Topical Treatment of Neuropathic Pain

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ABSTRACT

Pikes Peak Hospice & Palliative Care, Inc., provides care for more than 200 patients with terminal disease who reside at home, in long-term care facilities, in assisted-living facilities, or in its acute-care Inpatient Unit. Over the past 4 years, its pharmacy has evolved to provide individualized compounded preparations to meet the unique and complex needs of these patients. An integral part of this evolution was development and implementation of topical treatments for pain. These patients often have multiple medical conditions and complicated health issues. Nearly 50% of patients in the care of Pikes Peak Hospice receive a topical compound to treat any of a variety of conditions, including neuropathies, muscle skeletal pain, wound pain, agitation, and anxiety. Topical compounds give practitioners another option in managing patient maladies and, in many instances, compounded topicals have proven as effective, if not more effective, than commercially available products. In some cases, patients have been able to stop oral pain medications or reduce their dose because the topical preparation is so effective. All in all, the topical preparations described in this article have been invaluable to our patients’ comfort and an indispensable option for practitioners.

FIGURE 1. Pathways for pain perception and response.

Sensory Cortex
Thalamus and Limbic System
Hypothalamus
Spinal Tracts
Dorsal-root Ganglion
C-fibers and Aδ-fibers
AE-fibers

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Vince Vadaurri, RPh, BCPS
Palliative Pharmacy of Pikes Peak
Colorado Springs, Colorado

www.IJPC.com

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**TOPICAL ROUTE OF ADMINISTRATION**

This section defines the difference between topical and transdermal delivery systems, discusses the characteristics of topical delivery systems and their advantages, and enumerates the reasons for using drug combinations and drugs with multiple mechanisms of action in the treatment of neuropathic pain.

By definition, topical delivery systems act locally, while transdermal delivery systems (e.g., fentanyl patches, clonidine patches, nicotine patches), though applied peripherally, act systemically. A topical dosage form offers the following advantages over transdermal and other systemic dosage forms in treating neuropathic pain:

- Decreased potential for drug interactions
- High concentrations of the drug at the site of injury
- Low systemic drug levels
- Minimal adverse effects
- No need to titrate dose to tolerability

The bioavailability of topical nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported to be generally less than 5% to 15%, while drug concentration at the site of administration can be 30-fold higher than with an oral dose. As the molecular processes of neuropathic pain are untraveled, targeting specific pain mechanisms becomes more feasible. Because different sensitizing signal molecules acting on different receptors all contribute to the pain, neither inhibiting a single sensitizing agent nor using one drug is likely to completely ameliorate sensitized neurons. A multi-drug approach or a drug with multiple mechanisms of activity is the most sensible treatment. With these principles establishing the framework for the treatment of neuropathic pain, the remaining sections furnish the substance.

**PATHOPHYSIOLOGY OF NEUROPATHIC PAIN**

Specialized sensory neuronal fibers known as nociceptors innervate peripheral tissue, responding to noxious stimuli and initiating physiological pain. Nociceptors are categorized as small-diameter unmyelinated C-fibers, small-diameter myelinated Aδ-fibers, and large-diameter myelinated Aβ-fibers. C-fibers are dominant in clinical pain. Intact nociceptors are the first stimulus activating Aδ-fibers, while high-intensity stimuli activate Aβ-fibers and C-fibers, resulting in pain. Nociceptive sensory nerves consist of a variety of ion channels and receptors that are modified upon stimulation. The three most recognized stimuli are temperature changes, mechanical stimuli, and chemicals. These stimuli interact with specific ion channels to activate the sensory neuron, while other stimuli activate protein kinase A. Protein kinase A phosphorylates sodium channels, causing reduction of the sensory neuron threshold; activated ion channels similarly reduce the sensory neuron threshold. Besides modulating ion channels and sodium channels, noxious stimuli produce an inflammatory response involving infiltration of macrophages, neutrophils, and lymphocytes into the damaged tissue; these cells, with resident cells, produce and release proinflammatory cytokines and endogenous opioids. Moreover, cytokines, damaged tissue cells, and surrounding cells upregulate the expression of cyclooxygenase-2 and nitric oxide synthetases. Cyclooxygenase-2 produces prostanooids and nitric oxide synthetase produces nitric oxide; nitric oxide promotes...
vasodilation that facilitates entrance of immune cells and other mediators into the injury site. In other words, inflammation causes nociceptors to become sensitized and easily activated; this may explain the occurrence of mechanical allodynia and thermal hyperalgesia following tissue injury.\(^9\)

Since inflammatory mediators serve an essential role in nociceptor sensitivity, mitigating the inflammatory response should reduce pain. One category of agents used to block the inflammatory process is NSAIDs. NSAIDs inhibit cyclooxygenase enzymes, thus blocking production of prostanoids (e.g., prostaglandin 2). Diclofenac, ketoprofen, indomethacin, and ibuprofen are some of the NSAIDs that have been used to treat peripheral pain. In 2007, the U.S. Food and Drug Administration (FDA) approved two topical diclofenac products, Flector patch and Voltaren gel. The patch was approved for the treatment of acute pain in minor strains, sprains, and contusions, and the gel’s approved indication was osteoarthritis pain in joints. Other topical NSAIDs are in various stages of seeking FDA approval, and, in the near future, additional topical NSAIDs will be available in the U.S.

As already mentioned, inflammation facilitates access of lymphocytes, monocytes, macrophages, and granulocytes to the damaged areas; these immune cells secrete endogenous opioids: enkephalins, dynorphins, and endorphins; endogenous opioids couple to opioid receptors on nociceptors; inflammation causes dorsal root ganglia to increase the synthesis and expression of opioid receptors (Figure 2).\(^{10,11}\) Three opioid receptors, mu (\(\mu\)), kappa (\(\kappa\)), and delta (\(\delta\)), mediate inhibition of pain throughout the nervous system. Identification of opioid receptors and elucidation of their function in the peripheral sensory neurons have been areas of particular interest recently.\(^{12}\) When endogenous or exogenous opioids bind to the opioid receptor on nociceptors, G-protein is activated and inhibits adenyl cyclase. Inhibiting adenyl cyclase decreases cAMP levels, and this in turn suppresses the activity of voltage-gated sodium channels (VGSCs), high-voltage calcium channels, and inflammatory sensitive nonselective cation currents. The primary effect, however, is modulation of high-voltage calcium channels. Thus, delivery of exogenous opioids to neuropathic sites could result in significant attenuation of nerve excitability and consequently a decrease in pain. Moreover, exogenous opioids can work synergistically with endogenous opioids to further suppress pain. Overall, opioids hyperpolarize nociceptors, truncate propagation of action potentials, and prevent release of proinflammatory neuropeptides from sensory nerve terminals. The cumulative results of these actions are analgesia and reduction of inflammation.\(^{13,14}\)

Oral opioids have been shown to be effective in treating peripheral neuropathic pain but are associated with substantial rates of systemic side effects, such as constipation, dizziness, confusion, mood changes, dry mouth, and somnolence.\(^{15,16}\) Several studies have shown

**FIGURE 2.** Opioid receptor synthesis and expression.

**FIGURE 3.** Gabapentin acts by antagonizing voltage-activated calcium channels and modulating activity of GABA.
that topical opioids offer a beneficial effect in treating cutaneous ulcers, with systemic drug concentrations either undetectable or no more than 20% of the subcutaneous dose.12-21 In one study, topical methadone was effective in treating wound pain.22 Besides the benefits of topical administration already mentioned, patients treated with topical opioids do not develop tolerance.23 The plasticity of neuropathic pain and the findings of published studies offer a rationale for using topical opioids to treat peripheral neuropathies.

Calcium channels are implicated in neuron sensitivity, and within the chronic nociceptor stimulus model, calcium ion influx contributes to the pathological neuronal plasticity found in peripheral neuropathy.24 Calcium assists in protein kinase activation, which phosphorylates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Phosphorylation of AMPA and NMDA receptors increases synaptic efficiency.25 Antiepileptics represent one class of agents that affect calcium channels. Antiepileptics display several modes of action for the treatment of neuropathic pain. Gabapentin is probably the most widely recognized for its efficacy in this application. Its exact mechanism in relieving such pain has not been fully elucidated, but it does antagonize voltage-activated calcium channels (α2δ subunit) and modulates activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.26,27 The exact contribution of modulating GABA activity is still being investigated, but antagonizing voltage-activated calcium channels reduces calcium influx into the cell, which prevents neuron sensitivity (Figure 3). Clinically, gabapentin’s antinociceptive action attenuates mechanical and thermal hypersensitivity in peripheral neuropathic pain.28

Besides inhibition through interference in calcium-mediated activation, NMDA receptors can be blocked directly. NMDA receptors are ligand-gated and voltage-dependent ion channels, requiring both an appropriate ligand and appropriate current for activation. The excitatory neurotransmitter glutamate is the most commonly recognized ligand for NMDA receptor activation.29 Nociceptor terminals release glutamate in response to noxious stimuli. If the stimulus exceeds the neuronal threshold, the neuron depolarizes. When the membrane depolarizes, glutamate and glycine bind to an NMDA receptor, the receptor is activated, the receptor facilitates sodium and calcium ion influx and potassium efflux, and the neuron further depolarizes (Figure 3). At the site of injury and during the nociceptive transfer of information, not only are NMDA receptors activated, but they also are upregulated, which further sensitization. Under physiological conditions, intercellular magnesium blocks NMDA receptor activity, but magnesium binds weakly when the membrane is depolarized and, thus, in pathological conditions, magnesium inhibits the receptor less. NMDA receptors represent a relatively new drug target for the treatment of neuropathic pain. Current research seeks to develop an NMDA antagonist that will act specifically to block the pain process and not cause undue side effects. Studies show that NMDA antagonists mitigate neuronal sensitization and long-term potentiation and may lead to long-term neuronal resetting or downregulation. In other words, NMDA antagonists may diminish pain and correct underlying pathological processes.

Available exogenous NMDA antagonists include methadone, dextromethorphan, ketamine, and memantine. Methadone provides...
a superior pharmacodynamic profile because it acts not only as an NMDA non-competitive antagonist but also as an opioid agonist.

Under physiological conditions, the sensitized and excited terminal ends of nociceptors results in generation of action potentials being transmitted via VGSCs along the sensory nerve axons. VGSCs are obligatory for the initiation and propagation of action potentials.2,5 This communication system transfers information from the sensory nerve terminal to the dorsal horn and from the dorsal horn to the spinal cord, then to the thalamus and ultimately to the cortex (see Figure 1).6,7 In neuropathic pain, however, VGSCs convey unwarranted signaling, usually spontaneous and unprovoked (Figure 2).8 Besides generating unwarranted action potentials, VGSCs have an exaggerated response to innocuous stimuli, allodynia and noxious stimuli, and hyperalgesia; accumulation of aberrant VGSCs at the site of injury may also account for neuronal hyperexcitability and instability.2,9,10 Therefore, anesthetics, which block VGSCs, mitigate unregulated action potentials, prevent activation of accumulated channels, and reduce pain. Topical anesthetics (i.e., tetracaine, lidocaine, carbamazepine, mexiteline) show unequivocal evidence of alleviating pain in damaged tissue.2,9,10 This approach has proven efficacious with lidocaine patches.10,11,12

In neuropathic pain, all these molecular mechanisms are irreglar, which results in long-term neural plasticity; neuronal change manifests following repeated activation of nociceptive pathways.2,13,14 The culmination of these changes makes the nociceptive system more sensitive to subsequent stimuli, producing the clinical syndromes of allodynia and hyperalgesia.2

PHARMACOLOGICAL TREATMENTS FOR NEUROPATHIC PAIN

Based on the molecular changes in neuropathic pain and specific drugs that can inhibit or alter these changes, the rationale for drug treatment becomes fairly linear. Either a combination of drugs with different mechanisms of action (e.g., methadone, tetracaine) should be used, or a single drug with multiple modes of actions (e.g., methadone).

The vehicle to use will depend on whether the skin is intact or compromised. For intact skin, a Pluronic lecinthin organogel (PLO) or other penetrating gel will work well. Penetration enhancers, such as ethanol or D-limonene, may be used to increase absorption. Caution should be exercised in applying these gels to the jawline or face, because application in these areas has shown to result in significant systemic absorption.

Surgical gels or Manuka honey work well as vehicles on compromised skin such as wounds. Manuka honey has the added benefit of being antipenumatic, mild debrider, and a good barrier.

Table 1 shows the most common combinations, strengths, and vehicles used. If desired, the strengths may be increased for some of the formulations, but higher concentrations are usually not needed to achieve a therapeutic result, and at higher concentrations working with and maintaining the stability of the vehicles become more difficult. As mentioned in the introduction, other combinations of medications have been and can be used; the combinations listed here have been clinically successful and their molecular targets indicate that they address multiple abnormal sites in the neuropathic pain process. The agents used most frequently to treat pain in patients of Pikes Peak Hospice & Palliative Care, Inc. are the following:

- Gabapentin: long recognized for its efficacy in neuropathic pain
- Ketoprofen: excellent skin penetration; effectiveness in topical pain relief documented in numerous studies
- Methadone: dual activity as opioid agonist and NMDA antagonist, thus addressing neuropathic abnormalities at two distinct sites
- Tetracaine: more favorable pharmacokinetic properties than lidocaine with less skin irritation

CASE REPORTS

Case 1

Patient LM, a 79-year-old white woman, was admitted to hospice with a diagnosis of pulmonary hypertension. On admission, one of the patient's primary problems was, "My right lower leg is my trouble spot." The practitioner recorded the pain as "severe, shooting pain across the anterior lower leg that is very bothersome." To control the pain, the patient had been treated with nortriptyline 25 mg at bedtime and hydrocodone/acetaminophen 5/300 mg as needed. The patient continued on oral medications but the pain remained; the practitioner added PLO gabapentin 5%, to be applied 2 mL twice daily to the patient's lower leg. The next day, the patient reported no pain in the right lower leg, and, upon assessment 2 weeks later, the patient reported that, following treatment with the PLO gabapentin, her leg pain had decreased from a level 8 of 10 to 2 to 3 of 10.

Case 2

Patient EH, a 54-year-old white woman, was admitted to hospice with a diagnosis of terminal colon cancer. As a result of chemotherapy, the patient developed bilateral peripheral neuropathies in the hands and feet, and at the time of admission the patient's hands and feet could not

| TABLE 1. Topical Pain Preparations Most Frequently Used to Treat Patients of Pikes Peak Hospice & Palliative Care, Inc. |
|--------|--------|----------------|
| Drugs       | Strength | Vehicle         |
| Methadone/Tetracaine | 0.1-1% / 5% | Honey, surgical gel, PLO |
| Methadone/Ketoprofen | 0.1-1% / 10% | PLO |
| Ketoprofen  | 10%   | PLO |
| Tetracaine  | 5%    | Honey, surgical gel, PLO |

PLO = Pluronic lecinthin organogel

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### Methadone/Tetracaine 0.5%/5% in Honey

**For 60 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone hydrochloride</td>
<td>0.3 g</td>
</tr>
<tr>
<td>Tetracaine hydrochloride</td>
<td>3 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>5 mL</td>
</tr>
<tr>
<td>Honey</td>
<td>qS</td>
</tr>
<tr>
<td>Total</td>
<td>60 mL</td>
</tr>
</tbody>
</table>

**Method of Preparation**
1. Weigh methadone and tetracaine hydrochloride.
2. Weigh out honey in beaker with stir bar.
3. Add methadone hydrochloride, tetracaine hydrochloride, and water to the beaker.
4. Heat mixture until methadone and tetracaine dissolve in the honey.
5. Pour into a 60-mL syringe.
6. Mix well.

**Stability**
This formula has a beyond-use date of 30 days. Store at room temperature.

### Methadone/Ketoprofen 0.1%/10% Pluronic Lecithin Organogel

**For 60 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>6 g</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.06 g</td>
</tr>
<tr>
<td>Ethanol 95%</td>
<td>5.5 mL</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate solution</td>
<td>13.2 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% solution</td>
<td>qS</td>
</tr>
<tr>
<td>Total</td>
<td>60 mL</td>
</tr>
</tbody>
</table>

**Method of Preparation**
1. Weigh ketoprofen and methadone.
2. Place the lecithin and isopropyl palmitate solution in a 60-mL luer-to-luer locked syringe.
3. Add the ketoprofen, methadone, and ethanol to the syringe.
4. Bring final volume to 60 mL with Pluronic F-127 20% solution.
5. Exchange contents between syringes 15 times.
6. Package and label.

**Stability**
This cream-colored formula has a beyond-use date of 30 days. Store at room temperature.

### Methadone/Tetracaine 0.5%/5% Pluronic Lecithin Organogel

**For 60 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone hydrochloride</td>
<td>0.3 g</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>3 g</td>
</tr>
<tr>
<td>Ethanol 95%</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate solution</td>
<td>13 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% solution</td>
<td>qS</td>
</tr>
<tr>
<td>Total</td>
<td>60 mL</td>
</tr>
</tbody>
</table>

**Method of Preparation**
1. Weigh methadone and tetracaine.
2. Place the lecithin and isopropyl palmitate solution in a 60-mL luer-to-luer locked syringe.
3. Add the methadone hydrochloride, tetracaine, and ethanol to the syringe.
4. Bring to a final volume of 60 mL with Pluronic F-127 20% solution.
5. Exchange contents between syringes 15 times.
6. Package and label.

**Stability**
This cream-colored formula has a beyond-use date of 30 days. Store at room temperature.

### Methadone 0.1% Pluronic Lecithin Organogel

**For 60 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone hydrochloride</td>
<td>0.06 g</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate solution</td>
<td>6.6 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% solution</td>
<td>qS</td>
</tr>
<tr>
<td>Total</td>
<td>60 mL</td>
</tr>
</tbody>
</table>

**Method of Preparation**
1. Weigh methadone.
2. Place the lecithin and isopropyl palmitate solution in a 60-mL luer-to-luer locked syringe.
3. Add the methadone to the syringe.
4. Bring final volume to 60 mL with Pluronic F-127 20% solution.
5. Exchange contents between syringes 15 times.
6. Package and label.

**Stability**
This formula has a beyond-use date of 30 days. Store at room temperature.
be touched without causing excruciating pain. To control the pain, the patient was
taking oxycodone/acetaminophen 7.5/50mg every 4 hours as needed, tramadol 1 tablet
every 4 hours, and transdermal fenta-
ny1 25 mg patch, applying 1 patch and
changing every 72 hours. The neuropathy
persisted despite oral and transdermal
opioid administration. Oral and transder-
mal medications were continued, and the
patient was started on PLO gabapentin
5% to be applied 1 mL to each hand and
foot twice daily. Three days later, the
patient reported that the pain was improved,
and the staff said they could touch and
move the patient’s hands and feet without
caus ing pain. Ten days after starting the
PLO gabapentin, the patient reported that
the pain level in her hands and feet had
decreased from an 8 to 9 of 10 to a 2 of 10.

Case 3

Patient RH, a 91-year-old woman, was
admitted to hospice with a diagnosis of
delirium. Cardiovascular disease, pulmonary
disease, and type 2 diabetes have contribut-
ed to her decline. The patient has bilateral
peripheral neuropathies in her legs due to
her diabetes. At admission, she was not on
any medication to treat the neuropathy.
The hospice practitioner prescribed PLO
methadone/tetracaine 0.5/5%, applied 2 to
3 mL to each leg twice daily. Several days
later, the patient reported her pain level
had declined from a 7 of 10 to a 0 of 10,
and that she routinely gets about 15 hours
of pain relief after application of the PLO.

Case 4

Patient VT, a 61-year-old woman, was
admitted to hospice with a diagnosis of
malignant breast cancer. The patient expe-
crienced tumor eruptions in 80% of her an-
terior chest and 40% of her right posterior
chest. Two of the tumors, one anterior and
one posterior, spontaneously erupted and
bled, and eventually scabbed. The patient
rated her pain level at a background of
7 of 10, and sometimes as severe as 10 of 10.
Treatment with Oxycontin 40 mg, 1 tablet
twice daily, improved the pain, but she
continued to experience episodic pain at a
level of 8 of 10 in her anterior and posterior
chest. To the patient’s regimen the practi-
citioner added methadone/tetracaine 0.5/5%
in Manuka honey, to be applied 4 to 5 mL
to open lesions every dressing change.

After the honey compound was applied, the
patient reported her pain level dropped to 0
of 10, and the pain relief lasted 24 hours.
The formulations used in treating these
patients’ pain are included in this article.

CONCLUSION

Pikes Peak Hospice & Palliative Care, Inc., cares for more than 200 patients with
terminal disease who reside at home, in
long-term care facilities, in assisted-living
facilities, or its acute-care Inpatient Unit.
Over the past 4 years, the hospice pharmacy
has evolved to provide individualized
compounded preparations to meet the unique
and complex needs of our patients.
An integral part of this evolution is the
development and implementation of topical
treatments for pain. As illustrated by
the case presentations, patients in hospice care
often have multiple medical conditions and
complicated health issues. Nearly 50% of
our patients receive a topical compound to
treat any of a number of conditions, includ-
ing neuropathies, muscle skeletal pain,
wound pain, agitation, and anxiety. Topical
compounds give practitioners another op-
ion in managing patient maladies and, in
many instances, compounded topicals have
proven as effective, if not more effective,
than commercially available products.
In some cases, patients have been able to stop
oral pain medications or reduce their dose
because the topical preparation is so effective.
All in all, the topical preparations de-
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cic peripheral and central neuropathic
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METHADONE/TETRACAPE 0.1%/5% IN SURGILUBE

For 60 mL

Methadone hydrochloride 0.06 g
Tetracaine hydrochloride 3 g
Purified water 5 mL
Surgilube qs 60 mL

METHOD OF PREPARATION

1. Weigh methadone hydrochloride and tetracaine hydrochloride.
2. Fill luer-to-luer lock 60-mL syringes half-full of Surgilube.
3. Add methadone hydrochloride and tetracaine hydrochloride to Surgilube, along with 5 mL of purified water.
4. Bring to volume of 60 mL with Surgilube.
5. Place piston into syringe and eliminate air.
6. Exchange contents between syringes 15 times.

STABILITY

This gel formula has a beyond-use date of 30 days. Store in refrigerator.

TETRACAPE 5% IN PLURONIC LECITHIN ORGANOGEL

For 60 mL

Tetracaine 3 g
Ethanol 95% 2.5 mL
Lechitin and isopropyl palmitate solution 6.6 mL
Pluronic F-127 20% solution qs 60 mL

METHOD OF PREPARATION

1. Weigh tetracaine.
2. Place the lechitin and isopropyl palmitate solution in a 60-mL luer-to-luer locked syringe.
3. Add the tetracaine and ethanol to the syringe.
4. Bring final volume to 60 mL with Pluronic F-127 20% solution.
5. Exchange contents between syringes 15 times.
6. Package and label.

STABILITY

This formula has a beyond-use date of 30 days. Store at room temperature.


Address correspondence to Vince Vidaurri, RPh, BCPS, Supervi- sor, Palliative Pharmacy of Pikes Peak, Colorado Springs, CO 80903. E-mail: pharmacy@pikespeakospice.org