Health Technology Briefing
October 2022

Potassium citrate-potassium bicarbonate prolonged release granules for treating cystinuria

Company/Developer	Advicenne

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28642	NICE ID: 10438	UKPS ID: 660290

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

ADV7103 is currently in clinical development for the treatment of cystinuria in patients aged 1 year and above. Cystinuria is an inherited metabolic condition where irregular changes to genes called *SLC3A1* and *SLC7A9* results in abnormal transport of the amino acid, cysteine, in the kidney. This results in excessive amounts of cysteine excreted in the urine which does not dissolve. This leads to symptoms like sharp lower back pain, blood in urine, obstruction or infection in urinary tracts and development of kidney stones. There is currently no cure for cystinuria and no approved drugs.

ADV7103 is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (potassium bicarbonate) which are given orally as prolonged release granules. Both of these substances act as alkalising agents, which means they can neutralise acidity. ADV7103 stabilizes urinary pH which increases the solubility of cysteine. This can prevent kidney stone formation. ADV7103 has a formulation that maximises absorption of both potassium citrate and potassium bicarbonate. It is designed to slowly release the substances through several hours; maintaining its effects through the day and night. ADV7103 will be administered as oral granules. If approved, ADV7103 will provide a novel treatment option for cystinuria in children and adults.

Proposed Indication

Treatment of patients with cystinuria in patients aged 1 year and above.[a]

Technology

Description

ADV7103 (Sibnayal) is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate), formulated as prolonged release granules. Both substances act as alkalising agents and buffer the metabolic acidosis. ADV7103 provides a source of potassium to correct hypokalaemia. In addition, potassium citrate acts also as a calcium chelating agent.[1] ADV7103 stabilizes urinary pH, and this increase of pH is linked with solubility of cystine.[2] ADV7103 also prevents stone formation.[3]

ADV7103 is in clinical development for the treatment of cystinuria. In the phase II/III trial (NCT04137978), patients will be administered ADV7103 twice a day at an optimal dose, as oral prolonged-release granules.[4,5]

Key Innovation

There are currently no approved drugs, including potassium citrate/potassium bicarbonate, specifically indicated for the treatment of cystinuria in the UK. ADV7103 has a formulation that maximises absorption of both potassium citrate and potassium bicarbonate along the gastrointestinal tract.[6] The substances in ADV7103 are included in granules designed to slow down the release of the substances over several hours. After the medicine is taken by mouth, the slow release of the substances in the body is expected to maintain the medicine's effect throughout the day and especially during the night.[3] ADV7103 stabilizes urinary pH with only 2 doses per day. It significantly increases pH level with a positive dose-response, and has strong supportive information linking increase of pH with solubility of cystine.[2] If approved, ADV7103 would provide a novel treatment option for cystinuria.

Regulatory & Development Status

ADV7103 currently has a Marketing Authorisation in the UK for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older.[7] ADV7103 also currently has a Marketing Authorisation in the EU for the treatment of patients aged from one year with dRTA.[8]

ADV7103 is also currently in phase II/III trials for the treatment of dRTA.[9]

ADV7103 has the following regulatory designations/awards:[3]

- An Orphan Drug in the EU in 2020 for the treatment of cystinuria

Patient Group

Disease Area and Clinical Need

Cystinuria is an inherited metabolic disorder. It is caused by changes (mutations) in the *SLC3A1* and *SLC7A9* genes. These mutations result in the abnormal transport of cysteine in the kidney and this leads to the symptoms of cystinuria. People with cystinuria excrete abnormally high levels of cysteine, which remains

[a] Information provided by Advicenne

undissolved in the urine. The amino acids lysine, arginine, and ornithine are also excreted in massive amounts by people with this disorder, but they dissolve more readily in the urine and are not associated with any particular symptoms. The initial symptom of cystinuria is usually sharp pain in the lower back or side of the abdomen (renal colic). Other symptoms may include blood in the urine (haematuria), obstruction of the urinary tract, and/or infections of the urinary tract. Frequent recurrences ultimately may lead to kidney damage. People with cystinuria typically produce jagged stones that are small, though some form very large stones.[10]

Cystinuria mostly affects young people in their 20s and 30s who will experience recurrent painful episodes of kidney stones.[11] It is more common in Caucasians but affects men and women equally although men may have a more severe form of the disease.[12] Cystine stones account for only about 1% to 2% of all kidney stones but represent roughly 6% to 8% of all paediatric calculi.[13] It is estimated that 1 in 2000 people in the UK are affected by cystinuria.[14] If this is applied to the 2020 UK mid-year population figures, it can be estimated that there are around 29,860 people in England and Wales suffering from cystinuria.[15]

Recommended Treatment Options

There is currently no licensed pharmacological treatment for cystinuria, but it can be managed with little disruption to normal living. The aim of treatment is to keep cysteine dissolved in the urine so that it doesn't form crystals that build up to form stones. There are three ways of doing this:[16]

- Keeping urine dilute by drinking extra amounts of water and reducing salt intake.
- Making urine more alkaline either by dietary changes or having alkaline medicines such as liquid or effervescent potassium citrate. Sodium bicarbonate (bicarbonate of soda) has also been used in patients who cannot get along with potassium citrate.
- Chelating medicines are sometimes required by patients who continue to form stones in spite of the two steps above. They work by binding to the surface of a cysteine crystal, preventing more cysteine from building up on it. The three medicines most often used are tiopronin, D-penicillamine and Captopril.

Clinical Trial Information

Trial	NCT04147871, EudraCT-2017-002067-18; A Multicentre, Randomized, Controlled Versus Placebo, Double-blinded, 4 Parallel Arms, Dose-ranging Main Study, to Evaluate the Efficacy, Safety and Tolerability and Acceptability of Repeated Doses of ADV7103, After 7 Days of Treatment, in Patients With Cystinuria, and an Efficacy and Safety Exploratory Study in the Youngest Children **Phase II/III –** Recruiting **Location(s) –** 2 countries in EU **Primary completion date –** August 2020
Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N = 72 (estimated); Patient who has a diagnosis of cystinuria based on medical diagnosis or on genetic diagnosis; aged 6 months to 70 years
Intervention(s)	ADV7103 twice a day
Comparator(s)	Fixed ratio of 2mm 1/3 of green coated lactose granules and 2/3 of white coated lactose granules

Outcome(s)	**Primary outcome** • Percentage of urinary pH values ≥ 7.0 during 24h on Day 7 (after ADV7103 treatment period) [Time Frame: 24 hours]
Results (efficacy)	-
Results (safety)	-

Trial	NCT04137978, EudraCT-2017-002068-42; Open Label, Multicentre Study, Evaluating the Safety, Tolerability, Efficacy, Compliance and Acceptability of Alkalising Treatments at Long-term in Patients With Cystinuria **Phase II/III –** Recruiting **Location(s) –** 2 countries in EU **Primary completion date –** August 2022
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 97 (estimated); 6 months to 70 years
Intervention(s)	ADV7103 twice a day at optimal dose.
Comparator(s)	Standard of care
Outcome(s)	**Primary outcome** • Percentage of urinary pH values ≥ 7.0 during 24h on Day 7 (after ADV7103 treatment period) [Time Frame: 7 Days]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of ADV7103 was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE guideline. Renal and ureteric stones: assessment and management (NG118). January 2019.
- NICE quality standard. Renal and ureteric stones (QS195). July 2020.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- International Society of Nephrology. Cystinuria: clinical practice recommendation. September 2020.[17]

Additional Information

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