Managing **Primary Hyperoxaluria Type 1**

Alnylam PHARMACEUTICALS

Primary hyperoxaluria type 1 (PH1) is an ultra-rare, debilitating, inherited condition that typically presents in childhood and is characterized by painful kidney stones, often inevitable progression to end-stage kidney disease (ESKD) and increased morbidity and mortality.[1,2]

Cause of PH1[1,2]

PH1 is caused by mutations in the *AGXT* gene that render the liver enzyme alanine-glyoxylate aminotransferase (AGT) dysfunctional. AGT, when functional, helps rid the body of unwanted products of normal metabolism. In people with PH1, defective AGT causes an abnormal accumulation of oxalate — a waste product not used by the body — initially in the kidneys, and, when the disease advances, in other organs.

Role of oxalate in PH1[7]

Even in the absence of overt symptoms, oxalate is constantly being overproduced and can cause irreparable damage to the kidneys.

PH1 Facts

PH1 is ultra-rare:

~1,300 to 2,100

people diagnosed in the U.S. and EU[3,4,5]

Onset typically in **early childhood**[6]

Majority of people living with PH1 present with kidney stones. Kidney stones can result in:[1]

- **Flank pain**
- **Urinary tract infections**
- **Painful urination**
- **Blood in the urine**
- **Surgery for removal**

Oxalate is an end product of metabolism.

Oxalate **accumulates in the kidneys,** forming calcium oxalate crystals.

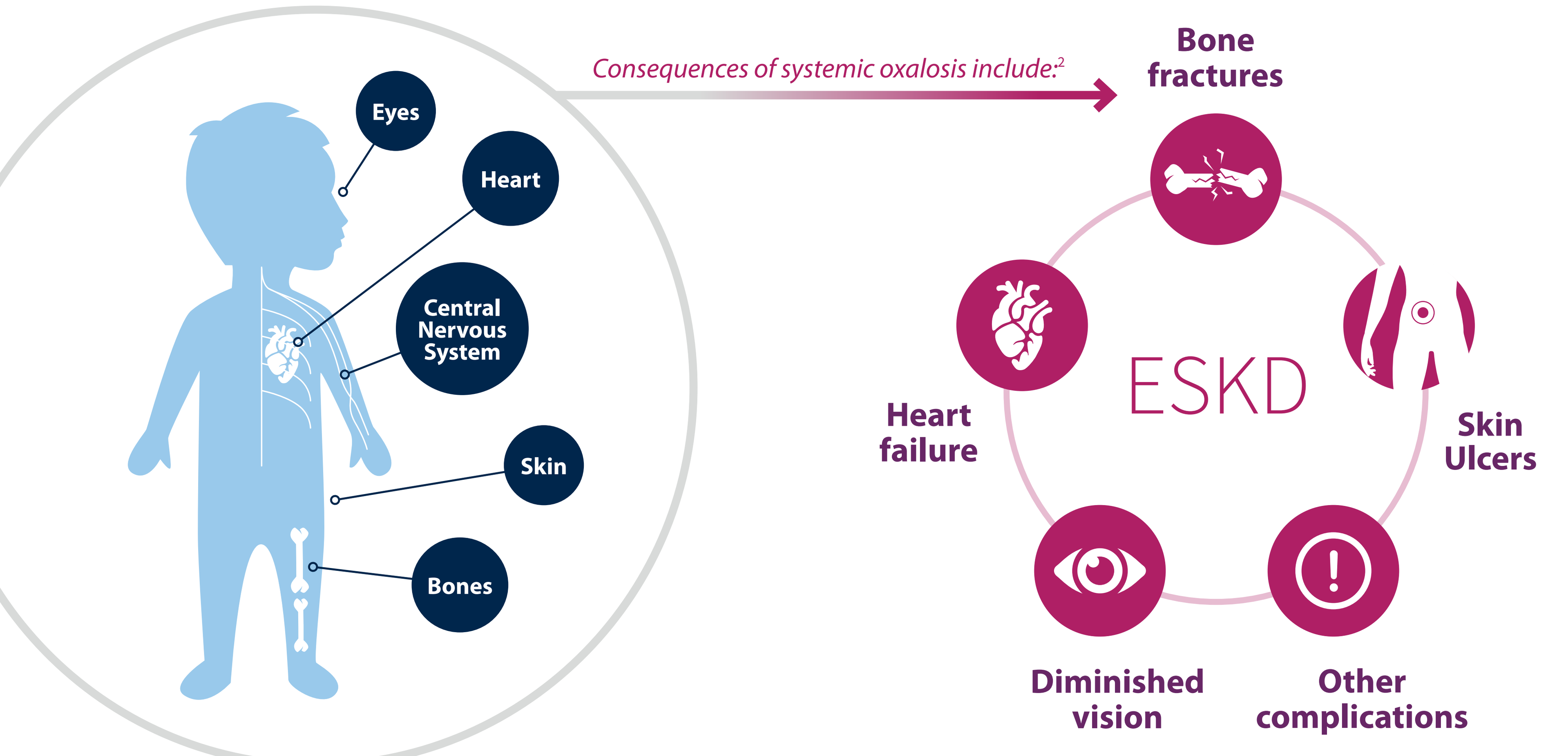
As nephrocalcinosis occurs, renal impairment causes crystals to be deposited throughout the body, **damaging major renal and non-renal organs.**

High levels of oxalate are toxic, and cannot be broken down by the body.

The crystals attach to renal tissues, where they can aggregate to **form kidney stones or lead to renal deposition of calcium oxalate crystals (nephrocalcinosis).**

ESKD is a looming threat for people living with PH1[2,8]

PH1 can ultimately result in ESKD, a life-threatening condition also known as kidney failure that prevents the kidneys from functioning properly.[2] Once kidney function has been compromised, oxalate can spread throughout the body, resulting in systemic oxalosis wherein oxalate crystals can deposit in the eyes, skin, bones, heart and central nervous system of people with PH1.[2]



UP TO **70%** **of people diagnosed** with PH1 present with ESKD[9,10,11,12,13]

6.1 times • **21** days
Average annual PH1 hospitalization rate[14]

The unpredictable and episodic nature of PH1 symptoms can cause anxiety and impact mental and emotional health.[14] The need for a procedure or a hospitalization to manage excruciating, PH1-related kidney stones can be sudden and unexpected.[14]

For example, children, adults and caregivers of those with PH1 experience the anxiety of not knowing:[15]

- **When will the next painful kidney stone episode occur?**
- **How long will their or their loved one's kidneys keep working?**
- **Will they/their child/loved one need to undergo an organ transplant?**

PH1 has limited treatment options[16,17]

Current medical management strategies aim to reduce the formation of kidney stones and delay progression to kidney failure but most are inadequate at preventing oxalate overproduction.

HYPERHYDRATION[2]

- Increased fluid intake: at least 3L/m^2 body surface area per 24 hours

5.25 liters of water each day for a 5'5" 150-pound person

- Pediatric gastrostomy: places a thin tube in the stomach of infants and small children for direct intake of fluids

CRYSTALLIZATION INHIBITORS AND PYRIDOXINE[1,8,18]

- Calcium oxalate crystallization inhibitors such as alkaline citrate
- High-dose pyridoxine (also known as vitamin B6) therapy, though data is limited and very few people living with PH1 are complete responders; a subset of people show a partial response

DIALYSIS[1,8]

- Serves as a bridge to transplantation or as an adjunct therapy after liver/kidney transplantation

4+ sessions/week of intensive dialysis required for people with PH1 with compromised renal function to filter out waste products

SEQUENTIAL OR DUAL LIVER/KIDNEY TRANSPLANTATION

- **Liver transplantation is currently the only treatment option that resolves the underlying metabolic defects associated with PH1.**[8]
  - In PH1, genetic mutations in the liver enzyme AGT render this enzyme defective and result in pathologic overproduction of oxalate. A liver transplant corrects this defect but carries a high risk of morbidity and mortality.[1,2,8]
- **As kidney function declines, a kidney transplant may be required.** Following dual liver/kidney transplant, oxalate levels will eventually decrease.[8]
  - Although effective at halting oxalate overproduction, there are clinically significant complications associated with transplantation, including:[19]

    - Renal vein thrombosis - Delayed graft function - Graft rejection - Infections

Five-year survival rate for people with PH1 who had undergone a dual liver/kidney transplant and who experience systemic oxalosis (spread of oxalate to organs outside of the kidneys)[20] **45%**

17,000* people on the current waiting list for a **liver transplant**[21]

93,000* people on the current waiting list for a **kidney transplant**[22]

20* **people die each day waiting** for an organ transplant[23]

*Statistics apply to U.S. population and are inclusive of people impacted by any condition, including PH1, that may require an organ transplant.

Diagnosing PH1

Inaccurate diagnoses pose a high risk of irreversible damage. Given the ultra-rare nature of the disease and symptoms that are often mistaken for that of other conditions, PH1 is frequently under– or misdiagnosed. Early diagnosis and oxalate management are crucial to preserve quality of life and avoid multi-system organ dysfunction.[3,11,13,24,25]

~50% of people living with PH1 may be undiagnosed, although data on prevalence are limited[9]

5.5 YEARS is the median delay in adults between onset of clinical manifestations and diagnosis[26]

current guidelines recommend metabolic testing consisting of 1-2 **24 hour urine collections**[8]

For more information on PH1, visit **AboutPH1.com**

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