NEW DRUG APPROVAL

Brand Name	Olinvyk®
Generic Name	oliceridine
Drug Manufacturer	Trevena, Inc.

New Drug Approval

FDA Approval Date: August 10, 2020

Review Designation: Standard

Type of Review: Type 1 - New Molecular Entity (NDA: 210730)

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acute pain is a type of pain that may last for just a few days or as long as six months. It is often related to an illness, injury, or medical procedure. Acute pain may be mild, moderate, or severe. It usually goes away once your injury has healed or you are no longer ill.

Acute pain is a complex process involving activation of nociceptors, chemical mediators, and inflammation. Medications can be used to target each of the key elements within the pain pathway and eliminate or reduce the sensation of pain. Pain management begins, when possible, prior to the tissue trauma and continues throughout the perioperative period. When acute pain is appropriately managed, patient's clinical outcomes and satisfaction are improved.

Each year, approximately 45 million hospital patients in the United States receive an IV opioid to treat their acute pain. Many of these patients are complex and difficult to treat, such as the elderly, obese, or renally-impaired. Current hospital trends suggest that the number of these complex patients is growing, representing an increasing burden on the healthcare system.

As per the analyst, of the population undergoing surgery in the US, nearly 80% experience acute postoperative pain, thereby contributing 41,766,061 patients to the Acute Pain population in 2017. Furthermore, among the patients with trauma injury in the US, 34,068,366 patients were contributed to the Acute Pain patient population.

Efficacy

Olinvyk® was studied in two Phase 3, randomized, double-blind, placebo and morphine-controlled trials in patients with moderate to severe pain following bunionectomy (APOLLO-1) [9] and abdominoplasty (APOLLO-2) [10]. In each of the studies, pain was measured using a patient-reported numeric scale (NRS). This is an 11-point scale ranging from 0–10, with zero representing no pain and 10 representing the worst pain imaginable.

Treatment began after discontinuation of general anesthesia in patients with an NRS > 4 within 9 hours after discontinuation of regional anesthesia in APOLLO-1, and an NRS >5 within 4 hours after end of surgery in APOLLO-2. Patients were randomized to one of three: Olinvyk® treatment regimens, a placebo control regimen, or a morphine-control regimen. Each treatment regimen consisted of a loading dose, incremental doses delivered as needed via PCA device, and supplemental doses, beginning 1 hour after the initial dose, and hourly thereafter, as needed.

The analgesic effects were measured using the Summed Pain Intensity Differences (SPID) over 48 and 24 hours in APOLLO-1 and APOLLO-2, respectively. The SPID was calculated by multiplying the pain intensity difference scores

at each timepoint (subtracting the pain intensity at a particular timepoint from the pain intensity at baseline) by the duration (in hours) since the preceding timepoint, then summing the values over the entire length of the study.

A summary of the two studies is provided in Table 1.

Table 1. APOLLO-1 (NCT02815709) and APOLLO-2 (NCT02820324) Study Summary

	APOLLO-1 (N = 389)	APOLLO-2 (N = 401)

Study Population	• Moderate to severe acute pain following bunionectomy
	• Mean age: 45 years
	• 85% female
	• Mean baseline pain intensity score: 6.7
	• Use of etodolac rescue:
	  ○ Olinvyk 0.1 mg: 41%
	  ○ Olinvyk 0.35 mg: 20%
	  ○ Olinvyk 0.5mg: 17%
	  ○ Placebo: 77%
		• Moderate to severe acute pain following abdominoplasty
		• Mean age: 41 years
		• 99% female
		• Mean baseline pain intensity score: 7.3
		• Use of etodolac rescue:
		  ○ Olinvyk 0.1 mg: 31%
		  ○ Olinvyk 0.35 mg: 21%
		  ○ Olinvyk 0.5 mg: 18%
		  ○ Placebo: 49%

Key Exclusion Criteria	BMI >35 kg/m^2, body weight <40 kg, pregnant or breastfeeding women, sleep apnea, chronic opioid therapy (defined as >15 morphine equivalent units/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 or respiratory insufficiency, or surgical/anesthetic complications.	
Interventions	• In each study, patients were randomized to one of three Olinvyk treatment regimens, a placebo-control regimen, or a morphine-control regimen. • **Olinvyk treatment regimen**: Loading dose was 1.5 mg; PCA demand doses 0.1, 0.35, or 0.5 mg; supplemental doses were 0.75 mg. • **Morphine treatment regimen**: Loading dose was 4 mg; PCA demand dose was 1 mg; supplemental doses were 2 mg. • The placebo-control regimen was volume-matched. • A lockout interval of 6 minutes was used for all PCA regimens. • Patients may have received rescue pain medication (pre-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.	
Endpoints	• SPID-48 • 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.	• SPID-24 • Secondary outcomes: Predefined composite measure of RSB, representing the cumulative duration of respiratory safety events, and the proportion of treatment responders versus morphine.

ms = milliseconds; NSAID = non-steroidal anti-inflammatory drug; PCA = patient-controlled analgesia; SPID = Summed Pain Intensity Differences over 48 or 24 hours

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The efficacy results for both trials are included in Table 2. 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. The analgesic effect was not significantly better in the Olinvyk® 0.1 mg treatment group than in the placebo group, and therefore, it is not included in the table.

Table 2. APOLLO-1 and APOLLO-2 Efficacy Results

APOLLO-1			
	SPID-48 (Average)	**Difference (Compared to Placebo)**	**95% Confidence Interval**
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)
APOLLO-2			
	SPID-24 (Average)	**Difference (Compared to Placebo)**	**95% Confidence Interval**
Placebo (n = 81)	75	-	
Olinvyk 0.35 mg regimen (n = 80)	90	14	(2, 26)
Olinvyk 0.5 mg regimen (n = 80)	94	18	(5, 30)
Morphine regimen (n = 83)	103	30	(17, 42)
SPID = Summed Pain Intensity Difference over 48 or 24 hours			

Safety

ADVERSE EVENTS

The safety profile of Olinvyk® is similar to other opioids. The most common (incidence ≥10%) adverse reactions in controlled clinical trials (Studies 1 and 2) were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.

WARNINGS & PRECAUTIONS

Potential for QT Prolongation with Daily Doses Exceeding 27 mg: May increase risk for QT interval prolongation. Do not exceed a cumulative daily dose of 27 mg.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Monitor closely, particularly during initiation and titration.

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement corticosteroids and wean the patient off the opioid.

Severe Hypotension: Monitor patients during initiation or titration. Avoid use of Olinvyk® in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for signs of sedation and respiratory depression. Avoid the use of Olinvyk® in patients with impaired consciousness or coma.

Addiction, Abuse, and Misuse: Olinvyk® contains oliceridine, a Schedule II controlled substance. As an opioid, Olinvyk® exposes users to the risks of addiction, abuse, and misuse. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Olinvyk®, and monitor all patients receiving Olinvyk® for the development of these behaviors or conditions.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of opioids during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants: Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Olinvyk® with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, or alcohol). Advise both patients and caregivers about the risks of respiratory depression and sedation when Olinvyk® is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs).

Risks of Use in Patients with Gastrointestinal Conditions: Olinvyk® may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders: Olinvyk® may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Olinvyk® therapy.

Withdrawal: Do not abruptly discontinue Olinvyk® in a patient physically dependent on opioids. When discontinuing Olinvyk® in a physically-dependent patient, gradually taper the dosage. Rapid tapering of oliceridine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.

Risks of Driving and Operating Machinery: Olinvyk® may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Olinvyk® and know how they will react to the medication.

Patient-Controlled Analgesia (PCA): Although self-administration of opioids by PCA may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

CONTRAINDICATIONS

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine

Clinical Pharmacology

MECHANISMS OF ACTION

Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The principal therapeutic action of oliceridine is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oliceridine.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Dose & Administration

ADULTS

IV - Intermittent bolus dosing:

- Initial: 1.5 mg per dose, healthcare providers can give supplemental dose of 0.75 mg beginning 1 hour after the initial dose, and hourly thereafter as needed.
- Maximum: 3 mg per dose IV; 27 mg per day IV.

PCA:

- Initial dose (administered by health care provider): 1.5 mg.
- Demand dose: Range: 0.35 to 0.5 mg.
- Lockout interval: 6 minutes.
- Supplemental dose (administered by health care provider): 0.75 mg; may be administered beginning 1 hour after the initial dose and repeated hourly as needed; may be used in addition to the demand dose if needed for adequate analgesia.

Maximum total cumulative daily dose: 27 mg.

PEDIATRICS

The safety and effectiveness of Olinvyk® in pediatric patients has not been established.

GERIATRICS

Refer to adult dosing. Use with caution; may require reduced dosage; titrate slowly.

RENAL IMPAIRMENT

No dosage adjustment necessary.

HEPATIC IMPAIRMENT

Mild to moderate impairment: No dosage adjustment necessary; may require less frequent dosing.

Severe impairment: There are no specific dosage adjustments provided in the manufacturer's labeling; use with caution; an initial dosage reduction is recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 1 mg/mL and 2 mg/2 mL (1 mg/mL) in single-dose vials
- 30 mg/30 mL (1 mg/mL) in single-patient-use vial, for PCA use only