Clinical Policy Title: Compounded pharmaceuticals

Clinical Policy Number: 00.02.03

Effective Date: March 1, 2014
Initial Review Date: October 16, 2013
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of compounded pharmaceuticals to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- The compounded pharmaceutical is clinically equivalent and non-inferior to branded products.
- The active ingredients in the compounded pharmaceutical are in therapeutic amount.
- The compounded pharmaceutical is prescribed for an indication supported in the peer-reviewed medical literature.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.
All other uses of compounded pharmaceuticals are not medically necessary.

- Prior authorization: If any of the ingredients of the compounded pharmaceutical require prior authorization, then the compounded product will also require prior authorization.
- No benefit: If compounded pharmaceuticals are not a covered benefit if the indication for prescription is not a benefit (e.g., cosmetic use, not medically necessary, convenience, or other benefit exclusions).

**Alternative covered services:**

Non-compounded medications as covered through the Prestige Health Choice formulary.

**Background**

Prescription drugs historically were compounded according to the instructions of the prescribing physician. In the 1930s and 1940s, an estimated 60 percent of prescriptions were compounded pharmaceuticals. Over the past six decades, the rise of manufactured pharmaceuticals has resulted in a decline in compounded drugs. The role of the pharmacist has shifted toward dispenser and educator rather than primarily the creator of personalized medicines through the mixing of active and inert ingredients. However, in the past decade, the use of compounding has increased. In a white paper authored by Rand, (Wynn, 2011) 2.3 percent of prescriptions for the California Workers’ Compensation system in 2006 were compounded drugs, convenience packs, and medical foods; by 2010, the percentage increased to 12.0 percent.

The recent rise in compounded drugs has paralleled the movement toward more personalized care. Examples of this rationale include reformulation of the vehicle of the active ingredients so a child or elderly person can swallow it. Children may not take liquid medications without the compounding of flavorings to make the drug more acceptable. Such strategies are designed to improve compliance with medication regimens and increase the likelihood of improved therapeutic outcomes. As the U.S. Food and Drug Administration (FDA) has indicated, “Pharmacy compounding can serve an important public health need if a patient cannot be treated with an FDA-approved medication” (FDA, 2012).

There is scant scientific evidence of class effect when comparing outcomes of patients treated with compounded pharmaceuticals and those with similar manufactured drugs. Studies generally have been limited to specific pharmaceuticals. During the debate over the drug Makena, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine issued a position paper on October 13, 2011, recommending, “Physicians should be permitted to prescribe drugs based upon medical considerations and patient need and access.” The two societies recognize that compounded and manufactured products are not identical, but that prescribing physicians weigh clinical outcomes, individual patient needs, and access to medications (ACOG, 2011).
Compounded pharmaceuticals are not overseen by the FDA at this time but fall under the jurisdiction of individual state regulations. An outbreak of fungal meningitis in October 2012 was traced to contamination of compounded injectable corticosteroids produced by the New England Compounding Center. Sixty-four deaths and 753 reported cases of illness were attributed to the tainted products in 20 states (CDC, 2015). This event has triggered renewed activity in Congress to develop legislation placing compounding of nontraditional products under the FDA through the Pharmaceutical Quality, Security and Accountability Act of July 2013. Evaluation of the New England Compounding Center’s operations demonstrated the lack of external oversight of quality control measures, especially for prevention of contamination of parenteral administered products.

A second event triggered significant debate with the approval by the FDA of Makena, a non-compounded 17-alpha-hydroxyprogesterone. Cindy Mann, Director of the Center for Medicaid and CHIP Services (CMCS), posted an Informational Bulletin on June 15, 2012:

“The U.S. Food and Drug Administration (FDA) updated its statement on compounded versions of hydroxyprogesterone caproate (the active ingredient in Makena) today. Please see http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm. As explained in a November 8, 2011, statement, FDA received information from Makena’s sponsor, K-V Pharmaceuticals regarding the potency and purity of samples of bulk hydroxyprogesterone caproate active pharmaceutical ingredients (APIs) and compounded hydroxyprogesterone caproate products. As explained in the updated statement, the FDA has also conducted its own sampling and analysis of compounded hydroxyprogesterone caproate products and the bulk APIs used to make them. FDA states that the analysis of this limited sample of compounded hydroxyprogesterone caproate products and the bulk APIs did not identify any major safety problems, but noted that approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products. Finally, FDA stated that the compounding of any drug, including hydroxyprogesterone caproate, should not exceed the scope of traditional pharmacy compounding. States may, under appropriate circumstances, cover APIs as incident to another service category or, as a pharmacy service, if such coverage is consistent with the State plan.

We would like to remind States of their responsibility to cover FDA approved products, such as Makena, that qualify as covered outpatient drugs under the Medicaid drug rebate program. Any prior authorization procedures for such drugs must be administered in accordance with Section 1927(d) of the Social Security Act, without imposing unreasonable conditions” (Mann, 2012).

The requirements for prior authorization are cited in Section 1927(d) of the Social Security Act, “Payment for Covered Outpatient Drugs,” and are defined in #5 Requirements of Prior Authorization
Programs. This section indicates that the approval of the drug before its dispensing for any medically accepted indication requires that Prestige Health Choice:

a.) Provides response by telephone or other telecommunication device within 24 hours of the request for prior authorization.
b.) Covers at least a 72-hour supply of the prescribed drug in an emergency situation, except for drugs subject to restrictions.
c.) Has the ability to impose limitations on the minimum or maximum quantities or number of refills as necessary to discourage waste or instances of fraud or abuse by individuals.

Where benefits exist, Prestige Health Choice encourages the appropriate use of compounded pharmaceuticals as outlined in this policy. Such drugs must be customized to the individual needs of the member, be non-inferior to any manufactured product in terms of efficacy and safety, and meet requirements to avoid waste.

Searches

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

Searches were conducted on September 21, 2016. Search terms were: “compounded pharmaceuticals.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

There are few peer-reviewed articles in scientific journals about compounding pharmaceuticals. A study of pharmacists’ views on compounding involved a questionnaire administered to 50 compounding and 50 non-compounding pharmacists. While both groups agreed that compounding was more profitable for pharmacies, compounding pharmacists believe that compounding has greater benefit, with potential cost-savings (Lobb, 2015). One analysis called the trend toward more compounding “alarming” due to
the potential use of substandard medicine that may raise risk of physician and pharmacist negligence (Randell, 2014).

Policy updates:

Two peer-reviewed references were added to this policy in 2016.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Nolan (2013)</td>
<td>Key points:</td>
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| Historical review of laws governing compounded pharmaceuticals, and their precedents | • In light of a fungal contamination of steroids in New England, renewed attention to oversight of compounding centers.  
• 1906 Pure Food and Drug Act.  
• 1938 Food, Drug and Cosmetic Act allowed interstate regulation.  
• 1962 Kefauver-Harris Drug Amendments — on-site powers after thalidomide crisis.  
• 1997 FDA Modernization Act — set to regulate compounding.  
• New efforts to allow FDA to regulate compounded pharmaceuticals. |
| FDA (2012)     | Key points:                       |
| FDA tests of hydroxyprogesterone and potential safety concerns | • FDA tested 16 samples of hydroxyprogesterone, including Makena, and found they were all between 97% and 103% potency.  
• Impurities were found higher than Makena but these did “not raise safety concerns.”  
• Thirteen samples from eight pharmacies were tested. One sample was 80% potent but the others were all 90% to 110% potent.  
• No identified safety concerns in the compounded sample. |

List of drugs subject to restriction in SSA § 1927 payment for covered outpatient drugs

The following drugs or classes of drugs, or their medical uses, may be excluded from coverage or otherwise restricted:

- (A) Agents when used for anorexia, weight loss, or weight gain.
- (B) Agents when used to promote fertility.
- (C) Agents when used for cosmetic purposes or hair growth.
- (D) Agents when used for the symptomatic relief of cough and colds.
- (E) Agents when used to promote smoking cessation.
- (F) Prescription vitamins and mineral products, except prenatal vitamins and fluoride preparations.
- (G) Nonprescription drugs, except, in the case of pregnant women when recommended in accordance with the guideline referred to in Section 1905(bb)(2)(A), agents approved by the FDA under the over-the-counter monograph process for purposes of promoting, and when used to promote, tobacco cessation.
- (H) Covered outpatient drugs which the manufacturer seeks to require as a condition of sale that associated tests or monitoring services be purchased exclusively from the manufacturer or its designee.
- (I) Barbiturates.
List of drugs subject to restriction in SSA § 1927 payment for covered outpatient drugs

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<td>(J)</td>
<td>Benzodiazepines.</td>
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<td>(K)</td>
<td>Agents when used for the treatment of sexual or erectile dysfunction, unless such agents are used to treat a condition, other than sexual or erectile dysfunction, for which the agents have been approved by the FDA.</td>
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**Glossary**

**API** — Active pharmaceutical ingredient. This is an active drug within the compounded pharmaceutical product.

**Bioidentical** — Refers to hormones or other biologic products that are produced to be molecularly identical to those within the individual.

**Compounded pharmaceuticals** — Medications customized by the mixing of active and inert ingredients into a vehicle for topical, oral, injectable, or infusible administration. Compounded pharmaceuticals are generally not commercially available.

**Inert** — Inactive ingredients in a compounded pharmaceutical. These may be used to stabilize the API; provide color, taste, or longevity; or may be the vehicle for delivering the API.

**17-P** — The abbreviation for 17-alpha-hydroxyprogesterone caproate, a synthetic hormone that has been demonstrated to inhibit uterine contractions. This biopharmaceutical is generally administered intramuscularly to pregnant women at risk for premature labor. 17-P has been compounded and used for a decade. In 2011, a commercially available formulation, Makena, was granted FDA approval.

**References**

**Professional society guidelines/other:**


American Society of Health-System Pharmacists (ASHP). The ASHP discussion guide for compounding sterile preparations.


Peer-reviewed references:

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med.* 2009;121(1):73–85.


**Clinical trials:**

CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.


Local Coverage Determinations (LCDs):


Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>J codes cannot be used as there is no corresponding NDC</td>
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