Drug Monograph
Drug Name: Olinvyk™ (oliceridine) Injection
Drug Class: Opioid Analgesic, Intravenous
Prepared For: MO HealthNet
Prepared By: Conduent

☐ New Criteria  ☐ Revision of Existing Criteria

Executive Summary

Purpose:
The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.

Dosage Forms:
Olinvyk is available as a 1 mg/ml, 2 mg/2 ml, and 30 mg/30 ml sterile, preservative-free solution for injection.

Manufacturer:
Distributed by: Trevena, Inc., Chesterbrook, PA 19087.

Summary of Findings:
The efficacy of Olinvyk was studied as a comparison to morphine and placebo in the APOLLO-1 and APOLLO-2 studies with a total of 790 patients post bunionectomy and post abdominoplasty. The primary efficacy endpoints were measured using the Summed Pain Intensity Differences (SPID) over 48 and 24 hours, in the respective studies. No formal non-inferiority assessments were conducted between Olinvyk and morphine response rates. Morphine demonstrated a greater reduction in pain intensity than both Olinvyk treatment regimens in both trials. Product labeling states that the adverse event reactions reported from clinical trials are not an adequate basis for comparison of rates between Olinvyk and morphine treatment groups, because the Olinvyk and morphine dosing regimens studied in the trials are not considered equipotent.

Status Recommendation:
☐ Clinical Edit  ☒ Open Access  ☐ PA Required  ☐ PDL

Type of PA Criteria:
☐ Appropriate Indications  ☐ Non-Preferred
☒ No PA Required  ☐ Preferred
Purpose
The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction (1,2,3,4)
Annually, approximately 45 million hospital patients in the United States receive an intravenous opioid to treat acute pain. More than 80% of patients who undergo surgical procedures experience acute postoperative pain, and 75% of those report the severity of pain as moderate, severe or extreme. One of the most common methods for controlling postoperative pain is by using patient-controlled analgesia (PCA). Traditional PCA implies on-demand, intermittent, IV administration of opioids under patient control (with or without a continuous background infusion). Basic variables include: initial loading dose, demand dose, lockout interval, background infusion rate, and 1-hour and 4-hour limits. All of the common opioid have been used successfully for IV-PCA. Whichever opioid is chosen, knowledge of its pharmacology is prerequisite for setting the dosing variables of the PCA device. Pure μ opiate-receptor agonists are the mainstay of PCA therapy. The μ agonists are equally effective at equianalgesic doses and there are no differences in side-effect profile. Metabolites and routes of elimination differ markedly between the groups, which provides one rationale for choosing an opioid for IV-PCA.

Dosage Form (3)
Olinvyk is available as a 1 mg/ml, 2 mg/2 ml, and 30 mg/30 ml sterile solution for injection.

Manufacturer (3)
Distributed by: Trevena, Inc., Chesterbrook, PA 19087

Indication(s) (3)
Olinvyk is an opioid agonist indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.

Clinical Efficacy (3,4,5) (mechanism of action/pharmacology, comparative efficacy)
Olinvyk is a full opioid agonist and is relatively selective for the mu-opioid receptor and has selective activation of G-protein signaling. The precise mechanism of action is unknown, but the principal therapeutic action is analgesia.

Pharmacokinetics:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Mean steady-state $V_d$ ranges from 90 to 120 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP3A4 and CYP2D6)</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine: approximately 70%</td>
</tr>
<tr>
<td></td>
<td>Feces: remainder</td>
</tr>
<tr>
<td>Half-life</td>
<td>1.3-3 hours</td>
</tr>
</tbody>
</table>
Onset of Action 2-5 minutes
Morphine equivalent 1 mg Olinvyk=5 mg morphine

Clinical Trials Experience

<table>
<thead>
<tr>
<th>STUDY DESIGN (APOLLO-1 and APOLLO-2)</th>
<th>Randomized, double-blind, placebo and morphine controlled trial (APOLLO-1 n=389; APOLLO-2 n=401) NCT02815709 and NCT02820324</th>
</tr>
</thead>
</table>
| INCLUSION CRITERIA                   | • Has undergone primary, unilateral, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures  
• Experiences a pain intensity rating of moderate to severe acute pain |
| EXCLUSION CRITERIA                   | • BMI >35 kg/m2  
• Body weight <40 kg  
• Pregnant of breastfeeding  
• Sleep apnea  
• Chronic opioid therapy (>15 MME/day for >3 days/week and for >1 month within 1 year of surgery)  
• Use of any analgesic medication within 5 half-lives before surgery  
• Chronic NSAID therapy  
• Use of agents that could affect analgesic response that were not stably dosed for ≥30 days prior to surgery  
• Use of oral or parenteral corticosteroids within 3 months prior to surgery  
• QTcF >450 ms in males and >470 ms in females  
• Renal or hepatic impairment  
• Evidence of hemodynamic instability  
• Respiratory insufficiency  
• Surgical/anesthetic complications |
| TREATMENT REGIMEN                    | Patients were randomized to one of three regimens:  
• Olinvyk: Loading dose of 1.5 mg; demand doses 0.1, 0.35 ro 0.5 mg; supplemental doses were 0.75 mg  
• Morphine: Loading dose was 4 mg; demand dose was 1 mg; supplemental doses were 2 mg  
• Placebo: doses were volume-matched  
A lockout interval of 6 minutes was used for all PCA regimens.  
Patients may have received rescue pain medication (Defined in the protocols as etodolac 200 mg every 6 hours, as needed) if the patient requested rescue pain medication and reported an NRS score ≥4. |
| RESULTS                              | APOLLO-1: Primary endpoint was SPID-48.  
|                                       | ![Table](https://via.placeholder.com/150)  
|                                       | Placebo (n=79) | 85 | - | - |
|                                       | Olinvyk 0.35 mg regimen (n=79) | 138 | 47.5 | (19, 75) |
|                                       | Olinvyk 0.5 mg regimen (n=79) | 164 | 80 | (52, 108) |
Morphine regimen (n=76) | 193 | 105 | (77, 132)

*The analgesic effect was not significantly better in the Olinvyk 0.1 mg treatment group than in the placebo group, and therefore it in not included in the table.

Secondary outcomes: Predefined composite measure of respiratory safety burden (RSB), representing the cumulative duration of respiratory safety events, and the proportion of treatment responders versus morphine.

APOLLO-2: Primary endpoint was SPID-24.

<table>
<thead>
<tr>
<th></th>
<th>SPID-24 (Average)</th>
<th>Difference (Compared to placebo)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=81)</td>
<td>75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olinvyk 0.35 mg regimen (n=80)</td>
<td>90</td>
<td>14</td>
<td>(2, 26)</td>
</tr>
<tr>
<td>Olinvyk 0.5 mg regimen (n=80)</td>
<td>94</td>
<td>18</td>
<td>(5, 30)</td>
</tr>
<tr>
<td>Morphine regimen (n=83)</td>
<td>103</td>
<td>30</td>
<td>(17, 42)</td>
</tr>
</tbody>
</table>

Secondary outcomes: Predefined composite measure of RSB, representing the cumulative duration of respiratory safety events, and the proportion of treatment responders versus morphine.

SAFETY
Discussed in the Adverse Effects section below.

Abbreviations: ms=milliseconds; NSAID=Non-Steroidal Anti-inflammatory Drug; PCA=patient-controlled analgesia; SPID=Summed Pain Intensity Differences over 48 or 24 hours

Contraindications (3)
- Significant respiratory depression
- Acute of severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine (e.g. anaphylaxis)

Warnings and Precautions (3,4)
- As an opioid, Olinvyk exposes users to the risks of addiction, abuse, and misuse.
- Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended.
- Prolonged use of opioids during pregnancy can result in withdrawal in the neonate.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Olinvyk with benzodiazepines or other CNS depressants.
- Potential for QT prolongation with daily doses exceeding 27 mg.
- Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients.
- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Olinvyk may cause severe hypotension, including orthostatic hypotension and syncope

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in ambulatory patients.

- In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Olinvyk may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure.

- Olinvyk may increase the frequency of seizures in patient with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures.

- Do not abruptly discontinue Olinvyk in a patient physically dependent on opioids; gradually taper dosage.

- Olinvyk may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

- Patient-controlled analgesia (PCA) administration has resulted in adverse outcomes and episodes of respiratory depression.

### Adverse Effects (3,4)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>29-75</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9-43</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9-35</td>
</tr>
<tr>
<td>Headache</td>
<td>1-26</td>
</tr>
<tr>
<td>Constipation</td>
<td>10-17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1-17</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5-20</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0-19</td>
</tr>
<tr>
<td>Sedation</td>
<td>4-14</td>
</tr>
<tr>
<td>Back pain</td>
<td>4-13</td>
</tr>
</tbody>
</table>

### Drug Interactions (3)

- Moderate to strong inhibitors of CYP2D6 can increase the plasma concentration of Olinvyk.
- Moderate to strong inhibitors of CYP3A4 can increase the plasma concentration of Olinvyk.
- Strong and moderate CYP3A4 inhibitors and CYP2D6 inhibitors: compared to inhibition of either metabolic pathway, inhibition of both pathways can result in a greater increase of the plasma concentrations of Olinvyk.
- Inducers of CYP3A4 can decrease the plasma concentration of Olinvyk.
- Due to additive pharmacological effect, the concomitant use of benzodiazepines or other ANS depressants, including alcohol, increases the risk of hypotension, respiratory depression, profound sedation, coma, and death.
- Concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
- Concomitant use of mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of Olinvyk and/or precipitate withdrawal symptoms.
- Olinvyk may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increase degree of respiratory depression.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**Dosage and Administration**\(^{(3,4)}\)
OLINVYK can be administered by a healthcare provider with an initial dose of 1.5 mg. For PCA, the initial dose can be followed by access to patient demand doses with a 6-minute lockout. The recommended demand dose is 0.35 mg. A demand dose of 0.5 mg may be considered for some patients if the potential benefit outweighs the risks. Supplemental doses of 0.75 mg OLINVYK can be administered by healthcare providers, beginning 1 hour after the initial dose, and hourly thereafter as needed. Do not administer single doses greater than 3 mg. The cumulative total daily dose should not exceed 27 mg. The safety of OLINVYK beyond 48 hours of use was not evaluated in controlled clinical trials.

**Cost**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Cost**/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine</td>
<td>Olinvyk™®</td>
<td>Trevena, Inc.</td>
<td>1.5 mg initial dose; 0.35 mg demand dose with 6 minute lockout.</td>
<td>$3.67 to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$17.50/ml</td>
</tr>
<tr>
<td>Morphine</td>
<td>Astramorph™, Duramorph, Infumorph, Mitigo™</td>
<td>Various</td>
<td>1 mg demand dose with 5-10 minute lockout</td>
<td>$0.64/ml</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Dilaudid®</td>
<td>Various</td>
<td>0.2 mg demand dose with 5-10 minute lockout</td>
<td>$5.43/ml</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Sublimaze®</td>
<td>Various</td>
<td>10 mcg demand dose with 5-8 minute lockout</td>
<td>$0.98/ml</td>
</tr>
</tbody>
</table>

** Wholesale Acquisition Cost

**Conclusion**
Opioids are a mainstay in the management of acute pain. Patient-controlled analgesia is a long-used mode of administration that utilizes multiple basic variables: initial loading dose, demand dose, lockout interval, background infusion rate, and 1-hour and 4-hour limits. These settings allow for the tailored approach to deliver adequate pain relief to individual patients. Trials of Olinvyk provide little clinically relevant data due to the lack of statistical analysis and poorly designed studies. In the APOLO-1 and -2 studies morphine demonstrated a greater reduction in pain intensity than both Olinvyk treatment regimens in both trials, but no formal non-inferiority assessments were made. An attempt to provide additional “real world” safety information from another study fell short due to the open-label design and lack of a control group (ATHENA). Although Olinvyk is the first novel chemical entity in the IV opioid agonist class in decades, it is not likely to be a strong competitor to the other cheaper and more proven agents such as
morphine, fentanyl, and hydromorphone for post-operative pain. Based on this information, utilization should be limited to only those cases which meet stringent prior authorization criteria.

**Recommendation**

MO HealthNet Division recommends Open Access status for this product.

**References**


Prepared by: April Ash, PharmD

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