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DATE NOTICE SENT TO ALL PARTIES: 02/15/16

IRO CASE #:

DESCRIPTION OF THE SERVICE OR SERVICES IN DISPUTE
The item in dispute is the prospective medical necessity of Phenytoin 5%, Misoprostol .003%, Allo 2 %, Metronidazole 2%, Levofloxacin 2%, and Prilocine 3%

A DESCRIPTION OF THE QUALIFICATIONS FOR EACH PHYSICIAN OR OTHER HEALTH CARE PROVIDER WHO REVIEWED THE DECISION
The reviewer is a Medical Doctor who is board certified in Orthopedic Surgery. The reviewer has been practicing for greater than 10 years.

REVIEW OUTCOME

Upon independent review the reviewer finds that the previous adverse determination/adverse determinations should be:

☒ Upheld (Agree)

☐ Overturned (Disagree)

☐ Partially Overturned (Agree in part/Disagree in part)

The reviewer agrees with the previous adverse determination regarding the prospective medical necessity of Phenytoin 5%, Misoprostol .003%, Allo 2 %, Metronidazole 2%, Levofloxacin 2%, and Prilocine 3%

PATIENT CLINICAL HISTORY [SUMMARY]:
The provider's patient sustained a crush injury. Documentation has included rigid foot and ankle contracture, calcaneal varus deformity and a painful gait associated with supination. Despite treatment with medications and immobilization; there has been an ongoing diagnosis of complex regional pain syndrome. The patient is also status post placement of a spinal cord stimulator. Clinical records reveal that on XX/XX/XX there were no particular complaints with a healing wound without issue. There was noted to be a history of intermittent paresthesias however.

ANALYSIS AND EXPLANATION OF THE DECISION INCLUDE CLINICAL BASIS, FINDINGS AND CONCLUSIONS USED TO SUPPORT THE DECISION.

There are limited large-scale, long-term references showing the safety and efficacy of the requested compound prescription. Extensive failure of first line medications was not evident. Not all of the medications are supported for topical utilization. There were no extenuating circumstances in this patient's clinical data to support otherwise. Therefore, this request is not medically reasonable or necessary, at this time.

Reference: ODG Treatment Index 11th Edition (Internet) 2013 Pain Chapter Topical Analgesics

Recommended as an option as indicated below. Largely experimental in use with few randomized controlled trials to determine efficacy or safety. Primarily recommended for neuropathic pain when trials of antidepressants and anticonvulsants have failed. These agents are applied locally to painful areas with advantages that include lack of systemic side effects, absence of drug interactions, and no need to titrate. Many agents are compounded as monotherapy or in combination for pain control (including NSAIDs, opioids, capsaicin, local anesthetics, antidepressants, glutamate receptor antagonists, α-adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists, γ agonists, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor). There is little to no research to support the use of many these agents. Any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of these compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required. Custom compounding and dispensing of combinations of medicines that have never been studied is not recommended, as there is no evidence to support their use and there is potential for harm. [Note: Topical analgesics work locally underneath the skin where they are applied. These do not include transdermal analgesics that are systemic agents entering the body through a transdermal means. For example, see Duragesic® (fentanyl transdermal system).]

Non-steroidal anti-inflammatory agents (NSAIDs): Recommended for the following indications:

Acute pain: Recommended for short-term use (one to two weeks), particularly for soft tissue injuries such as sprain/strains. According to a recent review, topical NSAIDs can provide good levels of pain relief for sprains, strains, and overuse injuries, with the advantage of limited risk of systemic adverse effects as compared to those produced by oral NSAIDs. They are considered particularly useful for individuals unable to tolerate oral administration, or for whom it is contraindicated. There appears to be little difference in analgesic efficacy between topical diclofenac, ibuprofen, ketoprofen and piroxicam, but indomethacin is less effective, and benzydamine is no better than placebo. The number needed to treat for clinical success, defined as 50% pain relief, for all topical NSAIDs combined vs. placebo was 4.5 (95% confidence interval [CI], 3.9 - 5.3) for treatment periods of 6 to 14 days. Current studies indicate 6 or 7 out of

10 patients have effective pain control with topical agents vs. 4 out of 10 with placebo. The reason for the high placebo rate is that most sprain/strain injuries improve on their own.
Osteoarthritis and tendinitis, in particular, that of the knee, elbow, and hand or other joints that are amenable to topical treatment: Recommended for short-term use (4-12 weeks). The American Academy of Orthopedic Surgeons recommends topical NSAIDs if there is increased GI risk with use of NSAIDs as one option for treatment. (Richmond, 2010) There are no studies evaluating topical ketoprofen for treatment of hand osteoarthritis. Topical ketoprofen gel has been compared to oral celecoxib, with WOMAC physical function scores significant for the later but not the topical treatment.
Osteoarthritis of the hip and shoulder: There is little evidence to utilize topical NSAIDs for treatment of osteoarthritis of the hip or shoulder.
Osteoarthritis of the low back: There is no evidence to recommend a NSAID dosage form other than an oral formulation for low back pain.
Widespread musculoskeletal pain: Not recommended.
Neuropathic pain: Not recommended as there is no evidence to support use.
General information: The theory behind using a topical NSAID is to achieve a therapeutic concentration in the tissue adjacent to the application, allowing for safe serum concentration. This would allow for less adverse GI events, eliminate first-pass metabolism and reduce risk of other GI events associated with higher systemic doses provided with oral formulations. Overall, a high concentration of drug is observed in the dermis and muscles (equivalent to that obtained orally), with less gastrointestinal effect. Plasma concentrations are 5% to 15% of those achieved systemically. Topically applied NSAIDs appear to reach the synovial fluid of joints, although the mechanism for delivery remains unclear. The efficacy in clinical trials for this treatment modality has been inconsistent and most studies are small and of short duration. Topical NSAIDs have been shown in meta-analysis to be superior to placebo during the first 2 weeks of treatment for osteoarthritis, but either not afterward, or with a diminishing effect over another 2-week period. When investigated specifically for osteoarthritis of the knee, topical NSAIDs have been shown to be superior to placebo for 4 to 12 weeks. The effect appeared to diminish over time and it was stated that further research is required to determine if results were similar for all preparations. These medications may be useful for chronic musculoskeletal pain, but there are no long-term studies of their effectiveness or safety. In terms of acute pain, topical NSAIDs were found to produce a 50% reduction in pain at one week, with the most significant results obtained with use of ketoprofen, while indomethacin was barely distinguished from placebo.
Pharmacokinetics and systemic availability: Absorption and penetration through the skin depends on the active medication, formulation (i.e. gel vs. solution), carrier-medicated transport, and penetration enhancement. Each of these differences produces differences in systemic levels attained. The carrier may also contribute to toxicity. Toxicity by dose has not been established (especially for trials that allowed for more than one joint to be treated). Excessive amounts of topical NSAID may produce higher than desired levels, hindering the advantage of a topical formulation.

Compounded formulations: There is little research available in terms of bioavailability and objective clinical endpoints for these agents.
FDA-approved agents: At this time, the only available FDA-approved topical NSAID is diclofenac.
Voltaren® Gel 1% (diclofenac): Indicated for relief of osteoarthritis pain in a joint that lends itself to topical treatment (ankle, elbow, foot, hand, knee, and wrist). It has not been evaluated for treatment of the spine, hip or shoulder. Maximum dose should not exceed 32 g per day (8 g per joint per day in the upper extremity and 16 g per joint per day in the lower extremity). The most common adverse reactions were dermatitis and pruritus. (Voltaren® package insert) Clinical trial data suggest that diclofenac sodium gel (the first topical NSAID approved in the US) provides clinically meaningful analgesia in OA patients with a low incidence of systemic adverse events. The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity. Voltaren Gel was effective in adults regardless of age. Treatment-related application site dermatitis was more common with Voltaren Gel, but gastrointestinal AEs were infrequent. It is recommended for osteoarthritis after failure of an oral NSAID, or contraindications to oral NSAIDs, or for patients who cannot swallow solid oral dosage forms. See also Voltaren® Gel separate listing, where it is not recommended as a first-line treatment.
Pennsaid® (diclofenac topical solution 1.5% containing 45.5% dimithyl sulfoxide): FDA-approved for osteoarthritis of the knee. A recent study on adverse effects of this agent compared to oral diclofenac found that the latter formulation had significantly higher events. Gastrointestinal AEs orally were 39% vs. 25.4% topically ($P< 0.0001$). Cardiovascular events were 3.5% orally vs. 1.5% topically ($P=0.055$). Liver function tests were increased more commonly in those taking oral agents. The most common adverse effect was application-site reaction. Dry skin is thought to result from the DSMO component. Long-term studies were recommended. (Roth, 2011) The dose is 40 drops to the knee four times a day. See also Pennsaid® (diclofenac sodium topical solution) separate listing, where it is not recommended as a first-line treatment.
Flector® Patch (diclofenac epolamine topical patch 1.3%): Indicated for acute strains, sprains, and contusions. Apply one patch twice daily to most painful area. See also Flector® patch (diclofenac epolamine) separate listing, where it is not recommended as a first-line treatment.
Non FDA-approved agents: Ketoprofen: This agent is not currently FDA approved for a topical application. It has an extremely high incidence of photocontact dermatitis and photosensitization reactions. Due to the high incidence of these reactions the French government removed this topical drug from the market in December 2009. This was subsequently overturned, with recommendations made to make the topical formulation available by prescription only, and by strengthening warnings as to adverse effects. Absorption of the drug depends on the base it is delivered in. Topical treatment can result in blood concentrations and systemic effect comparable to those from oral forms, and caution should be used for patients at risk, including those with renal failure.
Clinical trials: Numerous clinical trials are ongoing, including a phase III trial for a ketoprofen patch for treatment of soft tissue injury, acute sprain/strain, and non-

articular rheumatism, tendinitis and bursitis, a phase III trial for ketoprofen 10% cream for treatment of acute soft tissue injury, and a topical ketoprofen gel for muscle soreness. Clinical trials show similar results between Diclofenac gel and a ketoprofen patch formulation. See also Ketoprofen, topical separate listing, where it is not recommended in the U.S., as there are currently no FDA-approved versions of this product, but it is a first-line drug in Europe.
Piroxicam: There is no FDA-approved topical piroxicam agent. This drug also is known to produce drug-induced photosensitivity. Numerous adverse effects are noted with systemic delivery of piroxicam including elevated hepatic enzymes in 1-10% in patients who receive the drug.
Adverse effects of topical NSAIDs in general: Topical NSAIDs have a high safety margin with fewer severe gastrointestinal adverse effects. Adverse drug events occur on average in about 12% of individuals, with 75% of these including rash and/or pruritus at the application site. A recent systematic review of use of topical NSAIDs in older adults found the withdrawal rates from topical agents to be similar to that of oral NSAIDs. Gastrointestinal complaints and headaches were reported most frequently in both topical and oral NSAID groups. Anemia, liver function tests, renal abnormalities, and severe gastrointestinal events were higher in oral NSAID users. Examination of drug-related effects, including vehicles used and total dose is needed. (Makris, 2010) The use of oral NSAIDs concomitantly with topical agents is not recommended. (Peterson, 2011) See also NSAIDs, GI symptoms and cardiovascular risk; & NSAIDs, hypertension and renal function.
Cost effectiveness: Current FDA-approved topical agents are approximately six to ten times more expensive than oral over-the-counter preparations. Savings may occur due to lack of serious adverse GI effects, and the lack of necessity of taking an ulcer-protection medication.
Lidocaine: Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology. See Criteria for use below. Topical lidocaine, in the formulation of a dermal patch (Lidoderm®) has been designated for orphan status by the FDA for neuropathic pain. Lidoderm is also used off-label for diabetic neuropathy. No other commercially approved topical formulations of lidocaine (whether creams, lotions or gels) are indicated for neuropathic pain. Further research is needed to recommend this treatment for chronic neuropathic pain disorders other than post-herpetic neuralgia. Formulations that do not involve a dermal-patch system are generally indicated as local anesthetics and anti-pruritics. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of the use of topical lidocaine. Those at particular risk were individuals that applied large amounts of this substance over large areas, left the products on for long periods of time, or used the agent with occlusive dressings. Systemic exposure was highly variable among patients. Only FDA-approved products are currently recommended.
Indications: Recommended for localized pain that is consistent with a neuropathic etiology after there has been evidence of a trial of first-line therapy (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica). Topical lidocaine patches are generally not recommended for non-neuropathic

pain (including osteoarthritis or myofascial pain/trigger points). See Criteria for use below. Most studies have utilized the Neuropathic Pain Scale (NPS) as measure of neuropathy when there are questions of whether this is the cause of pain. There is limited information as to long-term efficacy and continued information as to outcomes should be provided to allow for on-going use. Discussion about specific details of these studies are given in detail with references. Second-line drugs such as capsaicin 8% patches had moderate to low effect sizes, but only low quality evidence was available for lidocaine patches and the NNT could not be calculated.
Trigger points & myofascial pain: Not recommended.
Osteoarthritis of the knee: Not generally recommended unless a component of neuropathy is indicated using measures such as the Neuropathic Pain Scale. All current available studies were sponsored by the manufacturer of lidocaine patches and are non-controlled, and of short-term in duration.
Axial back pain (including osteoarthritis): Not recommended unless neuropathy is suggested. Current studies as to use of Lidoderm patches for non-neuropathic low back pain are non-controlled, may or may not evaluate for the presence of neuropathic quality, have included multiple stages of pain (from acute to chronic), have included multiple diagnoses, show limited results in pain reduction, and are generally sponsored by the manufacturer. Acute groups have had better results than chronic pain patients, which may be attributed to natural recovery.
The FDA has approved a lidocaine/ tetracaine cream (Pliaglis®) for local analgesia. This is only indicated for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal
Criteria for use of Lidoderm patches:
(a) Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology.
(b) There should be evidence of a trial of first-line neuropathy medications (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica).
(c) This medication is not generally recommended for treatment of osteoarthritis or treatment of myofascial pain/trigger points.
(d) An attempt to determine a neuropathic component of pain should be made if the plan is to apply this medication to areas of pain that are generally secondary to non-neuropathic mechanisms (such as the knee or isolated axial low back pain). One recognized method of testing is the use of the Neuropathic Pain Scale.
(e) The area for treatment should be designated as well as number of planned patches and duration for use (number of hours per day).
(f) A Trial of patch treatment is recommended for a short-term period (no more than four weeks).
(g) It is generally recommended that no other medication changes be made during the trial period.
(h) Outcomes should be reported at the end of the trial including improvements in pain and function, and decrease in the use of other medications. If improvements cannot be determined, the medication should be discontinued.

(i) Continued outcomes should be intermittently measured and if improvement does not continue, lidocaine patches should be discontinued.
Capsaicin: Recommended only as an option in patients who have not responded or are intolerant to other treatments. Formulations: Capsaicin is generally available as a 0.025% formulation (as a treatment for osteoarthritis) and a 0.075% formulation (primarily studied for post-herpetic neuralgia, diabetic neuropathy and post-mastectomy pain). There have been no studies of a 0.0375% formulation of capsaicin and there is no current indication that this increase over a 0.025% formulation would provide any further efficacy.
Indications: There are positive randomized studies with capsaicin cream in patients with osteoarthritis, fibromyalgia, and chronic non-specific back pain, but it should be considered experimental in very high doses. Although topical capsaicin has moderate to poor efficacy, it may be particularly useful (alone or in conjunction with other modalities) in patients whose pain has not been controlled successfully with conventional therapy. The number needed to treat in musculoskeletal conditions was 8.1. The number needed to treat for neuropathic conditions was 5.7. Neither salicylates nor capsaicin have shown significant efficacy in the treatment of OA. See also Capsaicin.
Baclofen: Not recommended. There is currently one Phase III study of Baclofen-Amitriptyline-Ketamine gel in cancer patients for treatment of chemotherapy-induced peripheral neuropathy. There is no peer-reviewed literature to support the use of topical baclofen.
Other muscle relaxants: There is no evidence for use of any other muscle relaxant as a topical product.
Gabapentin: Not recommended. There is no peer-reviewed literature to support use.
Other antiepilepsy drugs: There is no evidence for use of any other antiepilepsy drug as a topical product.

A DESCRIPTION AND THE SOURCE OF THE SCREENING CRITERIA OR OTHER CLINICAL BASIS USED TO MAKE THE DECISION:

- ☐ ACOEM- AMERICAN COLLEGE OF OCCUPATIONAL & ENVIRONMENTAL MEDICINE UM KNOWLEDGEBASE
- ☐ AHCPR- AGENCY FOR HEALTHCARE RESEARCH & QUALITY GUIDELINES
- ☐ DWC- DIVISION OF WORKERS COMPENSATION POLICIES OR GUIDELINES
- ☐ EUROPEAN GUIDELINES FOR MANAGEMENT OF CHRONIC LOW BACK PAIN
- ☐ INTERQUAL CRITERIA
- ☒ MEDICAL JUDGEMENT, CLINICAL EXPERIENCE AND EXPERTISE IN ACCORDANCE WITH ACCEPTED MEDICAL STANDARDS
- ☐ MERCY CENTER CONSENSUS CONFERENCE GUIDELINES
- ☐ MILLIMAN CARE GUIDELINES
- ☒ ODG- OFFICIAL DISABILITY GUIDELINES & TREATMENT GUIDELINES
- ☐ PRESSLEY REED, THE MEDICAL DISABILITY ADVISOR
- ☐ TEXAS GUIDELINES FOR CHIROPRACTIC QUALITY ASSURANCE & PRACTICE PARAMETERS
- ☐ TEXAS TACADA GUIDELINES
- ☐ TMF SCREENING CRITERIA MANUAL
- ☐ PEER REVIEWED NATIONALLY ACCEPTED MEDICAL LITERATURE (PROVIDE A DESCRIPTION)
- ☐ OTHER EVIDENCE BASED, SCIENTIFICALLY VALID, OUTCOME FOCUSED GUIDELINES (PROVIDE A DESCRIPTION)