Zohydro ER (hydrocodone bitartrate)

STRENGTH	DOSAGE FORM	ROUTE	GPID
10, 15, 20, 30, 40, 50	Extended Release Capsules	ORAL	35365, 35504, 35505, 35506, 35507, 35525

MANUFACTURER

Zogenix

INDICATION

For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Limitations of Use:
• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Zohydro ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
• Zohydro ER is not indicated for use as an as-needed (prn) analgesic.

DRUG CLASS

PAIN MANAGEMENT – ANALGESICS; ANALGESICS, NARCOTICS

PLACE IN THERAPY

Zohydro ER is a new extended-release formulation of hydrocodone which joins many oral long-acting opioids currently available on the market, such as:

- MS Contin (morphine sulfate controlled-release tablets)
- Kadian and Avinza (morphine sulfate extended-release capsules)
- OxyContin (oxycodone hydrochloride controlled-release tablets)
- Opana ER (oxymorphone hydrochloride extended-release tablets)
- Exalgo (hydromorphone hydrochloride extended-release tablets)
- Dolophine (methadone hydrochloride tablets)
- Nucynta ER (tapentadol extended-release oral tablets)

Kadian, Avinza, MS Contin, Opana ER, Dolophine are available as a generic. Long-acting opioids are only indicated for chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Long-acting opioids should not be used as-needed (prn) analgesic or for breakthrough pain.

In terms of relative potency, morphine and hydrocodone are less potent than oxycodone. Oxycodone is less potent than oxymorphone and hydromorphone. Additionally, there are differences in how these agents are tolerated. A patient who experiences an adverse reaction to a natural phenanthrene (i.e.

morphine) may not exhibit the same reaction to a semisynthetic phenanthrene (hydrocodone, hydromorphone, oxymorphone, or oxycodone).

Methadone hydrochloride is a synthetic narcotic analgesic that differs from morphine in terms of pharmacokinetics and adverse reactions (i.e. QT prolongation, etc). Methadone prescribing is often limited to those who are specialists in pain management. Tapentadol (Nucynta) is a novel analgesic acts as a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor.

EFFICACY

The efficacy of Zohydro ER was examined in a clinical trial that consisted of a conversion/titration phase and a double-blind treatment phase. A total of 510 subjects currently on chronic opioid therapy entered an open-label conversion and titration phase (up to 6 weeks) with Zohydro ER dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. For inadequately controlled pain, Zohydro ER was increased by 10 mg per 12-hour dose, once every 3–7 days until a stabilized dose was identified, or a maximum dosage of 100 mg every 12 hours.

There were 302 subjects (59%) randomized at a ratio of 1:1 into a 12-week double-blind treatment phase with their fixed stabilized dose of Zohydro ER (taken as 20–100 mg, every 12 hours) or a matching placebo. Subjects randomized to placebo were given a blinded taper of Zohydro ER according to a pre-specified tapering schedule. During the treatment phase, subjects were allowed to use rescue medication (hydrocodone 5 mg/500 mg acetaminophen) up to 2 doses (2 tablets) per day. There were 124 treated subjects (82%) that completed the 12-week treatment with Zohydro ER and 59 subjects (39%) with placebo.

Treatment with Zohydro ER produced a greater number of responders, defined as subjects with at least a 30% improvement, as compared to placebo (67.5% vs. 31.1%). Subjects who did not complete the study were classified as non-responders.

SAFETY

Boxed warnings for Zohydro ER include risk of addiction, abuse and misuse which can lead to overdose and/or death; life-threatening or fatal respiratory depression; accidental consumption in children or others may result in a fatal overdose; use during pregnancy may result in life-threatening neonatal opioid withdrawal syndrome; and alcohol use with Zohydro ER may result in fatal plasma hydrocodone levels. Other warnings include increased risk of adverse effects for certain populations (elderly, cachectic, debilitated patients, and those with gastric obstruction, chronic pulmonary disease, head injury, or increased intracranial pressure). Concomitant use of CYP3A4 inhibitors may increase hydrocodone serum levels and risk of adverse effects. Other drug interactions include CNS depressants, mixed opiate agonists/antagonists, MAO inhibitors and tricyclic antidepressants.

Similar to other long-acting opiates, Zohydro ER is contraindicated in patients with significant respiratory depression, patients with acute or severe bronchial asthma or hypercarbia, and patients with or suspected of having paralytic ileus.

The most common adverse reactions reported in those taking Zohydro ER (versus placebo) include:constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor.

Zohydro ER is pregnancy category C.

DOSAGE

Capsules must be swallowed whole and are not to be chewed, crushed or dissolved.

For opioid-naïve and opioid non-tolerant patients, start with 10 mg orally every 12 hours. Increase Zohydro ER dosage in increments of 10 mg every 12 hours every 3 to 7 days as needed to achieve adequate analgesia.

For opioid tolerant patients (conversion from other oral opioids to Zohydro ER):
(*Opioid tolerance is defined as those who receive at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for one week or longer)*

Discontinue all other around-the-clock opioid drugs when Zohydro ER therapy is initiated.

- To calculate the estimated daily Zohydro ER dose using Table 1, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral hydrocodone daily dose. For patients using more than one opioid, calculate the approximate equivalent hydrocodone dose for each opioid and sum the totals to obtain approximate total hydrocodone daily dose. The calculated Zohydro ER daily dose should then be divided in half for administration every 12 hours.
- Always round down to the nearest dose. The dose of Zohydro ER can be gradually titrated by increments of 10 mg every 12 hours every 3 to 7 days, until adequate pain relief and acceptable adverse reactions have been achieved. Use low doses for patients with renal or severe hepatic impairment and monitor closely for adverse reactions (i.e. respiratory depression).

Table 1.
Conversion Factors to Zohydro ER (not equianalgesic doses)

Prior Oral Opioid	Oral Dose (mg)	Approximate Oral Conversion Factor
Hydrocodone	10	1
Oxycodone	10	1
Methadone†	10	1
Oxymorphone	5	2
Hydromorphone	3.75	2.67
Morphine	15	0.67
Codeine	100	0.10

The conversion ratios in this table are only to be used for the conversion from current opioid therapy to Zohydro ER.

†It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

COST

Drug	Cost/unit	Cost per 30 Days (sample regimen)*
Zohydro ER (hydrocodone bitartrate extended-release capsules): 10, 15, 20, 30, 40, 50mg	AWP=$7.02 (10mg) AWP=$7.50 (15mg) AWP=$7.74 (20mg) AWP=$7.98 (30mg) AWP=$8.22 (40mg) AWP=$8.58 (50mg)	$421-515
MS Contin (morphine sulfate controlled-release tablets): 15, 30, 60, 100, 200mg	MAC=$0.65 to $4.99	$39 to $450 (15mg BID; 200mg TID)
Kadian (morphine sulfate extended-release capsules): 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200mg	AWP=$6.10 to $49.46	$183 to $2968 (10mg daily; 200mg BID)
Avinza (morphine sulfate extended-release capsules): 30, 45, 60, 75, 90, 120mg	AWP= $6.36 to $21.93	$191 to $658 (30mg per day; Max dose 1,600 mg/day)
OxyContin (oxycodone hydrochloride controlled-release tablets): 10, 15, 20, 30, 40, 60, 80mg	AWP=$2.81 to $17.48	$169 to $1049 (10mg BID; 80mg BID)
Opana ER (oxymorphone hydrochloride extended-release tablets): 5, 7.5, 10, 15, 20, 30, 40mg	MAC=$1.69 to $9.49	$101 to $569 (5mg BID; 40mg BID)
Exalgo (hydromorphone hydrochloride extended-release tablets): 8, 12, 16, 32mg	AWP=$13.58 to $54.33	$407 to $1630 (8mg daily; 32 mg daily)
Nucynta ER (tapentadol extended-release oral tablets): 50, 100, 150, 200, 250mg	AWP=$3.23 to $9.78	$194 to $587 (50mg BID; Max dose 250mg BID)
Dolophine (methadone hydrochloride tablets): 5, 10mg	MAC=$0.08 (5mg) MAC=$0.13 (10mg)	$2.40 to $12 (2.5mg BID; Max dose at initiation= 10mg TID)

* With the exception of Avinza & Nucynta, there is often no well-established maximum dose for opioid narcotics. Unless max dose is specified, the price is based on lowest/highest formulation strength and frequency. Cost per 30 days may be higher for patients converting from very high doses of another opioid analgesic.

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Zohydro ER to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Zohydro ER [Prescribing Information]. San Diego, CA: Zogenix; October 2013.
- Drug Facts and Comparisons. [Online Database] St. Louis, MO : Wolters Kluwer Health, Inc, 2014.
- Zichterman, Anne. Opioid Pharmacology and Considerations in Pain Management. Available at: http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/105473/ Accessed on February 11, 2014.