

SKYSONA[®] (elivaldogene autotemcel)

Sample Letter of Medical Necessity

To the Treating Physician:

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Indication

SKYSONA is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

This indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)- free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use

SKYSONA does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy.

An immune response to SKYSONA may limit the persistence of descendent cells of SKYSONA, causing rapid loss of efficacy of SKYSONA in patients with full deletions of the human adenosine triphosphate binding cassette, sub family D, member 1 (*ABCD1*) transgene.

SKYSONA has not been studied in patients with CALD secondary to head trauma.

Given the risk of hematologic malignancy with SKYSONA, and unclear long-term durability of SKYSONA and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the appropriateness and timing of treatment for each boy, especially for boys with isolated pyramidal tract disease based on available treatment options since their clinical symptoms do not usually occur until adulthood.

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Important Safety Information

WARNING: HEMATOLOGIC MALIGNANCY

Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, has occurred in patients treated with SKYSONA (elivaldogene autotemcel). Patients have been diagnosed between 14 months and 7.5 years after SKYSONA administration, and the cancers appear to be the result of the SKYSONA lentiviral vector, Lenti-D, integration in proto-oncogenes. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through assessments for evidence for clonal expansion or predominance at least twice in the first year and annually thereafter; consider bone marrow evaluations as clinically indicated.

Hematologic Malignancy

Myelodysplastic syndrome (MDS), a hematologic malignancy, has developed in patients treated with SKYSONA in clinical studies. At the time of initial product approval, MDS had been diagnosed in three patients after administration of SKYSONA. The clinical presentation for the three patients varied. Two patients who were diagnosed at 14 months and 2 years after treatment with SKYSONA had preceding delayed platelet engraftment. The third patient had normal blood counts from 18 months to 5 years following treatment with SKYSONA and presented 7.5 years after SKYSONA administration with symptomatic anemia and thrombocytopenia and was subsequently diagnosed with MDS with increased blasts. All 3 patients underwent allogeneic hematopoietic stem cell transplant; 1 patient required pre-transplant chemotherapy and total body irradiation as treatment for excess blasts prior to transplant and 1 patient underwent total body irradiation as part of his conditioning regimen.

SKYSONA Lenti-D lentiviral vector integration into proto-oncogenes appears to have mediated the three cases of hematologic malignancy. The hematologic malignancies diagnosed at 14 months and 2 years involved integration into the *MECOM* proto-oncogene and increased expression of the oncoprotein EVI1. All patients treated with SKYSONA in clinical studies have integrations into *MECOM*; it is unknown which integrations into *MECOM* or other proto-oncogenes are likely to lead to malignancy.

Because of the risk of hematologic malignancy, carefully consider alternative therapies prior to the decision to treat a child with SKYSONA. Consider consultation with hematology experts prior to SKYSONA treatment to inform benefit-risk treatment decision and to ensure adequate monitoring for hematologic malignancy. Consider performing the following baseline hematologic assessments: complete blood count with differential, hematopathology review of peripheral blood smear, and bone marrow biopsy (core and aspirate) with flow cytometry, conventional karyotyping, and next generation sequencing (NGS) with a molecular panel appropriate for age and including coverage for gene mutations expected in myeloid and lymphoid malignancies; and testing for germline mutations that are associated with hematologic malignancy.

Early diagnosis of hematologic malignancy can be critically important, therefore, monitor patients treated with SKYSONA lifelong for hematologic malignancy. For the first fifteen years after treatment with SKYSONA, monitor via complete blood count (with differential) at least twice per year and via integration site analysis or other testing for evidence of clonal expansion and predominance at least twice in the first year and then annually. Consider appropriate expert consultation and additional testing such as more frequent complete blood count (with differential) and integration site analysis, bone marrow studies, and gene expression studies in the following settings after treatment with SKYSONA:

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Important Safety Information (cont'd)

- Delayed or failed engraftment of platelets or other cell lines (patients who do not achieve unsupported platelet counts of $\geq 20 \times 10^9/L$ on or after Day 60 appear to be at particularly high risk for developing malignancy); or
- New or prolonged cytopenias; or,
- Presence of clonal expansion or predominance (e.g., increasing relative frequency of an integration site, especially if $\geq 10\%$ and present in *MECOM* or another proto-oncogene known to be involved in hematologic malignancy).

If hematologic malignancy is detected in a patient who received SKYSONA (elivaldogene autotemcel), contact bluebird bio at 1 833 999 6378 for reporting and to obtain instructions on collection of samples for further testing.

Serious Infections

Severe infections, including life-threatening or fatal infections, have occurred in patients after SKYSONA infusion. Important opportunistic infections that have been diagnosed within the first 3 months after treatment with SKYSONA include BK cystitis, cytomegalovirus reactivation, human herpesvirus-6 viremia, candidiasis, and bacteremias. Opportunistic infections after the first 3 months include an atypical mycobacterium vascular device infection, pseudomonas bacteremia, and Epstein-Barr virus reactivations diagnosed as late as 18 months after treatment with SKYSONA. Serious infections involving adenovirus include a case of transverse myelitis at 6 months that was attributed to adenovirus and entero/rhinovirus infection, and a fatal adenovirus infection at 21 months in a patient with CALD progression who developed multisystem organ failure.

Grade 3 or higher infections occurred in 21% of all patients (12% bacterial, 3% viral, and 6% unspecified). The most common Grade 3 or higher infections were vascular device infections (7% of patients) diagnosed as late as 6 months after treatment with SKYSONA, and bacteremias (6% of patients) diagnosed as late as 8 months after treatment with SKYSONA.

Febrile neutropenia developed within two weeks after SKYSONA infusion in 72% of patients. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Monitor patients for signs and symptoms of infection before and after SKYSONA administration and treat appropriately. Administer prophylactic antimicrobials according to best clinical practices and clinical guidelines.

Avoid administration of SKYSONA in patients with active infections.

Prolonged Cytopenias

Patients may exhibit cytopenias, including pancytopenia, for > 1 year following conditioning and SKYSONA infusion.

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Boxed WARNING.

Important Safety Information (cont'd)

Grade 3 or higher cytopenias on or after Day 60 following SKYSONA (elivaldogene autotemcel) infusion occurred in 47% of patients and included low platelet count (14%), low neutrophil count (22%), low lymphocyte count (27%), and low hemoglobin (2%). Grade 3 cytopenias persisted beyond Day 100 in 15% of patients and included low platelet count (7%), low neutrophil count (9%), and low lymphocyte count (6%).

Serious adverse reactions of pancytopenia occurred in two patients who required support with blood and platelet transfusions as well as growth factors (G-CSF for up to 6 months and eltrombopag for up to 14 months) after SKYSONA administration. One patient had intercurrent parvovirus infection and his pancytopenia was ongoing at least two years after SKYSONA administration. Pancytopenia in the other patient was ongoing until he was diagnosed with myelodysplastic syndrome approximately two years after SKYSONA administration.

Monitor blood counts until normalization and assess patients for signs and symptoms of bleeding and/or infection prior to and after SKYSONA administration.

Delayed Platelet Engraftment

Delayed platelet engraftment has been observed with SKYSONA. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 14% of patients had a platelet count $\leq 50 \times 10^9/L$ beyond 60 days after treatment with SKYSONA.

Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Risk of Neutrophil Engraftment Failure

There is a potential risk of neutrophil engraftment failure after treatment with SKYSONA. Neutrophil engraftment failure was defined as failure to achieve 3 consecutive absolute neutrophil counts (ANC) $\geq 0.5 \times 10^9$ cells/L obtained on different days by Day 43 after infusion of SKYSONA. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with SKYSONA, provide rescue treatment with the back-up collection of CD34+ cells.

Hypersensitivity Reactions

Allergic reactions may occur with the infusion of SKYSONA. The dimethyl sulfoxide (DMSO) in SKYSONA may cause hypersensitivity reactions, including anaphylaxis which is potentially life-threatening and requires immediate intervention.

Anti-retroviral Use

Patients should not take anti-retroviral medications for at least one month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed. Anti-retroviral medications may interfere with manufacturing of the apheresed cells.

If a patient requires anti-retrovirals for HIV prophylaxis, mobilization and apheresis of CD34+ cells should be delayed until HIV infection is adequately ruled out.

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Important Safety Information (cont'd)

Laboratory Test Interference

SKYSONA (elivaldogene autotemcel) affects polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion. A PCR based assay should not be used to screen for HIV infection in patients treated with SKYSONA as a false positive test result is likely.

Adverse Reactions

Most common non-laboratory adverse reactions ($\geq 20\%$): mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, rash.

Most common Grade 3 or 4 laboratory abnormalities ($\geq 40\%$): leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, hypokalemia.

Vaccines

Vaccination is not recommended during the 6 weeks preceding the start of myeloablative conditioning, and until hematological recovery following treatment with SKYSONA. Where feasible, administer childhood vaccinations prior to myeloablative conditioning for SKYSONA.

Males of Reproductive Potential

Advise patients of the risks associated with mobilization and conditioning agents.

Males capable of fathering a child and their female partners of childbearing potential should use an effective method of contraception (intra uterine device or combination of hormonal and barrier contraception) from start of mobilization through at least 6 months after administration of SKYSONA.

Data are available on the risk of infertility with myeloablative conditioning. Advise patients of the option to cryopreserve semen before treatment if appropriate

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The following pages are a template that may be customized to use as a statement of medical necessity/appeal for your patients. The yellow highlighted text will need to be updated to include the patient's specific details.

[Today's Date]

[Name of Insurance Company]

[Address of Insurance Company]

[City], [State], [Zip Code]

Re: [Patient Name], [DOB], [Parent/Legal Guardian's Name (If Applicable)]

Policy Number: [Enter Number]

Group Number: [Enter Number]

Medicaid Number: [Enter Number (If Applicable)]

ICD-10-CM Diagnosis Code(s): [Enter Code(s)]

REQUESTING EXPEDITED REVIEW FOR TREATMENT WITH SKYSONA® (elivaldogene autotemcel)

Dear [Medical Director's Name],

I am writing on behalf of my patient, [Enter Name], to document the medical necessity of SKYSONA, gene therapy indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). My patient was diagnosed on [Enter Diagnosis Date]. I recently performed a consultation regarding the patient's clinical eligibility for SKYSONA on [Enter Date]. Given his age, early, active stage, and the progressive nature of the disease, I am requesting expedited review and approval of SKYSONA for my patient.

DISEASE OVERVIEW

Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder in which mutations in the *ABCD1* gene result in the dysfunction of the peroxisomal ALD protein (ALDP) and subsequent accumulation of very-long chain fatty acids (VLCFA), primarily in adrenal and nervous system tissues.¹ The estimated worldwide incidence of ALD is 1:21,000 newborn males.² Approximately 40% of boys with ALD will develop the most severe form of the disease, called cerebral ALD (CALD), marked by rapidly progressive inflammatory cerebral demyelination, which leads to progressive, irreversible loss of neurologic function and death.¹ Nearly half of patients with CALD who do not receive treatment die within 5 years of symptom onset.³ Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been the only effective therapeutic intervention for CALD, but it is associated with serious potential immune-related complications and mortality.⁴⁻⁷

My request for an expedited review takes into consideration that SKYSONA has the potential to slow progression of neurologic dysfunction.

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SKYSONA CLINICAL TRIALS OVERVIEW

FDA approval for SKYSONA® (elivaldogene autotemcel) was based on data from bluebird bio's completed Phase 2/3 ALD-102 (Starbeam) and ongoing Phase 3 ALD-104 studies. These are two 24-month, open-label, single-arm studies in patients with early, active CALD (N=67) as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement (GdE+) on magnetic resonance imaging (MRI), as well as a neurologic function score (NFS) of ≤ 1 , indicating limited changes in neurologic function. In addition, bluebird bio is conducting a long-term follow-up study, LTF-304, to continue monitoring patients who have participated in and completed the bluebird bio-sponsored clinical studies ALD-102 and ALD-104, through 15 years post-treatment.

The efficacy of SKYSONA was compared to an external untreated natural history control captured in a retrospective natural history study, ALD-101. Data were collected from existing medical records for untreated patients with CALD who had early, active disease at diagnosis. A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS ≥ 1) to time to first Major Functional Disability (MFD) or death (i.e., MFD-free survival) in subpopulations of the SKYSONA and natural history cohorts. The MFDs are defined as: loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. To be included in the analysis, patients had to have symptoms at baseline (NFS=1) or be asymptomatic (NFS=0) at baseline and have developed symptoms (NFS ≥ 1) during the course of follow-up in the study. Additionally, they had to have at least 24 months of follow-up after initial NFS ≥ 1 or have had an event (MFD or death). Estimated rates of MFD-free survival at Month 24 from time of first NFS ≥ 1 were 72% (95% CI: 35%, 90%) for the symptomatic SKYSONA subpopulation (N=11) and 43% (95% CI: 10%, 73%) for the natural history population (N=7), showing a slower progression to MFD or death from time of symptom onset for those early, active CALD patients treated with SKYSONA compared to the similar natural history cohort.

Comparison of SKYSONA with an external allo-HSCT control (pooled from patients in ALD-101 and from a mixed prospective and retrospective allo-HSCT data collection study, ALD-103) was performed for overall survival (OS) due to concerns about treatment-related toxicities. OS was analyzed as time-to-event Kaplan-Meier estimates comparing SKYSONA (entire efficacy population, N=61) to early, active allo-HSCT subpopulations by donor type: human leukocyte antigen (HLA)-Matched allo-HSCT subpopulation (N=34) and HLA-Mismatched allo-HSCT subpopulation (N=17). There were insufficient long-term data to compare OS beyond Month 24. However, a distinct difference in OS in the first 9 months following treatment was seen for the subpopulation who received allo-HSCT from an HLA-mismatched donor as compared to SKYSONA and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of SKYSONA, it does demonstrate a survival advantage of SKYSONA as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT subpopulation largely attributed to allo-HSCT-related toxicities.

Safety was based on 67 patients treated with SKYSONA. Data was obtained from both ALD-102 and ALD-104, and for 36 patients, from a long-term follow-up study (LTF-304). The median (min, max) duration of follow-up was 24 (1, 88) months. In the two trials, serious adverse reactions from SKYSONA infusion to last follow-up occurred in 54% of patients. The most common non-laboratory, serious adverse reactions ($\geq 3\%$

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incidence) that occurred after treatment with SKYSONA® (elivaldogene autotemcel) were febrile neutropenia (18%), pyrexia (fever) (18%), seizure (7%), myelodysplastic syndrome (4%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%). The most common non-laboratory adverse reactions ($\geq 20\%$) were mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, rash. The most common Grade 3 or 4 laboratory abnormalities ($\geq 40\%$) were leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, hypokalemia.

SKYSONA MECHANISM OF ACTION

SKYSONA adds functional copies of the *ABCD1* cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with Lenti-D lentiviral vector LVV. After SKYSONA infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP. Functional ALDP can then participate in the local degradation of VLCFAs, which is believed to slow or possibly prevent further inflammation and demyelination.

PATIENT SYMPTOMS SUMMARY

My patient was diagnosed at [Enter Age] and is currently [Enter Age]. Based on my evaluation, he is between 4-17 years of age and has the following symptoms associated with early, active cerebral adrenoleukodystrophy (CALD).

[Treating physician to provide patient level details that would identify the specific clinical criteria for the use of SKYSONA.]

- Loes score between 0.5 and 9 (inclusive)
- GdE+ on MRI
- NFS of ≤ 1

By treating this patient with SKYSONA, the goal is to slow the progression of neurologic dysfunction.

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RECOMMENDED MEDICAL INTERVENTION

As the treating physician, I am recommending SKYSONA® (elivaldogene autotemcel) for my patient, based on his diagnosis and medical history, and my clinical experience. In my professional opinion, SKYSONA is medically necessary for this patient. I have reviewed with the patient AND [patient's parents OR patient's legal guardians] the potential benefits and counseled on the risks associated with treatment of SKYSONA, including the steps for administration.

[Treating Physician to Insert Clinical Rationale for Prescribing Skysona Including Any Supportive Chart Notes]

[Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical conditions. Provide your clinical rationale for treatment while considering the health plan's possible medical policy criteria for SKYSONA.]

Please contact me if any additional information is required to ensure the prompt approval of the treatment(s) in question.

Sincerely,

[Enter Physician's Name and Signature]

References

1. Engelen M, et al. *Orphanet J Rare Dis.* 2012;7:51-64.
2. Bezman L, et al. *Ann Neurol.* 2001;49(4):512-7.
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4. Raymond G, et al. *Biol Blood Marrow Transplant.* 2019;25(3):538-48.
5. Miller W, et al. *Blood.* 2011;118(7):1971-8.
6. Mitchell R, et al. *Pediatr Transplant.* 2013;17(6):582-8.
7. Kuhl JS, et al. *JAMA Netw Open.* 2018; 1(3): e180769.
8. SKYSONA [prescribing information], Somerville, MA; bluebird bio, Inc.; September 2022.

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