

Cigna National Preferred Formulary Coverage Policy



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Coverage Policy Number NPF347

Prior Authorization Compounded Select Topical Medications

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Related Coverage Resources

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

NPF Coverage Policy

Drugs Affected:

- topical ketamine
- topical gabapentin
- topical diclofenac
- topical ketoprofen
- topical flurbiprofen
- topical nabumetone
- topical meloxicam
- topical hyaluronic acid
- topical mometasone furoate
- topical fluticasone propionate

Prior authorization is recommended for prescription benefit coverage of the following compounded topical medications: ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate. Due to the lack of robust clinical efficacy and safety data, in addition to the lack of standardized dosages and formulations, **approval is not recommended for any condition** for these non-FDA-approved topical compounded formulations of ketamine, gabapentin, diclofenac,

ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications).

Criteria

Approval is not recommended for any condition.

Conditions Not Covered

Compounded topical formulations of ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications) are considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

Topical Ketamine

1. **Neuropathic Pain.** There are published data available from four randomized, placebo-controlled studies assessing the efficacy of compounded topical ketamine, either alone or in combination with other agents (e.g., amitriptyline, baclofen) for the treatment of various types of neuropathic pain (e.g., peripheral neuropathy, diabetic neuropathy).¹⁻⁴ In summary, three of the four studies did not show any statistically significant efficacy differences compared with placebo. One study showed a trend towards improvement compared with placebo in individuals with CIPN.¹ All of the other published data with topical ketamine use for neuropathic pain are based on case reports, open-label studies, or pilot studies.
2. **Complex regional pain syndrome (CRPS).** There are very limited published efficacy data available with topical ketamine for the treatment of CRPS. One small double-blind, placebo-controlled study assessed the efficacy of ketamine 10% cream in individuals (n = 20) with CRPS type 1 (n = 18/20) and type 2 (n = 2/20) on two separate occasions.⁵ The primary aim was to determine whether topical ketamine inhibited sensory disturbances in the symptomatic limb of individuals. Topical ketamine did not lead to pain reduction, but allodynia to brushing the skin was reduced. Most of the other published evidence for topical ketamine use for CRPS is based on case reports.

Topical Gabapentin

1. **Neuropathic Pain.** There are no published efficacy or safety data available with compounded topical formulations of gabapentin either alone or in combination with other drugs for use in neuropathic pain.
2. **Complex regional pain syndrome (CRPS).** There are no published efficacy or safety data available with topical gabapentin use for the treatment of CRPS.
3. **Vulvodynia.** There is one retrospective study that assessed the efficacy of topical gabapentin 2% to 6% in women (n = 51) with vulvodynia.⁷ Though topical gabapentin was effective in reducing pain in about 80% of women, these data are limited by small sample size and study design. Large randomized trials are needed to establish the efficacy of topical gabapentin for vulvodynia.

Topical NSAIDs (diclofenac, ketoprofen, flurbiprofen, nabumetone, and meloxicam)

1. **Arthritis (e.g., osteoarthritis [OA], rheumatoid arthritis [RA]).** There are no published data available with the use of compounded, non-FDA approved topical formulations of NSAIDs such as topical diclofenac, topical ketoprofen, topical meloxicam, topical nabumetone, or topical flurbiprofen, either alone or in combination with other agents for the treatment of arthritis, such as OA. FDA-approved, commercially available topical NSAIDs such as Voltaren 1% gel, and Pennsaid 1.5% topical solution are indicated for the treatment of OA and have substantial efficacy and safety data supporting their use.¹⁰⁻¹¹ With the availability of effective and safe FDA-approved topical NSAIDs, the use of other compounded topical NSAIDs with no established efficacy and safety data is not recommended.

Topical Fluticasone Propionate and Mometasone Furoate

1. **Use in various types of skin conditions (e.g., dermatitis, wound care).** There are very limited to no published efficacy or safety data available with non-FDA approved, compounded formulations of fluticasone and mometasone for the treatment of skin conditions.

2. **Cosmetic Use (e.g., scar therapy, for minimizing stretch marks).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.
3. **Use as Intranasal Irrigation Solution for Chronic Rhinosinusitis.** One small study (n = 23) assessed the use of fluticasone propionate 3 mg in 240 mL saline, as irrigation solution twice daily in individuals with chronic rhinosinusitis who had undergone sinus surgery.¹⁶ The study mainly assessed for the effects of fluticasone on salivary cortisol levels and ocular changes. There are no other published efficacy or safety data with the use of corticosteroids in irrigation solutions.

Topical Hyaluronic Acid Derivatives

1. **Vaginal Atrophy.** Limited data are available with the use of hyaluronic acid derivatives in combination with other agents (e.g., vitamin E) for the treatment of vaginal atrophy;¹⁰⁻¹⁴ however, vaginal estrogen therapies are the recommended first-line agents for the treatment of symptomatic vaginal atrophy.¹⁵
2. **Osteoarthritis (OA).** There are no published efficacy data available to support the use of non-FDA -approved, compounded formulations of hyaluronic acid and its derivatives for use in any OA or other pain-related conditions. Hyaluronic acid intra-articular injections (e.g., Synvisc) are available as FDA-approved products for the treatment of OA of the knee.⁹
3. **Use in Any Other Medical Condition, Including, But Not Limited to Ophthalmic Procedures and Wound Care.** There are no published efficacy data available to support the use of non-FDA- approved, compounded formulations of hyaluronic acid and its derivatives for use in any medical condition.
4. **Cosmetic Use (e.g., treatment of frown lines).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

Background

Overview

Compounded products are used for a variety of indications from treating pain to hormone therapy. The compounded formulations can contain just one active drug in a base vehicle or they may contain a combination of active drugs. Compounded medications are not Food and Drug Administration (FDA) approved, thus the FDA has limited regulatory authority over compounding pharmacies since they are licensed by their respective state board of pharmacy. Compounded medications also do not undergo the rigorous drug review process to demonstrate safe and effective use in individuals that all commercially available prescription drugs must establish prior to widespread availability. Also, compounded medications generally do not have standardized dosages and duration for use; likewise, there are no standardized protocols to prepare each compound. For these reasons, compounded preparations are at a greater propensity to have batch-to-batch variability and the product sterility/purity cannot be guaranteed relative to the commercially available products.

Efficacy

There are very limited published controlled studies with established safety and efficacy data supporting use of compounded medications for any condition. The available efficacy data for the targeted topical compounds in this policy are described below.

Topical Ketamine

There are four randomized, placebo-controlled studies published assessing the use of compounded topical ketamine for neuropathic pain. Study 1 enrolled individuals (n = 208) with chemotherapy-induced peripheral neuropathy (CIPN) and randomized them to either a placebo gel or a compounded mixture containing baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in a pluronic lecithin organogel (BAK-PLO) vehicle base.¹ Individuals applied the gel twice daily (BID) for 4 weeks. There was a trend towards improvement in the sensory neuropathy scale (primary endpoint) compared with placebo, though it was not statistically significant (P = 0.053). Statistically significant improvement was noted with the motor subscale (P = 0.021). Study 2 enrolled individuals (n = 92) with mixed neuropathic pain (i.e., diabetic neuropathy [n = 20/92], post herpetic neuralgia [n

= 14/92], post-surgical/post-traumatic neuropathic pain [n = 58/92] with allodynia, hyperalgesia, or pinprick hyperthesia) and evaluated the application of one of four topical creams: topical amitriptyline 2%, topical ketamine 1%, a combination of topical amitriptyline 2% and topical ketamine 1%, or placebo (vehicle base).² Individuals applied 4 mL cream to the site of maximum pain three times daily (TID) for 3 weeks. Pain levels at the end of the study compared with baseline were not statistically significant between treatment groups. Study 3 evaluated the efficacy of topical ketamine 5% cream applied TID for 4 weeks in individuals (n = 17) with diabetic neuropathy.³ Seven different pain characteristics (i.e., intensity, sharpness, cold, hot, dull, sensitive, and itchy) were measured using a pain scale both before and after treatment. Diabetic pain measures were reduced in both treatment groups and the placebo effect was equally as strong as ketamine 5% cream. Study 4 was a cross-over trial that assessed the efficacy of (S)-ketamine 1% ointment or placebo applied four times daily (QID) for 15 days in individuals (n = 12) with post herpetic neuralgia.⁴ There was a wash-out period of 7 days in-between crossover. A numerical verbal scale was used to assess pain scores and efficacy of therapy during three different clinic visits. There was no statistical significance in pain scores during treatments with (S)-ketamine 1% ointment or placebo.

One small randomized, double-blind, placebo-controlled study assessed the use of compounded topical ketamine in individuals (n = 20) with complex regional pain syndrome (CRPS).⁵ CRPS has been described as a challenging pain syndrome usually starting after a trauma or surgery.⁶ CRPS can be classified into two types: individuals with CRPS type 1 do not have demonstrable nerve lesions and type 2 is based on objective nerve damage, most commonly caused by severe trauma. CRPS type 1 has also been recognized as a chronic neuropathic pain syndrome that typically develops in an extremity after tissue trauma. The above mentioned study⁵ concluded that topical ketamine did not lead to pain reduction in individuals with CRPS, but it did reduce allodynia to brushing.

Topical Gabapentin

There are no published data available with the use of compounded topical gabapentin for neuropathic pain.

The only published trial available is a retrospective study assessing the use of topical gabapentin 2% to 6% cream in women (n = 51) with vulvodynia (chronic, unexplained vulvar pain or discomfort, characterized by burning, stinging, irritation or rawness).⁷ After a minimum of 8 weeks of therapy with application of gabapentin cream TID, about 80% of the individuals demonstrated at least a 50% improvement in their pain scores. The British Society for the Study of Vulval Diseases guidelines (2010) for the management of vulvodynia do not list topical gabapentin as a therapeutic choice (oral gabapentin is considered an option).⁸

Topical Hyaluronic Acid Sodium Salt

Hyaluronic acid is a naturally occurring polysaccharide that is widely distributed in various body tissues.⁹ Sodium hyaluronate and other derivatives are used for a variety of conditions, such as osteoarthritis (OA), and as surgical aid in ophthalmic procedures. It is available commercially as FDA-approved products in various dosage forms: as intra-articular injections (e.g., Synvisc®) for the treatment of knee OA; as ophthalmic solution for irrigation (e.g., Vitrac®); and as topical spray, cream, and gel products for use in wound care (e.g., Hylase® wound gel, Bionect® topical gel, cream, spray). There are also multiple hyaluronic acid products available as intradermal injectable gel for use as wrinkle fillers in cosmetic procedures (e.g., Juvederm® XC). Most of the hyaluronic acid products were approved as devices by the FDA.

There are limited published data available with the use of compounded topical hyaluronic acid as vaginal suppositories for the treatment of vaginal atrophy in postmenopausal women.¹⁰⁻¹⁴ If over-the-counter (OTC) vaginal moisturizers were ineffective as initial treatment, prescription vaginal estrogen therapy is the recommended first-line agent for the treatment of symptomatic vaginal atrophy.¹⁵

Topical Corticosteroids – Fluticasone Propionate, Mometasone Furoate

Fluticasone propionate and mometasone furoate are corticosteroids which are used intranasally for the treatment of allergic and non-allergic rhinitis, by oral inhalation for the treatment of asthma and/or chronic obstructive pulmonary disease (COPD), and as topical preparations for the treatment of inflammatory and pruritic types of dermatoses and psoriasis.⁹ These two corticosteroids are available as FDA-approved, commercial products in the following strengths and dosage form: fluticasone propionate 0.05% cream, lotion, and as 0.005% ointment; mometasone furoate 0.1% cream, lotion, and ointment.

There are no published clinical trial data available for the use of compounded topical formulations of fluticasone propionate or mometasone furoate either alone or in combination with other products for the treatment of skin conditions. One small open-label study (n = 23) evaluated the use of intranasal irrigation of fluticasone propionate in post-endoscopic sinus surgery individuals with chronic rhinosinusitis.¹⁶ The main intent of this study was to assess the effects of fluticasone on adrenal function (whether or not it was suppressed) and its effect on intraocular pressure (IOP). The irrigation solution was prepared by emptying a 3-mg capsule of fluticasone propionate (provided by a compounding pharmacy) into 240 mL isotonic saline solution (available OTC as Sinus Rinse™ saline rinse kit) and used twice daily for 6 weeks. There were no significant changes with fluticasone irrigation use in measured salivary cortisol levels or IOP after 6 weeks. No other efficacy data are noted in this study.

Topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

The other compounded topical drugs targeted in this policy – topical diclofenac, ketoprofen, flurbiprofen, meloxicam, and nabumetone – all belong to the NSAID drug class. These agents are generally used for the treatment of pain (e.g., OA, musculoskeletal pain). There are several topical NSAID formulations that are FDA-approved and commercially available. Topical diclofenac is commercially available as Solaraze® 3% gel, Voltaren® 1% gel, Pennsaid® 1.5% topical solution, Voltaren® 0.1% ophthalmic solution, and as Flector® 1.3% topical patch.¹⁷⁻²¹ Voltaren gel is indicated for the treatment of OA in knees and hands, and Pennsaid is indicated for the treatment of OA of the knees.¹⁸⁻¹⁹ Topical flurbiprofen is commercially available as Ocufer® 0.03% ophthalmic solution and it is indicated for the treatment of intraoperative miosis.²² The American College of Rheumatology (ACR) guidelines (2012) for hand, hip, and knee OA recommend topical NSAIDs for the treatment of hand and knee OA.²³ It is important to note that these guidelines are only referring to FDA-approved topical NSAIDs, as literature searches were limited to only commercially available NSAID formulations in the US and Canada.

References

1. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011;19:833-841.
2. Lynch ME, Clark AJ, Sawynok J, et al. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes. *Anesthesiology*. 2005;103:140-146.
3. Mahoney JM, Vardaxis V, Moore JL, et al. Topical ketamine cream in the treatment of painful diabetic neuropathy. A randomized, placebo-controlled, double-blind initial study. *J Am Podiatr Med Assoc*. 2012;102:178-183.
4. Moreira de Barros GA, Braz AM, Borges MA, et al. Topical (S)-ketamine for pain management of postherpetic neuralgia. Communication. *An Bras Dermatol*. 2012;87:504-506.
5. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain*. 2009;146:18-25.
6. Kopsky DJ, Keppel Hesselink JM. Multimodal stepped care approach involving topical analgesics for severe intractable neuropathic pain in CRPS type 1: A case report. *Case Rep Med*. 2011 [Published online October 17, 2011].
7. Boardman LA, Cooper AS, Blais LR, et al. Topical gabapentin in the treatment of localized and generalized vulvodynia. *Obstet Gynecol*. 2008;112:579-585.
8. Mandal D, Nunns D, Byrne M, et al. Guidelines for the management of vulvodynia. *Br J Dermatol*. 2010;162:1180-1185.
9. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2014. Available at <http://www.clinicalpharmacology-ip.com/Default.aspx>. Accessed on February 11, 2014. Search term: hyaluronic, fluticasone, mometasone.
10. Constantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. *Eur Rev Med Pharmacol Sci*. 2008;12:411-416.
11. Ziaghham S, Abbaspoor Z, Abbaspour M. Effect of hyaluronic acid and vitamin E vaginal tablets on atrophic vaginitis: a randomized controlled trial. *Afr J Pharm Pharmacol*. 2012;6:3124-3129.

12. Ekin M, Yasar L, Savan K, et al. The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Arch Gynecol Obstet*. 2011;283:539-543.
13. Stute P. Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief? *Arch Gynecol Obstet*. 2013;288:1199-1201.
14. Morali G, Polatti F, Metelitsa EN, et al. Open, non-controlled clinical studies to assess the efficacy and safety of a medical device in form of gel topically and intravaginally used in postmenopausal women with genital atrophy. *Arzneimittelforschung*. 2006;56:230-238.
15. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause*. 2013;20(9):888-902.
16. Man LX, Farhood Z, Luong A, et al. The effect of intranasal fluticasone propionate irrigations on salivary cortisol, intraocular pressure, and posterior subcapsular cataracts in postsurgical chronic rhinosinusitis patients. *Int Forum Allergy Rhinol*. 2013;3:953-957
17. Solaraze® 3% gel [prescribing information]. Melville, NY: PharmaDerm A division of Fougera Pharmaceuticals Inc.; December 2012.
18. Voltaren® 1% gel [prescribing information]. Chatts Ford, PA: Endo Pharmaceuticals Inc.; October 2009.
19. Pennsaid® 1.5% topical solution [prescribing information]. Hazelwood, MO: Mallincrodt Brand Pharmaceuticals; January 2010.
20. Flector® patch [prescribing information]. Bristol, TN: King Pharmaceuticals Inc.; December 2012.
21. Voltaren Ophthalmic® 0.1% solution [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc.; October 2012.
22. Ocufen® 0.03% ophthalmic solution [prescribing information]. Irvine, CA: Allergan, Inc.; July 2012.
23. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465-474.

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Annual revision	No criteria changes	05/13/2020
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