Health Technology Briefing
October 2023

Aprocitentan for treating resistant hypertension

Company/Developer	Idorsia Pharmaceutical Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 14872	NICE ID: 10395	UKPS ID: 655363

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Aprocitentan is in clinical development for the treatment of resistant (difficult to control) hypertension (high blood pressure). The causes of high blood pressure are not always clear, but the risks are increased by factors such as being overweight, eating too much salt and lack of exercise. Resistant hypertension is defined as blood pressure that remains high even after using three or more different types of medication. It does not necessarily have symptoms until it is severe, and when symptoms occur, they include headaches, shortness of breath, chest pain and nosebleeds. Resistant hypertension can lead to an increased risk of heart attack, stroke and kidney failure. By definition, it is resistant to current medications and therefore there is a need for new treatments.

Aprocitentan is a type of receptor antagonist that blocks the action of a vasoconstrictor (agent that narrows blood vessels). When blood vessels become narrow, it takes more pressure for the blood to travel through them. Therefore, blocking the action of a vasoconstrictor could decrease blood pressure. Since resistant hypertension is by definition unresponsive to current drugs, new treatments are required. Aprocitentan is taken orally once daily. If licensed, aprocitentan would offer a new treatment option for people with resistant hypertension.

Proposed Indication

Difficult to control (resistant) high blood pressure (hypertension) in adults.[1]

Technology

Description

Aprocitentan (ACT-132577)[1] is a novel dual endothelin receptor antagonist that inhibits the binding of endothelin-1, a potent vasoconstrictor, to ET_A and ET_B receptors located on the vascular smooth muscle cells and the endothelial cells, respectively.[2] ET_A receptors activation leads to vasoconstriction. Blocking ET_A receptors would therefore prevent vasoconstriction, and since narrow blood vessels require more pressure for the blood to travel through the vessels,[3] stopping vasoconstriction could decrease blood pressure.

Aprocitentan is currently in clinical development for the treatment of resistant hypertension (RH). In phase II/III clinical trials patients are were given 25 mg or 12.5 mg aprocitentan, orally, once daily in the morning for 4 weeks in part 1; then 25 mg aprocitentan, orally, once daily in the morning for 32 weeks in part 2; then 25 mg, orally, once daily in the morning for 12 weeks in part 3 (NCT03541174); and either 5 mg, 10 mg, 25 mg or 50 mg aprocitentan orally once daily in the morning for 8 weeks (NCT02603809).[1,4]

Key Innovation

Resistant hypertension (RH) is a widespread disease with few symptoms until hypertensive crisis, and it increases the risk of potentially fatal diseases.[5] Existing drugs are unable to tackle all the underlying pathological pathways involved in RH and therefore further treatment options are necessary.[6] Aprocitentan blocks the ET_A receptors involved in causing high blood pressure, but also blocks the ET_B receptors involved in causing vascular leakage[6], which in turn leads to tissue oedema[7]. Therefore, aprocitentan offers a more balanced blockade of both ET_A and ET_B receptors.[6] Results from the phase II and III trials have shown that aprocitentan produced significant changes in blood pressure.[8,9]. Aprocitentan represents a novel, effective, and well tolerated treatment for resistant hypertension.[8]

If licenced, aprocitentan will provide a new treatment option for patients with resistant hypertension.

Regulatory & Development Status

Aprocitentan does not currently have marketing authorisation in the EU/UK for any indication.

Patient Group

Disease Area and Clinical Need

RH is defined as blood pressure that remains above 140/90 mmHg despite optimal use of three or more antihypertensive medications of different classes, including a diuretic.[10] Although it is not always clear what causes high blood pressure, the risks are increased by factors such as being overweight, eating too much salt and not doing enough exercise.[11] RH is more frequent in patients with diabetes, chronic kidney disease, and sleep apnoea obstructive syndrome than in those without these conditions.[12-14] RH substantially increases the risk of heart attack, stroke and kidney failure.[5] RH is not necessarily associated with symptoms, but may be felt when blood pressure first rises or during a hypertensive crisis, when levels are extremely high. These symptoms may include headaches, shortness of breath, chest pain and nosebleeds.[5]

In the UK, the age standardised incidence for RH in 2015 was 0.42 cases per 100 person years, and the age-standardised prevalence was 6.46%.[15] Globally, the prevalence of RH is 14%-16% of all patients with hypertension, equalling 140-160 million people.[15] In England, high blood pressure was estimated to contribute to 75,000 deaths in 2015.[16] In England in 2022-23, there were 42,901 finished consultant episodes (FCE) and 35,526 admissions for essential (primary) hypertension (ICD-10 code I10) which resulted in 35,037 FCE bed days and 3,033 day cases.[17] Of these, about 20% of the population are resistant.[5]

Recommended Treatment Options

NICE state that if hypertension is not controlled in adults taking the optimal tolerated doses of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker plus a calcium channel blocker and a thiazide-like diuretic, they are regarded as having RH. To treat RH, NICE currently recommends adding a fourth antihypertensive drug as step 4 treatment, further diuretic therapy with low-dose spironolactone in adults with who have a blood potassium level of up to 4.5 mmol/l or an alpha-blocker or beta-blocker.[18]

Clinical Trial Information

Trial	**PRECISION, NCT03541174;** Multi-center, Blinded, Randomized, Parallel-group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension (RHT) **Phase III:** completed **Location:** 12 EU countries, UK, USA, Canada and other countries. **Study completion date:** April 2022
Trial Design	Randomised, parallel assignment, triple-blinded
Population	N = 730 (actual); male and female participants aged over 18 years (or year of country specific majority); documentation of uncontrolled blood pressure despite at least three background antihypertensive medications; treated with at least three antihypertensive therapies of different pharmacological classes for at least four weeks before the screening visit; mean sitting systolic blood pressure ≥ 140 mmHg.
Intervention(s)	• 12.5 mg aprocitentan orally once daily

	• 25 mg aprocitentan orally once daily
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: mean change in trough sitting systolic blood pressure (time frame: day 1 to week 4). See trial record for full list of other outcomes.
Results (efficacy)	The study showed that the primary endpoint of changes in unattended office systolic blood pressure from baseline to week 4 was met. The least square mean (SE) change in office systolic blood pressure at 4 weeks was −15.3 (SE 0.9) mm Hg for aprocitentan 12.5 mg, −15.2 (0.9) mm Hg for aprocitentan 25 mg, and −11.5 (0.9) mm Hg for placebo, for a difference versus placebo of −3.8 (1.3) mm Hg (97.5% CI −6.8 to −0.8, p=0.0042) and −3.7 (1.3) mm Hg (−6.7 to −0.8; p=0.0046), respectively. The study also met the key secondary endpoint of changes in unattended office systolic blood pressure after 4 weeks of withdrawal: systolic blood pressure increased significantly with placebo compared with aprocitentan 25 mg (a difference of 5.8 mm Hg, 95% CI 3.7 to 7.9, p<0.0001).[8]
Results (safety)	There was mild-to-moderate oedema or fluid retention in 9%, 18%, and 2% of patients receiving aprocitentan 12.5 mg, 25 mg and placebo, respectively, during the 4-week double-blind part, and in 18% of patients, all of them receiving aprocitentan 25 mg, during the single-blind part 2. Overall, this event led to discontinuation in seven patients treated with aprocitentan. During the trial, a total of 11 treatment-emergent deaths occurred, none of which were related to study treatment.[8]

Clinical Trial Information	
Trial	NCT02603809; A Multi-center, Double-blind, Double-dummy, Randomized, Placebo- and Active-reference, Parallel Group, Phase 2, Dose-finding Study With ACT-132577 in Subjects With Essential Hypertension (Grade 1 and 2). **Phase II:** completed **Location:** US, Canada, Israel and Puerto Rico **Study completion date:** April 2017
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 1659 (actual); adults aged 18-75 years old; no contra-indication to stop anti-hypertensive treatment(s) at screening; mild-to-moderate essential hypertension with or without ongoing anti-hypertensive treatment(s); mean sitting diastolic blood pressure ≥ 90 to < 110 mmHg.
Intervention(s)	• 5 mg aprocitentan orally once daily • 10 mg aprocitentan orally once daily • 25 mg aprocitentan orally once daily • 50 mg aprocitentan orally once daily
Comparator(s)	• Active comparator: 20 mg Lisinopril orally once daily • Matched placebo

Outcome(s)	Primary outcome measure: mean change in diastolic blood pressure (time frame: day 1 to day 56). See trial record for full list of other outcomes
Results (efficacy)	Significant decreases in blood pressure were noted at doses of 10, 25, and 50 mg once daily with the optimum antihypertensive dose being 10 to 25 mg.[9]
Results (safety)	The present study reported four cases of peripheral oedema out of the 409 patients who completed the trial. Incidence of adverse events was similar in the aprocitentan groups (22.0%–40.2%) and the placebo group (36.6%).[9]

Estimated Cost

The cost of aprocitentan is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline in development. Implanting a baroreceptor stimulation device for resistant hypertension (GID-IP1180). Expected publication date to be confirmed.
- NICE clinical guideline. Hypertension in adults: diagnosis and management (NG136). August 2019, last updated March 2022.
- NICE quality standard. Hypertension in adults (QS28). March 2013, last updated: September 2015
- NICE interventional procedures guideline. Percutaneous transluminal renal sympathetic denervation for resistant hypertension (IPG754). March 2023.
- NICE interventional procedures guideline. Implanting a baroreceptor stimulation device for resistant hypertension (IPG533). October 2015.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). 2023 ESH Guidelines for the management of arterial hypertension. 2023.[19]
- Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. 2020.[20]

Additional Information

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