Pharmacy Focus:

Skysona® – A New Gene Therapy for Cerebral Adrenoleukodystrophy (cALD)

Childhood Cerebral Adrenoleukodystrophy (cALD) Overview and Current Treatment[1,2,3,4,5]

Childhood cerebral adrenoleukodystrophy (cALD) is a rare, progressive, genetic disorder that damages nerve cells in the brain. The gene responsible for cALD is the ABCD1 gene. When mutated, the metabolism of fatty acids is altered, which makes the brain vulnerable to damage.

ALD affects 1 in 17,000 newborns, and from there, approximately 40 percent of young males (as well as a small number of adult males) with ALD develop cALD. This condition has an X-linked inheritance pattern, leading to a higher prevalence in males, as they have only one copy of the X chromosome versus females, who have two X chromosomes. People born as biologic females do not go on to develop cALD. Other forms of X-linked adrenoleukodystrophy exist, including Addison's disease and Adrenomyeloneuropathy, but these will not be covered extensively in this document.

Symptoms of cALD usually become apparent in childhood between ages three and 10 years. The first symptoms of cALD are often seizures, but other noticeable early symptoms include behavioral changes or inattentiveness. As the disease state progresses, the individual may have difficulty swallowing and experience clumsiness, impaired vision, aggression and learning disabilities. Eventually, neurologic damage is so severe that the individual becomes completely unresponsive. The average time between the initial presentation of symptoms and this final stage of disease progression is two years, but it can range between six months and 20 years. If cALD is not diagnosed and treated early, it may lead to death by five to 10 years of age.

X-linked Adrenoleukodystrophy Traits[2,6]

Cerebral Adrenoleukodystrophy	Addison's Disease	Adrenomyeloneuropathy
• Cause: Altered metabolism of fatty acids • Symptomatic: 4 to 10 years old • Severe • Progressive	• Cause: Adrenal glands fail to produce enough hormones • Onset: Any age, but mostly 30 to 50 years old	• Cause: Altered metabolism of fatty acids • Symptomatic: Adulthood • Less severe • Slow progression
ICD Code: E71.520, E71.521, E71.522, E71.529	**IDC Code:** E27.2, E27.40, E71.529	**ICD Code:** E71.522, E71.529

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Standard Treatment Methods[7,8,9]

Current treatment approaches mostly work to correct complications with symptoms rather than manage disease progression. Adrenal hormone replacement can help relieve symptoms related to adrenal gland dysfunction where there is insufficient cortisol and aldosterone. Commonly, drugs containing hydrocortisone are used to replace cortisol, and drugs containing fludrocortisone are used to replace aldosterone. Other medications are typically used to treat seizures, stiffness and abnormal movements. The most common anti-seizure agents in these individuals are valproate and clonazepam. Some nonpharmacological options can help to manage cALD, including physical therapy and school modifications to improve daily living. Prior to the development of a gene therapy for this disease, the only effective option for slowing down the progression of cALD has been an allogeneic stem cell transplant. Stem cell transplantation is recommended only in the early stages of cALD and is not advised if symptoms have severely progressed. Transplant recipients can expect a lifetime of immune suppression therapy as well as other potential risks.

New Treatment Method: Skysona®[10,11]

Skysona® is a potential one-time gene therapy from bluebird bio indicated for males between 4 and 17 years of age with early, active cALD. It was approved by the FDA on September 16, 2022, and carries a price of $3,000,000. Early, active cALD is defined as asymptomatic disease or mildly symptomatic based on neurological function score, MRI findings and the specific range of Loes Score (an objective way to determine the cerebral severity of cALD). In addition to the one-time therapy cost, additional costs such as mobility pre-treatment and hospitalization post-treatment can be expected. Patients who receive Skysona® may be able to receive a stem cell transplant if a match becomes available.

Overall, the goal of this therapy is to stop the progression of cALD symptoms by providing functional copies of the ABCD1 gene to potentially enhance the previously altered fatty acid metabolism. Skysona® attempts to do this by using a lentiviral vector that transports functional copies of the ABCD1 gene to the person's own stem cells where they are expected to start replicating.

The initial phase II/III study followed 32 participants for 24 months after receiving Skysona® and recorded neurological function scores and disability free survival from six major functional disabilities, including loss of hearing/communication ability, sight, digestion changes, walking abilities and wheelchair dependency. Higher scores related to worse prognoses. Hospitalization was required for the administration of Skysona® with an average of 29 days reported for participants.

From the results reported, 29 of 32 participants did not experience any of the disabilities studied at 24 months post-infusion. Long-term survival will be monitored in additional studies through 15 years post-treatment. Adverse events, such as neutropenia and thrombocytopenia, were reported, as well as hospitalizations within the 24-month period after the initial hospitalization following the infusion.

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Treatment Option Comparison [8,9,10,12,13,14,15]

	Standard Care (Combination Therapy)	Skysona®	Stem Cell Transplant
Indication	cALD (ICD codes: E71.520, E71.521, E71.522, E71.529)	cALD (ICD codes: E71.520, E71.521, E71.522, E71.529)	cALD (ICD codes: E71.520, E71.521, E71.522, E71.529)
HCPCS Codes	**Hydrocortisone Injections:** J1700, J1710, J1720 **Seizure Care:** G0033 **Physical Therapy:** G0040, G8990-G8995, S8990, S9131	**Gene Therapy:** J3490, J3590, C9399 (temporary billing codes)	**Transplant:** S2142
Method	**Management of Complications Once Symptomatic:** • Hormonal deficiency correction: oral medications and injections • Attempt to limit seizures to maintain brain function: oral medication • Will not prevent progression	**One-time Gene Therapy:** • Insertion of functional genes • Potentially prevents disease progression • Not curative	**Transplant:** • Provides functional genes • Prevents disease progression in early stages • Considered only potentially curative treatment
Annual Price	**Hormonal Replacement:** • Fludrocortisone: $140-$575 PPY • Hydrocortisone injection: $810-$8,106 PPY (age based) **Seizure care:** Overall costs: <$10,000 PPY **Physical therapy:** $1,000-10,000 PPY	**Pre-treatment:** G-CSF **One-time treatment:** $3 million **Post-treatment:** Hospitalizations due to serious adverse events related to Skysona® possible	**Transplant:** • One-time procedure; price varies state to state • Expect ongoing immunosuppressive therapies indefinitely
Adverse Events	High blood pressure, aggression, high blood sugar, hyperactivity, weight changes	Myelodysplastic syndrome, anemia, thrombocytopenia, neutropenia, alopecia, GI side effects	Graft vs. host disease, infections

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Key Takeaways Regarding Skysona®

- Approved by FDA September 16, 2022
- One-time gene therapy that will provide functional ABCD1 genes to potentially halt disease progression
- Projected cost: $3,000,000, plus hospitalization costs
- 90.6% of responsive recipients are showing no change in their disability level post treatment

Cost Containment Considerations

As part of its HMConnects™ cost containment program, HM Insurance Group (HM) works to support cost management opportunities around the use of gene and cell therapies and other high-cost pharmaceutical treatment options that can impact our clients' bottom line. The Pharmacy Operations (RxOps) team watches the market – and our book of business – to anticipate how current and future advancements will impact financial risk levels for HM's client base. Standard practices include reviewing, auditing and collaborating on the content of current policies, monitoring trends and implementing appropriate cost savings techniques. Additional practices include identifying the stockpiling of medications, determining if prescriptions are filled via in-network pharmacies and confirming that prescriptions are properly dosed based on weight and lab values when appropriate. All of these services are provided to HM's clients at no additional cost to them.

Pharmacy Focus provides valuable information about pharmaceutical industry developments and their associated costs that can impact the growing claims trend in the self-funded insurance market. Be aware of influences and gain insight into approaches that may help to contain costs. Please share topic suggestions or feedback with **HMPharmacyServices@hmig.com**.

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Resources: [1]Childhood Cerebral Adrenoleukodystrophy (CALD), Adrenoleukodystrophy News, published 2013, accessed August 23, 2022, https://adrenoleukodystrophynews.com/childhood-cerebral-adrenoleukodystrophy-cald/; [2]Adrenoleukodystrophy – Symptoms and Causes, Mayo Clinic, published 2018, accessed August 23, 2022, https://www.mayoclinic.org/diseases-conditions/adrenoleukodystrophy/symptoms-causes/syc-20369157; [3]Leukodystrophy Diagnosis Less Likely in Children of Ethnic Minorities, Adrenoleukodystrophy News, Marques Lopes J., published January 25, 2019, accessed August 23, 2022, https://adrenoleukodystrophynews.com/2019/01/25/leukodystrophy-diagnosis-less-likely-young-racial-ethnic-minorities/#:~:text=Among%20the%20557%20identified%20patients%20%28336%20males%2C%20median; [4]Symptoms of Adrenoleukodystrophy, Adrenoleukodystrophy News, Iyer V., accessed August 24, 2022, https://adrenoleukodystrophynews.com/symptoms-of-adrenoleukodystrophy/?adlt=strict; [5]Adrenoleukodystrophy, United Leukodystrophy Foundation, published 2022, accessed August 24, 2022, https://ulf.org/leukodystrophies/adrenoleukodystrophy/?adlt=strict; [6]Addison's Disease: What It Is, Causes, Symptoms & Treatment, Cleveland Clinic, published July 6, 2022, accessed August 24, 2022, https://my.clevelandclinic.org/health/diseases/15095-addisons-disease?adlt=strict; [7]Rathore G. Cerebral Adrenoleukodystrophy, Child Neurology Foundation, published July 2021, accessed August 25, 2022, https://www.childneurologyfoundation.org/disorder/cerebral-adrenoleukodystrophy/; [8]Corticosteroid Replacement Therapy, Adrenoleukodystrophy News, accessed August 25, 2022, https://adrenoleukodystrophynews.com/corticosteroid-replacement-therapy/; [9]Seizures in Adrenoleukodystrophy and How to Deal with Them, Adrenoleukodystrophy News, accessed August 25, 2022, https://adrenoleukodystrophynews.com/2020/05/26/seizures-and-how-to-deal-with-them/; [10]FDA Advisory Committee Unanimously Endorses eli-cel Gene Therapy for Cerebral Adrenoleukodystrophy, bluebird bio, Inc., published 2022, accessed August 25, 2022, https://investor.bluebirdbio.com/news-releases/news-release-details/fda-advisory-committee- unanimously-endorses-eli-cel-gene-therapy; [11]bluebird bio. A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced with Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD), clinicaltrials.gov, published March 25, 2022, accessed August 25, 2022, https://clinicaltrials.gov/ct2/show/study/NCT01896102?term=bluebird&cond=Cerebral+Adrenoleukodystrophy&draw=2&rank=4; [12]Healthcare Utilization and Costs in Children with Stable and Uncontrolled Epilepsy. Cramer J, Wang Z, Chang E., *Epilepsy Behav*., 2014;32:135-141. doi:10.1016/j.yebeh; [13]Pediatric Physical Therapy: What Is It and How Does It Help Kids? Premier Ortho., published January 12, 2022, accessed August 26, 2022, https://www.premier-ortho.com/pediatric-physical-therapy/#:~:text=Depending%20on%20the%20pediatrician%E2%80%99s%20referral%2C%20your%20health%20insurance; [14]Costs of Allogeneic Hematopoietic Cell Transplantation with High-Dose Regimens. *Biology of Blood and Marrow Transplantation*, Saito AM, Cutler C, Zahrieh D, et al., 2008;14(2):197-207. doi:10.1016/j.bbmt.2007.10.010; [15]Outcomes of Allogeneic Hematopoietic Stem Cell Transplant in Patients with Cerebral Adrenoleukodystrophy (CALD): Results from an Ongoing, Large, Multicenter, Observational Study, *American Society for Transplantation and Cellular Therapy*, Orchard PJ, Boelens J, Duncan C, et al., March 1, 2019; 25(3): S312.

MTG-3459 (11/22)