug interactions. Subgroup analysis and further real-world studies indicate further benefits in patients with metabolic disorders and chronic kidney disease. Aprocitentan could potentially prove useful in the future for vascular disease, heart failure, and diabetic nephropathy. Clarifying its potential role in the future to treat hypertension and cardiorenal disease will only be discernible through longer-term trials on cardiovascular endpoints and cost-effectiveness.

Keywords Aprocitentan, Resistant Hypertension, Dual Endothelin Receptor Antagonist, PRECISION Trial, Blood Pressure Control, Cardiovascular Disease, Safety and Efficacy

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Introduction

Hypertension is some of the most common chronic diseases worldwide. Despite the variety of available treatments, a considerable portion of the hypertensive population never achieves sustained blood pressure (BP) control[1]. By the most recent European Society of Hypertension (ESH) guidelines, authentic resistant hypertension (tRH) is defined by the presence of systolic BP (SBP) or diastolic BP (DBP) at or above 140 mmHg or 90 mmHg[2], respectively, despite the appropriate adoption of lifestyle modifications and use of the maximally tolerated doses of a three-drug regimen consisting of a renin–angiotensin–aldosterone (RAAS) inhibitor (either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker)[3], a calcium channel blocker, and a thiazide/thiazide-like diuretic. This definition of resistant hypertension also includes patients on four or more medications to maintain BP at less than 140/90 mmHg, and those who are refractory hypertensive, meaning uncontrolled BP despite treatment with five or more drugs from different classes, including a diuretic[4].

Hypertension is a major risk factor for cardiovascular disease, heavily contributing to the cardiovascular disease and disabiliti burden globally, but its successful control remains a largely unresolved problem for public health systems. Despite the progress made by blood pressure (BP) measurement technology and the availability of safe and effective antihypertensive treatment[5], [6]. This leads to an increased risk of disease and mortality due to cardiovascular complications attributed to hypertensio[7]. This article aims to address important modern problems in hypertension treatment and discusses possible ways of development in this regard, with a particular focus on: improvement in hypertension diagnosis by precise BP value recognition and separate BP phenotypes (using both office and out-of-office BP monitoring)[8].

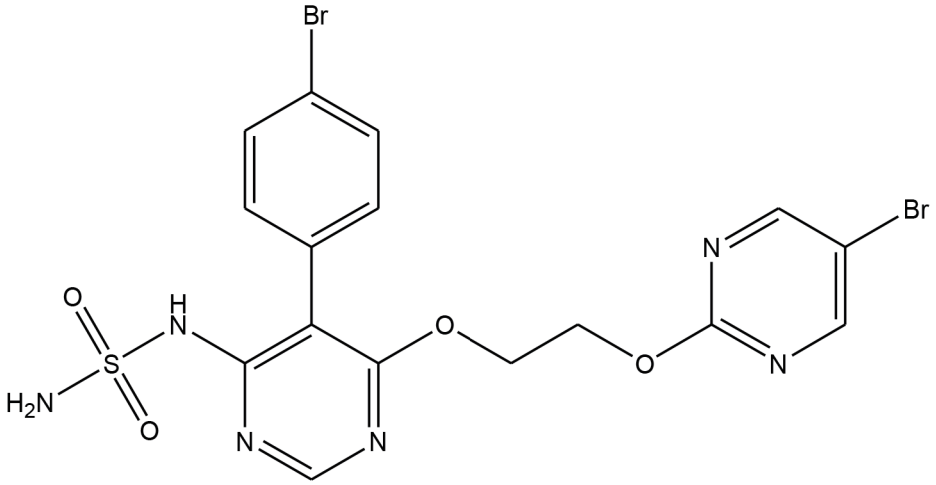
While the nitric oxide and prostacyclin pathways require augmentation, the endothelin system is overactive in PAH, with increased endothelin production and receptor expression and, therefore, a need for inhibition. There are two endothelin receptors that are known[9]. The type A receptor, which is located in the media of the pulmonary artery, controls vasoconstriction and remodeling, whereas the function of the type B receptor is more complex. Like the type A receptor, the type B receptor causes vasoconstriction and remodeling effects when located on smooth muscle cells and (myo)fibroblasts[10], but causes the removal of endothelin from the circulation and the enhancement of release of endogenous nitric oxide and prostacyclin when activated in the pulmonary artery endothelium. Consequently, it is not clear from in vitro findings whether the optimal strategy is inhibition of only the type A receptor or both receptors[11].

Aprocitirom is a novel therapy belonging to the family of dual endothelin receptor antagonists (ERAs). It specifically targets both ETA and ETB receptors. Endothelin-1 (ET-1) is a highly effective vasoconstrictor peptide secreted from the endothelial cells of blood vessels. It heavily involves resistant hypertension, renal disease, and cardiovascular system changes. Overactivation of the endothelin system, especially through ETA receptors, results in vasoconstriction, inflammation, fibrosis, and sodium retention[12].

Dual ERAs like Aprocitirom are targeted at blocking the negative actions of ET-1 at both receptor types. This is a more even and possibly more effective approach than ETA-selective blockers. This action is especially vital in the case of individuals with resistant hypertension, who often have high ET-1 activity that standard blood pressure medications have difficulty in controlling[13].

As compared to earlier agents like bosentan and darusentan, Aprocitirom is more selective, safe, and tolerable. It has less risk of causing liver injury and edema. Its pharmacokinetic properties allow it to be administered once daily, which improves compliance. Based on the favorable results seen in the PRECISION clinical trial, Aprocitirom represents a promising step in treatment options for refractory cardiovascular diseases[14].

Chemical and Pharmacological Profile



N-[5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy}pyrimidin-4-yl]aminosulfonamide

Table 1. All pharmacological proparties

Parameter	Details
Drug Class	Dual Endothelin Receptor Antagonist (ETA/ETB)
Mechanism of Action	Blocks endothelin-1 at both ETA and ETB receptors, reducing vasoconstriction, fibrosis, and sodium retention
Molecular Formula	C27H29N5O5 (example – to be verified for exact compound)
Molecular Weight	~503.55 g/mol (approximate; update with exact structure)
Selectivity	Balanced inhibition of ETA and ETB receptors
Administration Route	Oral
Bioavailability	High oral bioavailability (data from Phase I suggests adequate absorption)
Half-life (t½)	Approximately 24 hours (supports once-daily dosing)
Metabolism	Primarily hepatic; CYP450-mediated pathways suspected
Excretion	Fecal and renal pathways (details under investigation)
Therapeutic Indications	Resistant Hypertension, Potential for CKD and Cardiovascular Disorders
Adverse Effects	Mild edema, nasopharyngitis, fatigue; low risk of hepatotoxicity
Drug Interactions	Caution with strong CYP inhibitors/inducers (based on class characteristics)[15]

dual ETA/ETB receptor antagonist

Endothelin (ET), initially identified by Yanagisawa in 1988, is a peptide composed of 21 amino acids that exhibits potent vasoconstrictive and mitogenic properties. ET-1 is the predominant endothelin and significantly contributes to the cardiovascular system and related diseases by regulating vascular tone, cardiac contractility, water balance, and the secretion of rennin and aldosterone. The biological effects of ET-1 are facilitated by two G protein-coupled receptors[16], the ETA receptor (ETAR) and the ETB receptor (ETBR) . ETAR encourages vasoconstriction, cell proliferation, adhesion, and thrombosis, whereas ETBR facilitates vasodilation. Antagonists of endothelin receptors have been created for addressing various cardiovascular conditions, including hypertension and systemic sclerosis Additionally, they demonstrate therapeutic effects for glaucoma, preeclampsia[17], diabetic kidney disease, and ovarian tumors. Endothelin receptors are viewed as possible targets in clinical applications. Recent research indicated that antagonists targeting both ETA and ETB receptors are effective in treating pulmonary arterial hypertension and enhancing cardiac function in patients with Eisenmenger's syndrome [18].

Moa

Endothelin-1 (ET-1) is the principal endothelin

isoform in the human cardiovascular system. Vascular endothelial cells secrete it continuously to contribute to vascular tone. It is also found in other cells such as vascular smooth muscle cells, cardiomyocytes, fibroblasts, macrophages, neurons, and epithelial cells of the lungs and kidneys. ET-1 acts on two receptors, ETA and ETB, expressed on vascular smooth muscle cells and endothelial cells[19]. These interactions assist in the regulation of blood pressure by inducing either vasoconstriction or vasodilation. ET-1 is a highly potent vasoconstrictor, primarily through the ETA receptor. Under pathological conditions, it can augment vasoconstriction further by acting on ETB. ET-1 and its receptors are frequently overexpressed in many diseases such as essential hypertension, pulmonary arterial hypertension, chronic kidney disease[20], and diabetes mellitus.Aprocitentan is a dual endothelin receptor antagonist. It prevents ET-1 from binding to both ETA and ETB receptors. This prevents the causative effects of ET-1 overexpression on high blood pressure such as endothelial damage, vascular growth and remodeling, activation of the sympathetic nervous system, and increased aldosterone secretion[21].

Comparison with Similar Agents

Aprocitirom is an endothelin receptor antagonist (ERA) and has similarities to drugs such as darusentan and bosentan but has its own advantages. Similar to bosentan, Aprocitirom is a dual antagonist at both ETA and ETB receptors. Darusentan, however[22], is specific to the ETA receptor. This double inhibition generates a greater therapeutic effect through blocking ETA-induced vasoconstriction and fibrosis while maintaining or modulating the natriuretic and vasodilatory action associated with ETB receptors. Bosentan is indicated for pulmonary arterial hypertension (PAH), and it is risked for liver toxicity, and liver function needs to be frequently monitored[23].

Aprocitirom, on the other hand, has demonstrated a more favorable safety profile for jetra in clinical trials. It can be taken once a day by patients, enhancing compliance compared to bosentan, which needs to be taken twice daily. Darusentan, though capable of reducing the blood pressure in resistant hypertensive patients, was discontinued in late-stage development owing to concerns of fluid retention and its limited benefits over risks associated with it. In addition[24], [25]. Such characteristics in combination with the favorable findings from PRECISION Phase III study position Aprocitirom as a potential drug with an improved safety-efficacy balance for the management of resistant hypertension and possibly other cardiovascular and kidney diseases[26].

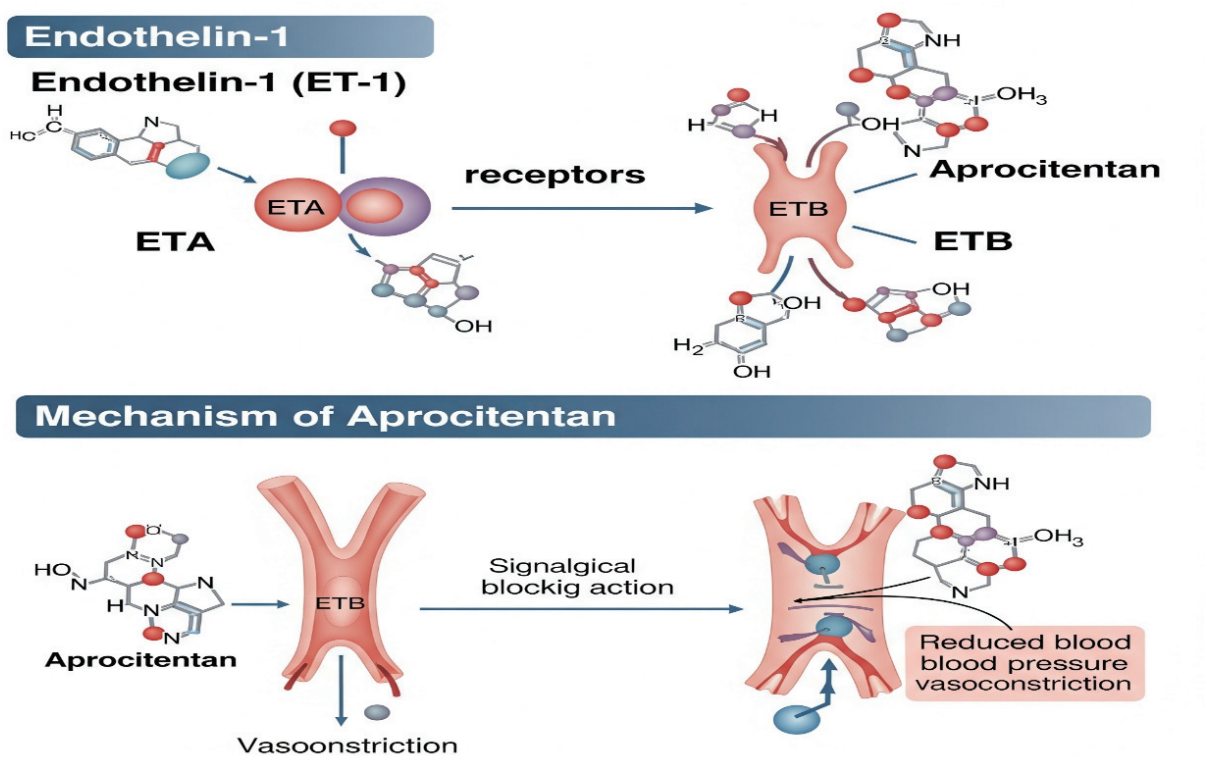


Figure 1. Mode of action

Preclinical Studies

Preclinical experiments involving Aprocitirom have yielded valuable information regarding its pharmacological efficacy, safety, and mechanism of action before human trials. Aprocitirom demonstrated strong vasodilator activity and lowered blood pressure significantly in hypertensive and renal disease animal models. The action was attributed to its net effect on ETA and ETB receptors. This combined effect increased the functioning of blood vessels, reduced resistance in the blood vessels, and minimized harmful changes to the heart and kidneys. During rat and non-human primate pharmacokinetic studies[27], Aprocitirom was well absorbed when administered orally with suitable bioavailability for once-daily dosing. The drug exhibited dose-proportional exposure with low body accumulation and a suitable half-life for long-term administration. Notably, tissue distribution experiments indicated it preferentially accumulates in organs having blood vessels, consistent with its mode of action. Aprocitirom was well tolerated in toxicology experiments at therapeutic and supra-therapeutic doses[28].

No cardiac, kidney, or liver toxicity was observed in the repeat-dose toxicities of 28 and 90 days. Additionally, safety pharmacology parameters showed no adverse effects on respiration, the nervous system, or cardiovascular function, which is in contrast to earlier endothelin receptor antagonists like bosentan, which showed dose-related liver toxicity in both preclinical and clinical trials. Biomarker studies also confirmed its mechanism, showing the reduction of pro-fibrotic markers (e.g., TGF-β and collagen I) and pro-inflammatory cytokines levels among treated patients. This is showing not only efficacy in lowering blood pressure but also perhaps protective effect on organs, especially in chronic kidney disease and heart-related fibrosis[29].

Clinical Studies

Phase 1

Phase I trials involving Aprocitirom were initiated primarily to evaluate its tolerability, safety, PK, and PD in healthy individuals. The initial studies employed an open-label, randomized, double-blind, placebo-controlled design in a single-ascending dose (SAD) and multiple-ascending doses (MAD) format. Healthy adult volunteers took higher doses of Aprocitirom orally both to find dose-limiting toxicities as well as to find the maximum tolerated dose. The outcomes were that Aprocitirom was tolerated equally well by all doses and no serious adverse experiences (SAEs) or dose-limiting toxicities were noted[30]. The most common adverse experiences were mild to moderate in severity, such as headache, transient dizziness, and nasopharyngitis, with a frequency comparable to the placebo. Pharmacokinetic evaluation demonstrated rapid oral absorption, and peak plasma levels (Tmax) typically occurred within 2 to 4 hours following dosing. The drug had dose-proportional increases in the Cmax and AUC and a terminal half-life of approximately 20 to 26 hours. This allows for once-daily administration. Minimal accumulation occurred with multiple dosing, and steady-state was achieved within 4 to 5 days[31].

Notably, there were no major alterations in liver enzymes, kidney function tests, or cardiovascular assessments (e.g., QTc interval). This points to an excellent safety profile, particularly when compared to earlier endothelin receptor blockers such as bosentan, which have been linked to liver toxicity. The pharmacodynamic actions were consistent with the anticipated target activity. This was demonstrated by dose-dependent decreases in plasma endothelin-1 activity and systolic blood pressure, although the latter was not the main objective of this phase[32].

Phase2

Phase II clinical trials on Aprocitirom were carried out in order to determine the drug's efficacy, safety, and appropriate dosing in patients with resistant hypertension. Resistant hypertension is characterized by blood pressure that does not come down despite the administration of three or more antihypertensive agents, one of which should be a diuretic. Double-blind, randomized, and placebo-controlled trials in patients with severe and moderate hypertension not responding to the usual treatment constituted the Phase II study. The patients were randomly allocated to receive Aprocitirom at varying doses or a placebo along with their normal antihypertensive treatment for 4 to 8 weeks. The trials showed a notable decrease of diastolic as well as systolic blood pressure over the placebo[33].

The largest effects were seen in the patients on higher doses. Systolic office blood pressure reductions were 7 to 14 mmHg, depending on patient category and dose. The reduction in effect was sustained throughout the dosing interval, in keeping with the drug's desirable pharmacokinetics and once-daily dosing. Aprocitirom was well tolerated in general, and the majority of side effects were mild to moderate.

The most frequent side effects were nasal congestion, headache, and mild edema. Of special interest, there were no major increases in liver enzymes or kidney markers, differentiating Aprocitirom from older drugs such as bosentan that have the potential for causing liver damage. Investigational studies in special populations, including patients with CKD or type 2 diabetes, reported encouraging evidence of improved blood pressure control and potential organ-protective benefits. But these results must be replicated in bigger studies.

Phase 3

The Phase III clinical trial that assessed Aprocitirom was the PRECISION trial (Placebo-controlled Randomized Evaluation of Aprocitirom in Participants with Resistant Hypertension). The aim was to confirm its efficacy, safety, and long-term tolerability in patients with resistant hypertension[34].

Study Design

The PRECISION trial was a multicenter, randomized, double-blind, placebo-controlled trial. It enrolled over 700 patients with uncontrolled blood pressure even after increased standard care involving a diuretic. The participants were assigned to receive either Aprocitirom (10 mg or 25 mg once daily) or a placebo on top of their usual antihypertensive regimen. The study had a run-in period, an 8-week double-blind treatment phase, and a 32-week open-label extension phase to evaluate long-term outcomes. Effectiveness Results[35].

Aprocitirom showed clinically significant and statistically significant reductions in both systolic.

In week 4, patients taking 25 mg of Aprocitirom

Clinical trials								
ClinicalTrials.gov Identifier	**Title / Publication**	**Phase**	**Study Design**	**N (Participants)**	**Key Population**	**Dosing**	**Primary Outcome**	**Key Results (vs. Placebo)**
NCT03541174 (PRECISION)	A Study to Show the Effect of Aprocitentan in Resistant Hypertension	Phase 3	Randomized, Double-blind, Placebo-controlled, Withdrawal	730	Adults with resistant hypertension (BP geq140/90 mmHg on geq3 meds)	12.5 mg, 25 mg QD	Change in sitting SBP at Week 4	Aprocitentan 12.5 mg: -3.8 mmHg (p=0.0042); Aprocitentan 25 mg: -3.7 mmHg (p=0.0046)
NCT02603809	Phase 2 Dose-Response Study in Essential Hypertension	Phase 2	Randomized, Double-blind, Placebo/Active-controlled	490	Adults with essential hypertension (DBP 90–109 mmHg)	10, 25, 50 mg QD	Change in sitting SBP/DBP at Week 8	Dose-dependent BP reduction; clinically significant vs. placebo/lisinopril
AC-080-101 (Sidharta et al. 2019)	Single/Multiple-Dose PK/PD in Healthy Subjects	Phase 1	SAD/MAD, Randomized, Double-blind, Placebo-controlled	70	Healthy adults & elderly	Up to 600 mg (SAD); Up to 100 mg QD (MAD)	Tolerability, PK/PD (ET-1 levels)	Well-tolerated; Dose-proportional ET-1 elevation; t½ ~44 hrs; no major age/sex differences
NCT02708004	Fluid Homeostasis Study in Healthy Subjects	Phase 1	Randomized, Double-blind, Placebo-controlled, Cross-over	28	Healthy subjects on high sodium diet	10, 25, 50 mg QD	Body weight change, hemodilution markers	Dose-dependent weight gain (<1 kg); hemodilution (Hb/Hct decrease); no significant sodium retention

experienced a mean reduction in systolic blood pressure and diastolic blood pressure compared with placebo[36].of 13.7 mmHg. For the 10 mg group, the reduction was 11.3 mmHg, while the placebo group had a reduction of 5.5 mmHg. The effects were sustained throughout the treatment period and were consistent in subgroups, including the elderly, patients with chronic kidney disease, and those with diabetes. Ambulatory blood pressure monitoring (ABPM) confirmed the persistent control of blood pressure over 24 hours. Daytime and nighttime measurements revealed significant reductions, which are crucial for the prediction of cardiovascular events[37].

Safety and Acceptability

Aprocitirom was well tolerated in general, with a safety profile similar to that of the placebo. The commonest side effects were nasopharyngitis, peripheral oedema, and mild gastrointestinal symptoms. Most importantly, there was no significant increase in liver transaminases, and no cases of drug-induced liver injury were reported. This addressed concerns associated with earlier endothelin receptor antagonists like bosentan.

Mechanistic Insights

PRECISION was a blinded, randomized, parallel-group, phase 3 multicenter study that was carried out in research units or hospitals in Europe, North America, Asia, and Australia. Patients were eligible to be randomized if their systolic blood pressure when sitting was 140 mm Hg or higher despite receiving standardized background therapy consisting of three antihypertensive drugs, one of which was a diuretic[38]. The study consisted of three sequential parts: segment 1 was the 4-week double-blind, randomized, and placebo-controlled part, in which patients received aprocitentan 12·5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio; segment 2 was a 32-week single (patient)-blind part, in which all the patients were treated with aprocitentan 25 mg;[39] and segment 3 was a 12-week double-blind, randomized, and placebo-controlled withdrawal part, in which patients were re-randomized to aprocitentan 25 mg or placebo in a 1:1 ratio. The primary and significant secondary endpoints were changes in unattended office systolic blood pressure from week 4 to baseline and from week 40 to withdrawal baseline, respectively. Secondary endpoints included changes in 24-hour ambulatory blood pressure[40].

Table 2. Comparing the aprocitentan to other available antihypertensive drugas in market

Feature	Aprocitentan (ERA)	Other ERAs (e.g., Bosentan, Macitentan)	Spironolactone (MRA)	ACE Inhibitors (e.g., Lisinopril)
Primary Indication	Resistant Hypertension	Pulmonary Arterial Hypertension (PAH)	Resistant HTN, Heart Failure, Edema	HTN, Heart Failure, Post-MI, Diabetic Nephropathy
Mechanism	Dual ETA/ETB blockade (Endothelin system)	Dual ETA/ETB blockade (Endothelin system)	Aldosterone receptor antagonism	RAAS inhibition (Angiotensin II reduction)
Key Advantage	Novel target for resistant HTN; low DDI risk (CYP-independent)	Effective for PAH	Add-on for resistant HTN (esp. volume/ aldosterone)	First-line, cardio/ nephroprotective
Key Concern	Fluid retention, anemia, teratogenicity (REMS)	Hepatotoxicity, teratogenicity (REMS), high DDI risk (CYP)	Hyperkalemia, endocrine AEs	Cough, hyperkalemia, angioedema
Metabolism	CYP-independent	Hepatic (CYP3A4/ 2C9 - high DDI)	Hepatic	Renal (low DDI)

Comparative Evaluation Safety, Tolerability, and Drug Interactions of Aprocitentan

1. Common Adverse Effects

The most frequent side effects of aprocitentan in clinical studies are:

Edema/Fluid Retention: This is a common and dose-related effect of ERAs. Swelling, particularly in the face, legs, and ankles, as well as potential weight gain, can be experienced by patients. Monitoring for fluid retention signs and symptoms and deteriorating heart failure is necessary. Adjustment in diuretic therapy can be done if fluid retention is significant[41]

Anemia/Decreased Hemoglobin: Reduction in hematocrit and hemoglobin level has been observed. It tends to appear early, stabilize, and reverse when the drug is discontinued. Monitoring of hemoglobin level before and during treatment is recommended. Aprocitentan is not recommended for patients with active anemia.

Headache: Common to many antihypertensive drugs, headache has been observed.

Nasopharyngitis: Cold-like symptoms[42]

2. Hepatotoxicity and Fluid Retention

Hepatotoxicity: While less common and severe than with some traditional ERAs (such as bosentan), risk exists for liver abnormalities, including abnormal rise of liver enzymes (aminotransferases). Patients should immediately report to their doctor if they experience symptoms indicating liver dysfunction, including nausea, vomiting, upper right quadrant pain, dark urine, jaundice, fever, or pruritus. Unexplained increases in aminotransferases that are persistent or accompanied by rising bilirubin may require a decision to discontinue aprocitentan[43].

Fluid Retention: This is a recognized consequence of ERAs. The endothelin system is involved in the regulation of fluid and sodium balance. Blocking endothelin receptors may subtly increase body weight and result in hemodilution (demonstrated by decreased hemoglobin and hematocrit). This effect is usually tolerable but requires careful attention, particularly in patients with pre-existing heart failure or conditions predisposing to fluid overload.[44]

3. Drug-Drug Interactions

A major advantage of aprocitentan over previous ERAs is its low potential for drug-drug interactions. In contrast to bosentan and macitentan, which are dependent upon cytochrome P450 (CYP) enzymes (e.g., CYP3A4, CYP2C9) and interact with numerous other drugs, the metabolism of aprocitentan does not significantly involve CYP450 pathways[45]. This minimizes the risk of cross-reactivity with commonly prescribed drugs that utilize CYP pathways or are inhibitors. The pharmacokinetics of drugs metabolized by CYP3A (such as midazolam) or transported by BCRP or OATP1B1/1B3 (such as rosuvastatin) are not significantly affected by aprocitentan, according to studies. Nevertheless, clinicians should be aware of the possibility of additive blood pressure-lowering effects when co-prescribing aprocitentan with other agents lowering blood pressure[46].

4. Long-term Safety Issues

Embryo-fetal Toxicity: Similar to other ERAs, aprocitentan is harmful to the fetus, causing congenital anomalies or death of the fetus, as per animal studies. It is not safe to administer during pregnancy. This risk previously necessitated a US Risk Evaluation and Mitigation Strategy (REMS) program for aprocitentan (TRYVIO REMS), which involved required pregnancy testing upon entry and during therapy and certain contraceptive use in pregnant patients. CRITICAL UPDATE (as of July 2025): The US FDA has recently removed the REMS requirement for aprocitentan (TRYVIO) and other ERAs for embryo-fetal toxicity. This shift was founded on new human pregnancy data analyses spanning two decades, which revealed no pattern of congenital malformations against predictions from animal studies. Even though REMS is lifted, information regarding embryo-fetal toxicity and the importance of effective contraception is retained in the label, and pregnancy testing prior to initiation of therapy is still [47]advised.Reduced Sperm Counts: Like other ERAs, aprocitentan might influence sperm generation and potentially male fertility. Patients who were capable of reproducing should be warned of this risk. It is not yet established whether these effects on fertility are reversible[48].

Overall Long-Term Tolerability: Long-term findings in the PRECISION trial (through 48 weeks) suggested continued efficacy and an overall safety profile that was generally well managed. Continuing post-marketing surveillance will continue to provide additional longer-term safety data on a larger patient population. The frequent appearance of common side effects such as fluid retention and anemia suggests these will be important areas for monitoring[49].

Possible Application in Other Diseases

Pulmonary Arterial Hypertension (PAH)

Rationale: Dual ERAs such as bosentan and macitentan are usual therapies for PAH. Aprocitentan is a metabolite of macitentan and functions similarly, so it could be of value for PAH.

Current Status: Macitentan, the parent molecule of aprocitentan, is employed for PAH. Aprocitentan itself is not yet approved or in active PAH clinical trials, though. Its development primarily for systemic hypertension can take advantage of its distinctive metabolic profile and improved tolerability compared to older ERAs. Future studies will be most likely dedicated clinical trials[50].

Active Trials and Future Indications

Resistant Hypertension (Primary Indication): Aprocitentan's primary development and regulatory approval—FDA in March 2024 and EMA in June 2024—are for resistant hypertension. Post-marketing surveillance and real-world data collection will continue to evaluate its long-term safety and efficacy.

No Other Major Indication Trials Currently Listed: To date, there are no publicly listed large-scale Phase 2 or Phase 3 clinical trials for aprocitentan for new indications like PAH, diabetic nephropathy, or CKD progression. While the biological justification underlies these applications and encouraging findings have been observed in specific subgroups, individual landmark trials will be necessary for new indications adrenalrenalrenalFocus on Subgroup Analyses and Real-World Evidence[51]: Considerable future knowledge about aprocitentan's broader impact on cardiovascular and kidney health will originate from:

More nuanced subgroup analyses of the PRECISION trial, such as particular kidney function groups and long-term renal outcomes.Real-world evidence studies and registries once the drug is being used more extensively, observing its influence on varied patient populations and comorbidities.Exploratory studies by investigators that could study its application in other diseases[52].

Conclusion

Aprocitentan provides a new and effective way to manage resistant hypertension by blocking two types of endothelin receptors. Clinical trials, especially the PRECISION study, show that it effectively lowers blood pressure and has a good safety record. With regulatory approvals secured, it is a promising treatment for hard-to-treat hypertension. Future studies should look at its long-term effects and potential benefits for related heart and kidney conditions.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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