Effective Date: 12/11/2025
Current Effective Date: 12/11/2025
Last P&T Approval/Version: 10/29/2025
Next Review Due By: 07/2026
Policy Number: C29883-A

Sephience (sepiapterin)

PRODUCTS AFFECTED

Sephience (sepiapterin)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hyperphenylalaninemia (HPA) in patients with sepiapterin-responsive phenylketonuria (PKU)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. HYPERPHENYLALANINEMIA:
   1. Documented diagnosis of phenylketonuria (PKU)
      AND
   2. Documentation of uncontrolled blood phenylalanine (Phe) concentrations (>600 mcmol/L) [DOCUMENTATION REQUIRED]

AND

3. Prescriber attests that dietary management will be maintained (phenylalanine-restriction) while on Sephience (sepiapterin) therapy
   AND
4. Sephience (sepiapterin) will be used as monotherapy and NOT in combination with Palynziq (pegvaliase-pqpz) or Kuvan (sapropterin dihydrochloride)
   NOTE: There is no data available to support the concomitant use of Sephience and pegvaliase and/or sapropterin. In the Sephience pivotal studies, patients were required to discontinue use of other agents prior to using study drug.
   AND
5. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.

CONTINUATION OF THERAPY:

A. HYPERPHENYLALANINEMIA:
   1. Prescriber attests to compliance/adherence to a phenylalanine-restricted diet in conjunction with sepiapterin therapy
      AND
   2. Sephience continues to be used as monotherapy
      AND
   3. (a) Documentation that member's blood Phe decreased (at least a 30% reduction in Phe levels) after 2 weeks of treatment at 60 mg/kg/day (responders to treatment with sepiapterin) [DOCUMENTATION REQUIRED]
      OR
      (b) If member has not been titrated to appropriate max dose for effect within 2 months: Prescriber must provide treatment plan of titration, revaluation, and monitoring [DOCUMENTATION REQUIRED]
      OR
      (c) Member has adequate blood Phe level control with continued use (monitored for hyper- and hypo-phenylalaninemia)

DURATION OF APPROVAL:

Initial authorization: 2 months, Continuation of Therapy: 6 months
MOLINA REVIEWER NOTE: For Illinois Marketplace, Kentucky Marketplace, Mississippi Marketplace, Ohio Marketplace, and Kentucky Medicaid, please see Appendix.

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified medical geneticist or physician experienced in the management of metabolic disorders or phenylketonuria (PKU) [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

1 month of age and older

QUANTITY:

Starting dose based on age, administered once daily
Less than 6 months of age: 7.5 mg/kg once daily
6 months to less than 1 year of age: 15 mg/kg once daily
1 year to less than 2 years of age: 30 mg/kg once daily
2 years of age and older: 60 mg/kg once daily

Maximum Quantity Limits – 60 mg/kg once daily

PLACE OF ADMINISTRATION: The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Phenylketonuria Treatment - Agents

FDA-APPROVED USES:
Indicated for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients 1 month of age and older with sepiapterin-responsive phenylketonuria (PKU). Sephience is to be used in conjunction with a phenylalanine (Phe)- restricted diet.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Illinois (Source: Illinois General Assembly)
"(215 ILCS 200/60) Sec. 60. Length of prior authorization approval. A prior authorization approval shall be valid for the lesser of 6 months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined by the patient's health care professional or the renewal of the plan, and the approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug prescribed by the health care professional. All dosage increases must be based on established evidentiary standards and nothing in this Section shall prohibit a health insurance issuer from having safety edits in place. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids. Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the care, treatment, or services are medically necessary.
(Source: P.A. 102-409, eff. 1-1-22.)"
"(215 ILCS 200/65) Sec. 65. Length of prior authorization approval for treatment for chronic or long-term conditions. If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, the approval shall remain valid for the lesser of 12 months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids. Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the

care, treatment, or services are medically necessary.
(Source: P.A. 102-409, eff. 1-1-22.)"

Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) "Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization." (Subsection 3) "Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program."

Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

Mississippi (Source: Mississippi Legislature)
"SECTION 13. Length of approvals. (1) A prior authorization approval shall be valid for the lesser of six (6) months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined by the patient's health care professional or the renewal of the policy or plan, and the approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug prescribed by the health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his/her health care professional may extend a prior authorization approval for a longer period, by agreement. All dosage increases must be based on established evidentiary standards, and nothing in this section shall prohibit a health insurance issuer from having safety edits in place. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment or services are medically necessary. SECTION 14. Approvals for chronic conditions. (1) If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, including, but not limited to, chemotherapy for the treatment of cancer, the approval shall remain valid for the lesser of twelve (12) months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his or her health care professional may extend a prior authorization approval for a longer period, by agreement. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment, or services are medically necessary."

Ohio (Source: Ohio Revised Code)
Chapter 3923 Sickness And Accident Insurance Section 3923.041 Policies with prior authorization

requirement provisions “(B)(6)(a) For policies issued on or after January 1, 2017, for a prior approval related to a chronic condition, the insurer or plan shall honor a prior authorization approval for an approved drug for the lesser of the following from the date of the approval: (i) Twelve months; (ii) The last day of the covered person's eligibility under the policy or plan. (b) The duration of all other prior authorization approvals shall be dictated by the policy or plan.”

State Medicaid

Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) “Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization.” (Subsection 3) “Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or Page 5 of 8 Drug and Biologic Coverage Criteria Molina Healthcare, Inc. confidential and proprietary © 2024 This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare. benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program.”
Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Sephience is indicated to reduce blood phenylalanine (Phe) levels in patients with sepiapterin-responsive phenylketonuria (PKU). The medication should be used in conjunction with a Phe-restricted diet. Sephience works by increasing the activity of phenylalanine hydroxylase (PAH), the enzyme responsible for breaking down phenylalanine. In responsive patients, blood Phe levels may begin to decrease within 2 weeks of treatment, although maximal effect may take up to 6 weeks. The recommended starting dose of Sephience is weight- and age-based:1 to <6 months: 7.5 mg/kg/day. 6 months to <1 year: 15 mg/kg/day. 1 to <2 years: 30 mg/kg/day. ≥2 years of age: 60 mg/kg/day (maximum dose). Sephience is administered orally once daily with food. For doses under 1,000 mg, the powder should be mixed with water or apple juice. For doses of 1,000 mg or more, it may also be mixed with soft foods like applesauce or strawberry jam. Therapy response is determined by changes in blood Phe levels after treatment for a period of 2 weeks. Blood Phe levels should be checked within 1–2 weeks of starting treatment and monitored regularly. Patients whose blood Phe does not decrease after 2 weeks of treatment at the maximum dose of 60 mg/kg/day are considered non-responders, and treatment with Sephience should be discontinued.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Sephience (sepiapterin) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Sephience (sepiapterin) include: No labeled contraindications.

Exclusions/Discontinuation:

Avoid concomitant use of drugs known to inhibit folate synthesis dihydrofolate reductase (DHFR) (e.g., trimethoprim, methotrexate, trimetrexate, pemetrexed, pralatrexate, raltitrexed, and piritrexim) while taking Sephience. Concomitant administration of such drugs may reduce sepiapterin metabolism to tetrahydrobiopterin (BH4). If concomitant use is not avoidable, monitor blood Phe levels.
Avoid concomitant use of sepiapterin reductase (SR) inhibitors with Sephience. Concomitant administration of such drugs may reduce sepiapterin metabolism to BH4. If concomitant use is not avoidable, monitor blood Phe levels.

OTHER SPECIAL CONSIDERATIONS:

None

CODING/BILLING INFORMATION

CODING DISCLAIMER *Codes listed in this policy are for reference purposes only and may not be all- inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Sephience PACK 250MG
Sephience PACK 1000MG

REFERENCES

1. Sephience (sepiapterin) oral powder [prescribing information]. Warren, NJ: PTC Therapeutics, Inc.; July 2025.
2. Vockley J, Anderson HC, Antshel KM, et al; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: Diagnosis and management guideline [published correction appears in Genet Med. 2014;16(4):356]. GenetMed. 2014;16(2):188- 200.[PubMed 24385074]10.1038/gim.2013.157
3. Singh, Rohr, Frazier, etc al, Recommendations for the nutrition management of phenylalanine hydroxylase deficiency, Genetics in Medicine, 2014, doi:101038/gim.2013.179

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q4 2025