PRIOR AUTHORIZATION POLICY

POLICY: Compounded Select Topical Medications Prior Authorization Policy

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

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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 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 patients 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.

Clinical 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.[1-4] *Study 1* enrolled patients (n = 208) with chemotherapy-induced peripheral neuropathy 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 vehicle base.[1] Patients applied the gel twice daily 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 patients (n = 92) with mixed neuropathic pain (i.e., diabetic neuropathy [n = 20/92], postherpetic 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] Patients 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 significantly different between treatment groups. *Study 3* evaluated the efficacy of topical ketamine 5% cream applied TID for 4 weeks in patients (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 crossover trial that assessed the efficacy of (S)-ketamine 1% ointment or placebo applied four times daily for 15 days in patients (n = 12) with postherpetic neuralgia.[4] There was a washout 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 patients (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: patients 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 study[5] concluded that topical ketamine did not lead to pain reduction in patients with CRPS, but it did reduce allodynia

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 patients demonstrated at least a 50% improvement in their pain scores. The American College of Obstetricians and Gynecologist committee opinion (2016) [reaffirmed 2018] on persistent vulvar pain mention oral gabapentin as a therapy option, but do not mention compounded gabapentin.[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 aids in ophthalmic procedures. It is available commercially as FDA-approved products for intra-articular injections (e.g., Synvisc®) for the treatment of knee OA and for use as an ophthalmic surgical aid (e.g., Amvisc™). There are also multiple hyaluronic acid products available as intradermal injectable gel for use as wrinkle fillers in cosmetic procedures (e.g., Juvederm® XC). Over-the-counter (OTC) products can contain hyaluronic acid, including some artificial tear formulations and certain vaginal moisturizers.

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 and lotion, and 0.005% ointment; mometasone furoate 0.1% cream, lotion (topical solution), 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 patients with chronic rhinosinusitis following endoscopic sinus surgery.[11] 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 Nonsteroidal 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 diclofenac sodium 3% gel, Voltaren® Arthritis 1% gel (OTC), diclofenac 1.5% and 2% topical solution, diclofenac 0.1% ophthalmic solution, diclofenac epolamine 1.3 % topical patch (Flector®), and Licart® topical patch .[12-16,21] OTC Voltaren Arthritis gel is for the temporary relief of arthritis pain, and diclofenac topical solution is indicated for the treatment of OA of the knees.[13,14] Topical flurbiprofen is commercially available as a 0.03% ophthalmic solution and it is indicated for the treatment of intraoperative miosis.[17] The American College of Rheumatology (ACR) guidelines (2019) for hand, hip, and knee OA recommend topical NSAIDs for the treatment of hand and knee OA.[18] As there are multiple FDA-approved topical NSAIDs, the guidelines do not address compounded products.

POLICY STATEMENT

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).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of 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) is not recommended in the following situations:

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 patients with chemotherapy-induced peripheral neuropathy.[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 patients (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 patients. 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, and 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 Topical 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.** Multiple small studies have assessed the use of fluticasone and mometasone nasal irrigations.[11,19] Results are not definitive and larger studies are needed to analyze differences between nasal sprays vs. irrigation.[19]

Topical Hyaluronic Acid Derivatives

1. **Vaginal Atrophy.** Limited data are available with the use of compounded hyaluronic acid derivatives. According to the North American Menopause Society guidelines on genitourinary syndrome of menopause (2020), there is no evidence that products with hyaluronic acid have a greater benefit than nonhyaluronic acid lubricants or moisturizers.[10] Additionally, vaginal products containing hyaluronic acid are available without a prescription.

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., Euflexxa) 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 small studies showing some efficacy data surrounding the active hyaluronic acid ingredient[20], but there are no FDA-approved indications for topical hyaluronic use.

4. **Cosmetic Use (e.g., treatment of frown lines).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

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