

Zolgensma® (Onasemnogene Apeparvovec-Xioi) (for Pennsylvania Only)

Policy Number: CSPA2024D0079F

Effective Date: January 1, 2024

[➔ Instructions for Use](#)

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Related Policies
None

Application

This Medical Benefit Drug Policy only applies to the state of Pennsylvania.

Coverage Rationale

Zolgensma is proven and medically necessary for one treatment per lifetime for the treatment of spinal muscular atrophy (SMA) in patients who meet all of the following criteria:

- Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation or deletion of genes in chromosome 5q resulting in **one** of the following:
 - Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); **or**
 - Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])
- and**
- **One** of the following:
 - Diagnosis of symptomatic SMA by a neurologist with expertise in the diagnosis of SMA; **or**
 - Diagnosis of SMA based on results of SMA newborn screening
- and**
- For use in a neonatal patient born prematurely, the full-term gestational age has been reached; **and**
- Patient is less than 2 years of age; **and**
- Patient is not dependent on invasive ventilation or tracheostomy; **and**
- Zolgensma is prescribed by a neurologist with expertise in the treatment of SMA; **and**
- Patient is not to receive routine concomitant SMN modifying therapy [e.g., Spinraza (nusinersen), Evrysdi (risdiplam)] (patient’s medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval); **and**
- Patient does not have an elevated anti-AAV9 antibody titer above 1:50; **and**
- Patient will receive prophylactic prednisolone (or glucocorticoid equivalent) prior to and following receipt of Zolgensma in accordance with the United States Food and Drug Administration (FDA) approved Zolgensma labeling; **and**

- Patient will receive Zolgensma intravenously in accordance with the FDA approved labeling; **and**
- Patient has never received Zolgensma treatment in their lifetime; **and**
- Authorization will be issued for no more than one treatment per lifetime and for no longer than 45 days from approval or until 2 years of age, whichever is first

Additional Information Relevant to the Review Process but Not Impacting the Determination of Medical Necessity

- Physician attests that the patient, while under the care of the physician, will be assessed by one of the following exam scales during subsequent office visits[†]:
 - Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale during subsequent office visits while the patient is 2 to 3 years of age or younger; **or**
 - Hammersmith Functional Motor Scale Expanded (HFMSSE) during subsequent office visits while the patient is 2 to 3 years of age or older
- and**
- Physician attests that the patient will be assessed via an age-appropriate validated exam scale within two weeks of Zolgensma administration to establish a baseline functional assessment[†]

[†]For quality purposes only, this information will not be considered as part of the individual coverage decision.

Zolgensma is not proven or medically necessary for:

- The treatment of symptomatic later-onset SMA older than 2 years of age; **or**
- SMA without chromosome 5q mutations or deletions; **or**
- The routine combination treatment of SMA with concomitant SMN modifying therapy

Requests outside of this criteria will be reviewed for medical necessity on a case-by-case basis.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10 ¹⁵ vector genomes

Diagnosis Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other SMAs and related syndromes
G12.9	Spinal muscular atrophy, unspecified

Background

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disease that affects the survival of motor neurons of the spinal cord.² SMA is caused by the deletion/mutation of the SMN1 gene.² The estimated annual incidence of SMA is 5.1 to 16.6 cases per 100,000 live births. Approximately 1/40 to 1/60 people are SMA carriers, equating to 3.5 to 5.2 million and 12 to 18 million individuals in the United States and Europe, respectively.²⁻⁶ SMA is characterized by the degeneration of motor neurons of the spinal cord, resulting in hypotonia and muscle weakness. Five phenotypic subtypes of SMA (0-IV) have been described based on age of symptom onset and motor function achieved.⁵ Current literature indicates that the number of copies

of the SMN2 gene that a patient has is the best predictor of clinical phenotype. The table below summarizes the clinical and genetic characteristics of the SMA subtypes.²⁻⁶

Clinical SMA Diagnosis	% of SMA Cases	Usual Number of SMN2 Copies	Typical Age of Symptom Onset	Life Expectancy	Motor Development
Type 0	Very rare	1	In utero	Death occurs shortly after birth	None
Type I	58%	2	< 6 months	< 24 months	Never able to sit
Type II	29%	2-4 (80% have 3 copies)	< 18 months	70% alive at 25 years	Unable to walk without assistance
Type III	13%	95% have ≥ 3 copies		May be normal	Able to stand and walk without assistance, but lose ability as disease progresses
Type IV	< 5%	≥ 4	20-30 years	Normal	Ambulatory. May experience mild muscle weakness

Zolgensma (onasemnogene abeparvovec, AVXS-101) is a one-time SMN1 gene replacement therapy that treats the root cause of SMA, deletion or loss of function of the SMN1 gene, by delivering a copy of the human SMN gene via an adeno-associated virus serotype 9 (AAV9), which crosses the blood-brain barrier. Zolgensma is designed with a self-complementary DNA structure and a continuous promoter that allows for immediate and sustained expression of SMN protein, providing a rapid onset of effect. Motor neurons are non-dividing cells; thus, a stable SMN gene supplemented via a viral vector would not be expected to be lost as children grow, potentially allowing for long-term, sustained SMN protein expression with a one-time dose, and providing a durable therapeutic effect. The use of Zolgensma in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma infusion is to be delayed until full-term gestational age is reached.^{1,7-12}

Clinical Evidence

Type 1 SMA

A phase 1, open-label, single site, dose-escalation study (CL-101) evaluated the safety and efficacy of a one-time IV administration of Zolgensma in 15 patients with type 1 SMA with 2 copies of survival motor neuron 2 (SMN2) 9 months of age or younger who developed symptoms of SMA prior to 6 months of age. Three of the patients received a low dose (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2.0×10^{14} vg per kilogram). The dosage received by patients in the low-dose cohort was one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of Zolgensma received by patients in this completed clinical trial are unclear due to a change in the method of measuring Zolgensma concentration, and to decreases in the concentration of stored Zolgensma over time. The retrospectively estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg. The primary outcome was safety. The secondary outcome was the time until death or the need for permanent ventilatory assistance. As of the data cutoff for the manuscript publication on August 7, 2017, all 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. In the high-dose cohort, a rapid increase from baseline in the score on the CHOP INTEND scale followed gene delivery, with an increase of 9.8 points at 1 month and 15.4 points at 3 months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, 9 rolled over, 11 were fed orally and could speak, and 2 walked independently. Elevated serum aminotransferase levels occurred in 4 patients and were attenuated by prednisolone.^{11,12,14}

A follow-up presentation of the CL-101 study showed that at all patients were alive and without the need for ventilation at 24 months. In the high dose cohort (cohort 2), all patients achieved at least one motor milestone with 11 of 12 achieving motor milestones rarely seen in the type 1 SMA population. All 11 patients who achieved these milestones were 6 months of age or less at the time of gene therapy administration. The one patient not experiencing advanced motor milestone achievement was 8 months of age at the time of gene therapy administration. Patients treated with Zolgensma had a marked, early, and rapid improvement in CHOP-INTEND score, in contrast with untreated SMA type 1 patients who experienced a 10.7-point drop in CHOP-INTEND scores from 6–12 months of age. At 24 months follow-up, patients had a mean CHOP-INTEND score increase of

25.4 points from baseline (n = 12). The maintenance of scores of more than 40 points on the CHOP-INTEND scale has been considered to be clinically meaningful in SMA. Eleven of 12 patients achieved and maintained a score > 40 points for a mean of 19.5 months. In contrast, one recent natural history study reported that SMA type 1 children neither achieve nor maintain CHOP-INTEND scores > 40 points after 6 months of age. None of the patients in the low dose cohort were able to sit without support, or to stand or walk; in the high dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for ≥ 30 seconds, and 2 patients (16.7%) were able to stand and walk without assistance. As of April 2018, the oldest subject in cohort 2 was 46.2 months of age with 40.6 months of follow-up.

A pivotal, Phase 3, multicenter, open-label trial (STRIVE) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 months of age with type 1 SMA based on genetic confirmation of a bi-allelic mutation of the SMN1 gene with 1 or 2 copies of the SMN2 gene who are not dependent on invasive or non-invasive ventilatory support for greater than 6 hours a day. Enrollment in the study is complete with 22 patients with 2 copies of SMN2 receiving Zolgensma. The patient population and baseline characteristics closely match those studied in the CL-101 study. The mean baseline age was 3.7 months with a range of 0.5-5.9 months. The mean baseline CHOP-INTEND score was 32 (range 17-52). As of March 2019, 19 of 20 patients (95%) who had reached 10.5 months of age survived without permanent ventilation and 13 of 15 patients (87%) who had reached 13.6 months of age were surviving without permanent ventilation. The average increase in CHOP-INTEND scores were 6.9, 11.7, and 14.3 at months 1, 3, and 5, respectively. Twenty-one of 22 (95%) patients achieved CHOP-INTEND score of 40 or greater. Eleven of 22 (50%) patients were able to sit without support at a mean age of 13.8 months. No patient screened for AAV9 antibodies had exclusionary AAV9 antibody titers.^{8,10,22}

Pre-Symptomatic Patients Likely to Develop Type 1 SMA

A phase 3, multicenter, open-label trial (SPR1NT) is currently underway evaluating the safety and efficacy of a one-time intravenous administration of Zolgensma in patients less than 6 weeks of age with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with 2 or 3 copies of the SMN2 who have yet to develop symptoms who have a baseline compound muscle action potential (CMAP) > 2 mV at baseline. Enrollment is underway with planned enrollment of at least 27 patients in cohorts with 2 and 3 copies of SMN2. Patients are to receive a one-time intravenous administration of Zolgensma at a dose on 1.1×10^{14} vg per kg.

As of June 11, 2020, 29 patients have received Zolgensma in the trial with positive interim results.^{9,15,20,27} All patients were alive and free of ventilatory support at median age at follow up of 15 months. All patients fed orally and did not require feeding tube support of any kind.

Among the cohort of patients with two copies of SMN2, 11 of 14 patients (79%) achieved the study's primary endpoint of sitting without support for at least 30 seconds. Ten of these patients achieved this within the WHO window of normal development. Five patients (36%) could stand independently, three of whom achieved this milestone within the WHO window of normal development. Four patients (29%) could walk independently, three of whom achieved this milestone within the WHO window of normal development. All patients achieved CHOP INTEND scores of ≥ 50, and 13 (93%) achieved a CHOP INTEND score ≥ 58.

Among the cohort of patients with three copies of SMN2, 8 patients (53%) achieved the study's primary endpoint of standing alone for at least three seconds, and 6 patients (40%) walked independently. These motor milestones were all achieved within the WHO window of normal development. Of those patients who had not yet achieved these milestones, all were still within the WHO window of normal development. All patients had steady gains in mean raw score of Bayley-III fine and gross motor scales.

Prediction of SMA Phenotype Based on SMN2 Copy Number

As stated above, current literature indicates that the number of copies of the SMN2 gene that a patient has is the best predictor of clinical phenotype, however the correlation is not absolute. A recent publication assessed the correlation of SMN2 copy number to SMA phenotype in 3459 patients worldwide from reports published after 1999. Analysis of the North American cohort showed similar findings. Seventy-three percent of patients of patients with 2 copies were diagnosed with type I SMA, accounting for 79% of all type I SMA cases. Patients with 3 copies of SMN2 were the most numerous in the entire cohort accounting for approximately half of the cases. Fifteen percent of patients with 3 copies of SMN2 were diagnosed with Type I SMA. Ninety-five percent of patients with type II SMA and 54% of patients with type III SMA had 3 copies or less of SMN2. Approximately 15% of patients in the worldwide cohort had 4 copies of SMN2. Patients with 4 copies of SMN2 were highly unlikely to be diagnosed with type I SMA as greater than 99% of cases were diagnosed with non-type I SMA, with approximately

90% of patients with 4 SMN2 copies developing type III SMA. Patients with 4 copies or more of SMN2 accounted for 0.3% of all cases diagnosed with type I SMA and approximately 5% of all cases diagnosed with type II SMA.^{6, 19}

Type 2 SMA

A phase 1, multicenter, open-label, dose-escalation trial (STRONG) is currently underway evaluating the safety and efficacy of a one-time intrathecal administration of onasemnogene abeparvovec in patients with SMA based on a genetic confirmation of a bi-allelic mutation of the SMN1 gene with 3 copies of SMN2, who are able to sit but cannot stand or walk at the time of study entry with onset of SMA symptoms occurring before 12 months of age. These patients would be classically considered patients with likely type 2 SMA. Patients will receive onasemnogene abeparvovec in a dose comparison safety study of two potential therapeutic doses (3 patients at each dose). Patients will be stratified in two groups, those < 24 months of age at time of dosing and those ≥ 24 months and < 60 months of age at time of dosing. Fifteen patients < 24 months (cohort 1) will be enrolled, and twelve patients ≥ 24 < 60 months (cohort 2) will be enrolled. The first cohort will enroll 3 patients (cohort 1) < 24 months of age who will receive intrathecal administration of 6.0×10^{13} vg of onasemnogene abeparvovec (Dose A). After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose B, in which 3 patients less than 60 months of age will receive 1.2×10^{14} vg of onasemnogene abeparvovec intrathecally. After review of the data from cohort 1 by the Data Safety Monitoring Board (DSMB), a determination will be made to advance to Dose C, in which 3 patients from cohort 2 will receive 2.4×10^{14} vg of onasemnogene abeparvovec intrathecally. Three patients in cohort 1 received dose A. Based on demonstrated acceptable safety, three additional patients in cohort 2 received dose B. Given ongoing demonstration of acceptable safety, 13 additional patients in cohort 1 and 9 in cohort 2 were treated with dose B. Primary endpoints were safety/tolerability, optimal dose, ability to stand unsupported ≥ 3 sec (cohort 1), and Hammersmith Functional Motor Scale-Expanded score (cohort 2). As of March 2019, 30 patients have been enrolled and received intrathecal onasemnogene abeparvovec. Interim data from this multicenter study showed improvements in motor function in patients with type 2 SMA. 44% of patients in cohort 1 gained motor milestones following treatment. 25% of patients in cohort 2 gained motor milestones following treatment. In patients greater than 24 months of age, the mean increase in HFMSSE was 4.2 points after an average therapy duration of 7.5 months. In cohort 2, 50% of patients experienced a 3 point or greater increase in HFMSSE after 1 month of treatment. No dose limiting toxicity was observed, permitting dose-escalation to dose C (2.4×10^{14} vg) in 2 patients aged less than 24 months.^{16,21} On October 30, 2019 the FDA placed partial hold on clinical trials for intrathecal administration of onasemnogene abeparvovec based on findings from a pre-clinical study in which animal findings showed dorsal root ganglia mononuclear cell inflammation, sometimes accompanied by neuronal cell body degeneration or loss. The partial hold did not apply to any intravenous onasemnogene abeparvovec clinical trials.

Professional Societies

Cure SMA Working Group

In the 2018 Cure SMA Working Group treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. This treatment algorithm was published prior to the approval of onasemnogene abeparvovec. The group recommends the development of dependable and validated screening techniques to enable treatment of presymptomatic patients who may be more responsive to treatment than those already experiencing symptoms. For presymptomatic patients with SMA and three or fewer copies of the *SMN2* gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of *SMN2* who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with more than four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, but the working group recommends against immediate treatment with a disease modifying therapy.¹⁸

In September 2019, Cure SMA reconvened the multidisciplinary working group to reassess the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. The working group has updated their position to a recommendation for immediate treatment for infants diagnosed with SMA via NBS with four copies of SMN2. The working group also revisited the published recommendation to wait to treat for infants with five copies of SMN2 and unanimously voted to uphold the recommendation of watchful waiting. The working group acknowledged that current laboratory assays designed to detect SMN2 copy number often have difficulty distinguishing high copy numbers of SMN2 and that many laboratories report results as four or more SMN2 copies, being unable to give an exact number. Recognizing this fact, the working group encouraged follow-up with a laboratory able to distinguish exact SMN2 copy number.²³

2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy²⁴

A group of 13 European neuromuscular experts, conveyed to help aid the rational use of Zolgensma and presented 11 consensus statements covering qualification, patient selection, safety considerations and long-term monitoring after the European Medical Agency (EMA) approval of Zolgensma. A consensus greater than 95% was considered “strong consensus”, between 75 and 95% “consensus”, and between 50 and 75% “majority consensus”. If less than 50% approved a statement, it was labelled as “no consensus”. The following recommendations were presented with 100% consensus from the European expert panel:

- **Consensus statement 1:** Traditional SMA types (e.g., type 0, 1, 2, 3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment.
- **Consensus statement 2:** In presymptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on SMN2 copy number. Determination of SMN2 copy number needs to be performed in an expert laboratory with adequate measures of quality control.
- **Consensus statement 3:** Approval of gene therapy for SMA with Zolgensma® is based on clinical trials with patients with SMA less than 6 months of age. Additional data of patients up to 2 years and weighing up to 13.5 kg are made public through congress presentations. These data mainly come from non-systematic data collection in the US, where Zolgensma is approved up to the age of 2 years. When administered after the age of 6 months and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety. In this patient population it is particularly important for physicians to discuss the benefit/risk ratio and to carefully manage parents’ or patients’ expectations.
- **Consensus statement 4:** In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.
- **Consensus statement 5:** Since the risk of gene therapy increases with the dose administered and since the dose is directly proportional with the weight, patients above 13.5 kg should only be treated in specific circumstances. For these patients, treatment with other disease modifying therapies or future intrathecal administration of Zolgensma should be considered as an alternative.
- **Consensus statement 6:** Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone.
- **Consensus statement 7:** Centers performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects.
- **Consensus statement 8:** There is convincing evidence that early initiation of treatment –ideally in the presymptomatic stage of the disease – is associated with markedly better outcome as compared to later start of treatment. Spinal muscular atrophy is therefore a good candidate for inclusion in newborn screening programs. In newly diagnosed patients any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive course of the disease.
- **Consensus statement 9:** Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centers should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.
- **Consensus statement 10:** On the basis of the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with Zolgensma for patients with a body weight > 13.5 kg should only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy. This data collection might be best achieved in a clinical trial setting.
- **Consensus statement 11:** As the use of Zolgensma will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Limitations of Use

- The safety and effectiveness of repeat administration of Zolgensma have not been evaluated
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated

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Policy History/Revision Information

Date	Summary of Changes
01/01/2024	<p>Coverage Rationale</p> <ul style="list-style-type: none"> Replaced language indicating “authorization will be for no longer than 14 days from approval or until 2 years of age, whichever is first” with “authorization will be <i>issued for no more than one treatment per lifetime</i> and for no longer than 45 days from approval or until 2 years of age, whichever is first” <p>Supporting Information</p> <ul style="list-style-type: none"> Archived previous policy version CSPA2023D0079E

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its

Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual[®] criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.