

Category

Best Pharmaceutical Product

General Information**Company Name ***

Ardelyx, Inc.

Product/Solution Name *

XPHOZAH®

Compound/Tech Name*

tenapanor

Trade Name *

XPHOZAH®

Corporate Name *

XPHOZAH®

Date of Approval *

2023-10-17

Indications *

XPHOZAH, 30 mg BID, is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

words remaining :

457

Therapeutic Areas *

Nephrology

words remaining :

499

*Kindly clearly label your files with company name and asset name.

Background information and need for drug / device

(please be as specific as possible in your description; limit 500 words)

Chronic kidney disease (CKD) is the progressive decline of kidney function, which affects an estimated 37 million people in the U.S. The kidneys' primary responsibility is to filter excess water and waste out

of the blood. They also balance salts and minerals that circulate in the blood and make red blood cells and hormones that regulate blood pressure. Once the kidneys have failed, dialysis is needed to filter and remove toxins from the blood. Without dialysis or a kidney transplant, kidney failure results in the accumulation of waste products that may ultimately cause death.

The kidneys are responsible for removing excess phosphorus from the body. As kidney function deteriorates, phosphorus is not adequately eliminated, resulting in elevated levels of serum phosphorus, or hyperphosphatemia. Excess phosphorus in the blood causes calcium-phosphate complexes to be deposited throughout the body, leading to vascular calcification and arteriosclerosis. This can result in systolic hypertension, widened pulse pressure and subsequent left ventricular hypertrophy, and can lead to increased cardiovascular events and mortality. The normal concentration of phosphorus in the serum ranges from 2.5mg/dL to 4.5mg/dL. The Kidney Disease Improving Global Outcomes (KDIGO) organization recommends chronic kidney disease patients on dialysis target serum phosphorus levels toward the normal range.

Since the 1970s, CKD patients on dialysis with elevated phosphorus only had a single class of drugs available: Phosphate binders (PBs). Despite widespread use of PBs, the majority of patients on PB therapy continue to have hyperphosphatemia and are unable to achieve guideline-established target serum phosphorus levels.

XPHOZAH, discovered and developed by Ardelyx, is a first-in-class, phosphate absorption inhibitor with a differentiated mechanism of action that works locally in the gut to inhibit sodium hydrogen exchanger 3 (NHE3). This results in a modification of the epithelial tight junctions, thereby significantly reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption. XPHOZAH is a single tablet, taken twice daily. The drug was designed to attach to two NHE3 antiporters at the same time so XPHOZAH would have a prolonged duration of action. It has a large molecular weight, which results in minimal absorption into the blood stream. The chemical structure was so novel that the United States Adopted Name (USAN) or generic name assigned to XPHOZAH (tenapanor) created a new stem "panor" since there were no compounds with similar structures.

The FDA approval of XPHOZAH is based on a comprehensive development program, including a diverse population of more than 1,000 patients in three Phase 3 clinical trials evaluating the efficacy and safety of XPHOZAH as monotherapy and in combination with PB therapy, all of which met their primary endpoints (PHREEDOM, BLOCK and AMPLIFY). Data from the three clinical trials demonstrated that XPHOZAH significantly reduced serum phosphorus in patients receiving maintenance hemodialysis with hyperphosphatemia.

Ardelyx also completed two open-label clinical trials (OPTIMIZE and NORMALIZE) to evaluate different options for integrating XPHOZAH into clinical practice.

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

Ardelyx initiated a drug discovery program at the beginning of 2009 with the goal of finding drugs that were minimally absorbed systemically, worked in the gastrointestinal (GI) tract and had effects outside the GI tract on diseases with an unmet medical need. XPHOZAH was discovered in 2009 utilizing an in vitro (cell culture) and in vivo (animal models) screening process. After comprehensive nonclinical safety studies, first-in-man studies were initiated at the beginning of 2010, followed by proof-of concept Phase 2a studies and clinical pharmacology studies (drug interaction, food effect,

ADME studies). After analyzing urine and stool samples from these studies it was discovered that XPHOZAH inhibited the absorption of dietary phosphorus. With the discovery that XPHOZAH could be beneficial for the treatment of hyperphosphatemia in patients with CKD on dialysis, an international Phase 2b study was initiated in 2014, followed by three US Phase 3 studies (BLOCK 2015, PHREEDOM 2017 and AMPLIFY 2019).

The approval of XPHOZAH by the FDA in October 2023 was supported by a comprehensive development program that included more than 1,200 patients in three Phase 3 clinical trials evaluating the safety and efficacy of XPHOZAH, all of which met their primary endpoints (PHREEDOM, BLOCK and AMPLIFY), as well as two additional Phase 4 open-label clinical trials (OPTIMIZE and NORMALIZE).

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

XPHOZAH is approved by the U.S. Food and Drug Administration to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

Hyperphosphatemia, excess phosphorus in the blood, is a significant and severe problem among CKD patients on dialysis, and the standard-of-care, phosphate binders, is not sufficient for the majority of patients. XPHOZAH is the first new mechanistic treatment option for this patient population in more than 30 years.

Of the 550,000+ CKD patients on dialysis in the U.S., 80% require prescription treatment for hyperphosphatemia. Published data demonstrates that approximately 70% of patients treated with phosphate binders are unable to consistently maintain target phosphorus levels over a six-month period of time. Hyperphosphatemia is independently associated with increased morbidity and mortality in CKD patients.

Ardelyx had the idea that one could make medicines that worked only in the gastrointestinal (GI) tract, limiting systemic exposure, but had effects outside the GI tract. Since Ardelyx began its internal research, more is understood about the GI tract and its ability to affect many diseases. For example, the effects on the microbiome and disease of the brain-gut interaction. This breakthrough concept has opened the door for other research interrogating the gut as a site for novel drugs treating non-GI diseases.

XPHOZAH has a novel mechanism of action that specifically blocks paracellular phosphate absorption in the GI tract via local inhibition of NHE3 and is a first-in-class phosphate absorption inhibitor.

XPHOZAH has been shown in clinical trials with more than 1,000 patients, to be effective both as a monotherapy and in combination with phosphate binders with an acceptable safety profile.

XPHOZAH is dosed as one pill taken twice daily, a critical development for this patient community.

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*Kindly clearly label your files with company name and asset name.

Please provide appropriate references (PubMed, Abstract, Website) *

Please see uploaded documents for relevant publications as well as the XPHOZAH MOA.

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Attached Files:

- [Block_K360_2021 PHREEDOM.pdf](#)
- [Fishbane_KM_2021.pdf](#)
- [KalantarZadeh_K3602023.pdf](#)
- [Martin_NDT_2021.pdf](#)
- [McCullough_CM_2021.pdf](#)
- [Pergola_JASN_2021 APMPLIFY.pdf](#)
- [Silva_K360_2023 NORMALIZE.pdf](#)
- [Sprague_K360_2024 OPTIMIZE.pdf](#)
- [Sprague_KI_2021.pdf](#)
- [Yee_AJN_2021.pdf](#)
- [2023 XPHOZAH MOA Video audio and ISI 1.mp4](#)