The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

**FDA Approval Information**

**Description / Mechanism of Action**

Oxycodone HCl/Acetaminophen extended-release (OXY/APAP XR) is a combination oxycodone (OXY) and acetaminophen (APAP) analgesic in a bilayer formulation containing both immediate-release (IR) and extended-release (XR) components.

Each tablet of OXY/APAP XR consists of 7.5mg of OXY and 325mg of APAP. When taken as a single dose of two tablets, the IR layer delivers approximately 3.75/325mg of OXY/APAP, followed by the release of approximately 11.25/325 mg of OXY/APAP over the remainder of the dosing interval.

The XR component of OXY/APAP XR contains a proprietary formulation (AcuForm™ by Depomed) primarily consisting of high molecular weight polyethylene oxide (PEO) designed to promote gastric retention and extend the duration of drug release.

Oxycodone HCl is a pure opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia.

Acetaminophen is a non-opiate, non-salicylate analgesic, and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined.

**Indication(s) Under Review in this Document**

FDA-approved Indication(s): Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use: Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, OXY/APAP XR should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) have been ineffective, not tolerated, or otherwise inadequate. OXY/APAP XR is not indicated for as-needed (prn) analgesia.

**Dosing and Administration**

Refer to the Prescribing Information for complete and up-to-date dosing and administration information.

OXY/APAP XR is not interchangeable with other combination oxycodone and acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration. The dosing regimen should be initiated for each patient individually, taking into account the patient's prior analgesic treatment experience, hepatic, and renal function, and risk factors for addiction, abuse, and misuse (see Special Populations). Total daily dose of acetaminophen from all drug products should be ≤ 4000mg.

The recommended dosage of OXY/APAP XR is 2 tablets every 12 hours. The second dose of 2 tablets may be administered as early as 8 hours after the initial dose to maintain analgesia; subsequent doses should then be administered as 2 tablets every 12 hours.

OXY/APAP XR tablets should be swallowed whole without breaking, chewing, crushing, cutting dissolving, or splitting; these actions can result in uncontrolled delivery of oxycodone and possibly lead to overdose or death. Tablets should be taken with adequate water to ensure complete swallowing immediately after placing in mouth. OXY/APAP XR can be administered with or without food.

Patients who may be physically dependent on OXY/APAP XR and no longer require therapy should have a gradual downward titration of the dose of 50% every 2 to 4 days to prevent signs and symptoms of withdrawal.

**Dosage Form(s) Under Review**

Extended-release tablets each containing oxycodone hydrochloride 7.5mg and acetaminophen 325mg
**REMS**  □ REMS  ☑ No REMS

*See Other Considerations for additional REMS Information.*

**Pregnancy Rating**  Category C

*See Special Populations for additional information*

### Executive Summary

| Efficacy | • A twice-daily extended-release formulation of oxycodone HCl/acetaminophen (OXY/APAP XR) was shown to provide effective analgesia over 48 hours in a randomized, double-blind, placebo-controlled study of patients with acute pain following bunionectomy (a model for efficacy in acute pain).
  • No active comparator studies were found. |

| Safety | • OXY/APAP XR has extended-release characteristics but, unlike other extended-release CII drugs, there is no REMS requirement.
  • Choking, obstruction of the airway, and GI obstruction are potential risks associated with OXY/APAP XR due to its polyethylene oxide content which causes the tablet to swell and become sticky when wet.
  • Safety data beyond 42 days is lacking.
  • Boxed Warnings are similar to other CII ER opioid analgesics. |

| Other Considerations | • When the subjective effects of OXY/APAP XR were compared in controlled fashion to those of IR combinations containing the same amounts of OXY and APAP, the XR product resulted in significantly less drug liking, drug high, and ‘good’ drug effects. For most subjective measures, crushed high dose XR tablets produced significantly lesser effects than crushed high dose IR tablets and crushed high dose XR tablets produced similar peak positive subjective effects compared to intact high dose XR tablets. |

| Potential Impact | • Projected Place in Therapy: OXY/APAP is the first extended-release opioid product to carry an acute pain indication; it can be considered for initial opioid treatment of acute pain where non-opioids have proven inadequate. Its every 12 hour dosing may prove to be more convenient than other dosing intervals required for IR opioid combination products. |

### Background

**Purposes for review**

OXY/APAP XR was approved by the FDA in March, 2014; it is the first extended release opioid product to carry an acute pain indication.

*The purposes of this abbreviated monograph* are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering OXY/APAP XR for addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

*Also to be determined:* Does OXY/APAP XR have clinical advantages over existing alternatives? What safety issues need to be considered?

### Other therapeutic options

<table>
<thead>
<tr>
<th>Formulary Alternatives</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone/Acetaminophen (oral liquid, cap, tab)</td>
<td></td>
</tr>
<tr>
<td>Codeine/Acetaminophen (elixir, tab)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonformulary Alternatives</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone/Acetaminophen (oral liquid, tab)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone/aspirin (tab)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone/ibuprofen (tab)</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone/ibuprofen (tab)</td>
<td></td>
</tr>
</tbody>
</table>

Products listed are combinations (containing CII opioid with non-opioid analgesic) commonly used for treatment of surgical or non-surgical acute pain.

*Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or vawww.pbm.va.gov*
Efficacy (in FDA-approved Indications)

Literature Search Summary
A literature search was performed on PubMed/Medline (2011 to August 2015) using multiple search terms and combinations of terms including MNK-795, oxycodone and Xartermis XR. The search was limited to studies performed in adult humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials.

The OXY/APAP XR clinical development program included 12 phase I studies and 2 phase III studies [a double-blind, randomized, placebo-controlled parallel-group efficacy study (study 0182) and an open-label safety study (study 0181; see Safety Considerations)] designed to support an indication for the management of acute pain where the use of an opioid analgesic would be appropriate. 3, 5

Review of Efficacy 3, 6, 7
- Decades of experience with approved analgesic combination products containing oxycodone and APAP prompted FDA to allow the submission of a single well-controlled study to support efficacy of OXY/APAP XR.
- The March, 2014 FDA approval of OXY/APAP XR was based upon a multicenter, randomized, double-blind, placebo-controlled phase III study (#0182) conducted in patients undergoing primary unilateral first metatarsal bunionectomy. 3 The bunionectomy pain model has been identified as having good assay sensitivity for determination of analgesic efficacy up to 72 hours following the surgical procedure; FDA has agreed that this pain model is generalizable to the target population of patients with acute pain. 6, 7
- 329 patients with acute postoperative pain of moderate to severe intensity (a score ≥ 4 on a 10 point numerical rating scale) were enrolled and randomized on the first post-operative day to receive OXY/APAP XR 2 tablets twice daily or identical placebo tablets. Patients remained at the study site for the duration of the 48 hour study.
- Patients were age 18-75 and were required to be in generally good health with BMI ≤ 33 kg/m². Patients were excluded who had medical conditions that could affect study participation or alter the pharmacokinetics of OXY/APAP XR including: previous bariatic surgery, history of allergy, intolerance, or insensitivity to study drug components, use of simple analgesics within 30 days, and his/her last bariatric surgery, history of allergy, intolerance, or insensitivity to study drug components
- Ibuprofen 400mg could be taken for supplemental analgesia as needed up to six times daily.
- The primary efficacy endpoint was the summed time-weighted pain intensity difference (PID) scores over the 48 hour study period (SPID48). The PID at a given time was the difference between the pain intensity score at baseline (0 hour, before the first dose of study medication) and the score at the time of interest.
- Secondary endpoints included: SPID calculated over 0–4, 0–12, 0–36, 12–24, 24–36, and 36–48 hours; total pain relief (TOTPAR) during the same periods (calculated as the sum of time-weighted total pain relief scores at each time point over the designated time period); and proportion of patients with a 30% or greater reduction in pain intensity scores (defined as a clinically meaningful response).
- 266 patients completed the study (135 on OXY/APAP XR and 131 on placebo). Patients receiving OXY/APAP XR had significantly less pain throughout the 48 hour double-blind treatment phase compared to those administered placebo. The primary efficacy endpoint, SPID48 (mean ± SE), was significantly increased in the OXY/APAP XR group compared to the placebo group (114.9 ± 7.6 versus 66.9 ± 7.6, respectively); the mean treatment difference was 48.0 ± 10.5 (95% CI, 27.3–68.6; p < 0.001). Mean pain intensity score was reduced from 6.2 to 3.1 over the first 2 hours during treatment with OXY/APAP XR compared to a 6.0 to 4.7 reduction over the same period in placebo-treated patients (p < 0.0001). Mean PID was significantly higher (indicating greater pain relief) in the OXY/APAP XR group than in the placebo group at 30 minutes and at most assessment intervals over the 48 hours (p ≤ 0.01).
- Mean TOTPAR values (± SE) during the first 48 hours after surgery were 91.3 ± 3.5 with OXY/APAP XR and 70.9 ± 3.4 with placebo, resulting in a mean treatment difference of 20.5 ± 4.9 (95% CI, 11.0–30.0; p < 0.001). TOTPAR values over every assessment interval were significantly higher with OXY/APAP XR than with placebo, indicating that OXY/APAP XR provided better pain relief than placebo over the 48 hour double-blind phase.
- The proportion of 30% responders was significantly higher with OXY/APAP XR than with placebo from as early as 30 minutes after the first dose and the difference increased over the subsequent 90 minutes (p < 0.05).

Potential Off-Label Use
This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s Guidance on “Off-label” Prescribing (available on the VA PBM intranet site only).

There is potential use of OXY/APAP XR in the management of pain not severe enough to require daily, around-the-clock, long-term opioid treatment and/or for which alternative treatment options have not yet been trialed or shown to be inadequate.

The following trials are listed at www.clinicaltrials.gov (accessed August 3, 2015).
- A study of MNK-795 has been conducted in subjects with osteoarthritis or chronic low back pain; the study was completed in July 2012 but results are not yet available (ClinicalTrials.gov NCT01451385)
- Recruitment is ongoing for an open-label study of OXY/APAP XR to treat post-operative pain following arthroscopic knee surgery; off-label dosing scheme(s) [flexible dosing and titration] will be investigated (ClinicalTrials.gov NCT02391844).

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### Safety 1, 5, 7
(For more detailed information refer to the Prescribing Information.)

| Boxed Warning | • Addiction, abuse, and misuse which can lead to overdose and death  
|               | • Serious, life-threatening or fatal respiratory depression  
|               | • Accidental exposure, especially in children, can result in fatal overdose  
|               | • Neonatal opioid withdrawal syndrome when used during pregnancy  
|               | • Contains acetaminophen which can cause acute at higher than maximum doses or if taken concomitantly with alcohol.  
| Contraindications | • Significant respiratory depression  
|                 | • Acute or severe bronchial asthma or hypercarbia  
|                 | • Paralytic ileus, known or suspected  
|                 | • Hypersensitivity to oxycodone, acetaminophen or any other components of the product  
| Warnings/Precautions | • OXY/APAP XR is not interchangeable with other oxycodone/acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration.  
|                     | • OXY/APAP XR, as with any opioid medication, should be used with caution in patients who are experiencing or who are at risk for:  
|                     |   o Misuse, abuse, or diversion of opioid medications  
|                     |   o CNS depression from other medications; profound sedation, respiratory depression, and death may occur; consider dose reduction of one or both drugs  
|                     |   o Life-threatening respiratory depression; in particular, in the elderly, or in cachectic or debilitated patients, or those with chronic pulmonary disease  
|                     |   o Hepatic impairment  
|                     |   o Head injury/increased intracranial pressure  
|                     |   o Hypotension/circulatory shock  
|                     |   o Biliary tract disease, including acute pancreatitis  
|                     |   o Symptoms associated with possible allergy or hypersensitivity to the product or components of the product  
|                     | • OXY/APAP XR, as with any opioid medication, may impair the mental and physical abilities; use caution when performing potentially hazardous activities  
|                     | • Due to the potential for acetaminophen hepatotoxicity at doses higher than 4000 mg/day, OXY/APAP XR should not be used with other products containing acetaminophen  
|                     | • Concomitant use of CYP3A4 inhibitors may increase opioid effects  
|                     | • Accidental exposure to OXY/APAP XR, especially in children, can result in fatal overdose of oxycodone.  

### Safety Considerations 1, 5, 7

FDA recognized that the oxycodone-acetaminophen combination of drugs had been marketed for decades and that safety concerns were generally well-known.

Safety data is available from 834 subjects exposed to a dosing regimen of 2 tablets every 12 hours of either placebo or OXY/APAP XR; however, the two pooled phase III studies provide the most useful information (607 and 163 patients were given active drug or placebo, respectively). Study #01802 was the previously-described 48-hour controlled efficacy study (see Review of Efficacy, page 3) and study #0181 was an open-label extension of #0182. In these studies the maximum duration of OXY/APAP treatment was 42 days and the mean duration of exposure was 20 days.

### Adverse Events 1, 5, 7

#### Common Adverse Events

<table>
<thead>
<tr>
<th>Events</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>44.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>7.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>44.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26.2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16.3%</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>8.1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Approximately 54% of subjects receiving OXY/APAP XR reported at least one treatment-related adverse event (TEAE) compared to 21% of the placebo group. Incidence of TEAEs in ≥ 2% of patients in placebo-controlled trial were related to the opioid component of the combination. Over a treatment period of up to 5 days these TEAEs included constipation (3.5%), nausea (44.2%), vomiting (26.2%), dizziness (16.3%), headache (8.1%), and somnolence (7.0%). Most TEAEs were mild to moderate in severity and usually decreased in incidence with increased duration of exposure with the exception of constipation (10.2% at 5-10 days; 12.4% at ≥ 10 days).

There were no unusual or unexpected findings on laboratory (hematology, serum chemistry, and urinalysis), vital sign, or ECG evaluations in patients taking OXY/APAP XR.

Treatment emergent liver function test abnormalities (increases in AST, ALT, GGT) occurred in 2% (12 subjects) given OXY/APAP and in no subjects given placebo. All increases were transient.

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and reduced to normal or near-normal in all subjects. The hepatic-related safety findings were considered consistent with the known safety profile of acetaminophen.

### Deaths/Serious Adverse Reactions

There were no deaths in the phase I studies and 2 deaths in the open-label phase III study. Neither of these deaths appeared attributable to OXY/APAP XR; one event was due to cardiorespiratory arrest in a 71 year old male with significant CV risk factors, while the other came as a result of a MVA in a patient who had had no study medication for 4 days prior to the accident.

Two of the five non-fatal serious adverse effects recorded for phase III study subjects given active drug were gastrointestinal in nature and may have been related to drug administration. The 3 remaining events did not appear to be causally related. One subject given placebo experienced a possible allergic reaction which may have been caused by an excipient in the placebo tablet formulation.

Choking, obstruction of the airway, and GI obstruction are potential risks associated with OXY/APAP XR due to its formulation with polyethylene oxide (PEO) which causes the tablet to swell and become sticky when wet. One phase I study patient was reported to have experienced dysphagia following administration of 2 tablets of OXY/APAP XR. There were no reported cases of choking, airway obstruction, or GI obstruction in studies but FDA reviewers believed a safety concern exists (see Other Considerations).

### Discontinuations Due to Adverse Events

In the pooled phase III studies, 14.2% of patients taking OXY/APAP XR experienced at least 1 adverse event (AE) that led to discontinuation. Vomiting and nausea were the AEs most likely to result in discontinuation; dizziness, hepatic enzyme increase, somnolence, and chest discomfort were implicated less frequently. One patient given placebo (0.6% of placebo patients) discontinued OXY/APAP XR due to tachycardia.

Hepatic enzyme elevation led to discontinuation of OXY/APAP XR in 6 of 12 patients with such elevation.

### Drug Interactions

#### Cytochrome P450 Interactions

The CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone; drugs that alter CYP3A4 activity may cause changes in oxycodone clearance and alteration of oxycodone plasma concentrations. If co-administration is necessary, caution is advised when initiating OXY/APAP XR in patients currently taking or discontinuing CYP3A4 inhibitors or inducers. Blockade of the CYP2D6 pathway alone has not been shown to be of clinical significance for oxycodone.

**CYP3A4 Inhibitors:**

Drugs that inhibit CYP3A4 activity such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration of OXY/APAP XR with CYP3A4 inhibitors, alone or with 2D6 inhibitors, should prompt monitoring of patients for respiratory depression and sedation at frequent intervals; consider dose adjustments until stable drug effects are achieved.

**CYP3A4 Inducers:**

CYP450 3A4 inducers (e.g., rifampin, carbamazepine, and phenytoin) may reduce plasma concentrations of oxycodone, leading to potential lack of efficacy or withdrawal syndrome in patients who have physical dependence to oxycodone. If co-administration with OXY/APAP ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

#### CNS Depressants:

Concomitant use of OXY/APAP XR and other CNS depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol) may increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving these combinations for signs of respiratory depression, sedation and hypotension; consider dose reduction of one or both agents.
Mixed Agonist / Antagonist Opioid Analgesics:

Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) may reduce the analgesic effect of OXY/APAP XR and/or precipitate withdrawal symptoms in patients with physical dependence to oxycodone. Avoid use of these agents in patients receiving OXY/APAP ER.

Monoamine Oxidase Inhibitors (MAOI):

The use of OXY/APAP XR is not recommended for patients taking MAOIs or within 14 days of discontinuation of an MAOI, as MAOIs have been reported to potentiate the effects of at least one opioid drug causing anxiety, confusion, significant respiratory depression or coma.

Neuromuscular Blocking Agents:

Opioid analgesics, including oxycodone, may enhance the neuromuscular blocking action of skeletal muscle relaxants and thereby potentiate respiratory depression.

Anticholinergics:

Medications with anticholinergic activity used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention, constipation, respiratory depression and central nervous system depression.

Risk Evaluation

As of 3 August 2015

<table>
<thead>
<tr>
<th>Sentinel event advisories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of opioids in hospitals: Respiratory depression, generally preceded by sedation.</td>
</tr>
</tbody>
</table>

Look-alike / sound-alike error potential

Based on clinical judgment and an evaluation of LASA information from three data sources, the following drug names may cause LASA confusion:

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>First DataBank</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone/acetaminophen 7.5mg/325mg XR tab</td>
<td>Hydrocodone/acetaminophen</td>
<td>None</td>
<td>None</td>
<td>Oxycodone/acetaminophen IR Oxycodone/paracetamol Oxycodone/ibuprofen Oxymorphone ER</td>
</tr>
</tbody>
</table>

| Xartemis XR | None | None | None | Xarelto |

Other Considerations

Comparative Subjective Effects of OXY/APAP XR and IR formulations in Recreational Drug Users:

Subjective pharmacodynamic outcomes were assessed in a phase I randomized, double-blind, double-dummy, active- and placebo-controlled, 7-way crossover designed study of 55 recreational drug users confirmed able to detect the subjective effects of oxycodone and also confirmed not to be physically dependent on opioids. As assessed by visual analogue scales, subjective effects for drug liking, drug high, and ‘good’ drug effects were all significantly lower for intact XR tablets versus intact IR tablets at higher (30/1300) and lower (15/650) oxycodone and acetaminophen dosages (p < 0.001). For most subjective measures, crushed high dose XR tablets produced significantly lesser effects than crushed high dose IR tablets (p < 0.001) and crushed high dose XR tablets produced similar peak positive subjective effects compared to intact high dose XR tablets (with the exception of ‘good’ drug effect, p < 0.05). The authors concluded that the lower subjective drug effects associated with XR may reduce interest in its abuse.

Food effects on the Pharmacokinetics of OXY/APAP XR:

An open-label randomized single-dose crossover phase I study conducted in 31 subjects revealed small but clinically insignificant differences in Cmax under fed versus fasting conditions indicating that OXY/APAP XR may be administered with or without food.

Evaluation of tamper-resistance:

In a comparative study with IR OXY/APAP, OXY/APAP XR was shown to have greater resistance to particle size reduction (crush resistance), solvent extraction and preparation for snorting and injection than the IR formulation. Once crushed, the powder from an OXY/APAP XR tablet combined with a solvent formed a thick gel unsuitable for absorption through the nasal mucosa or for drawing into a syringe. The authors concluded that OXY/APAP XR may have less potential for abuse involving tampering compared to IR OXY/APAP tablets.
Safety Concerns Regarding Swallowing of OXY/APAP XR: As a result of the PEO formulation, OXY/APAP XR tablets can swell and become sticky when wetted. Alternative analgesics should be considered in patients who have difficulty swallowing and in patients who are at risk for gastrointestinal obstruction. Patients should be instructed a) not to pre-soak, lick, or otherwise wet OXY/APAP XR tablets prior to swallowing and b) to take one tablet at a time with adequate water to insure complete and immediate swallowing.

REMS: While the formulation of OXY/APAP XR has extended-release characteristics; the amount of oxycodone in each tablet (7.5 mg) is the same as that available in some IR combination oxycodone and acetaminophen products and the total daily dose of oxycodone from OXY/APAP XR has the same limitations as IR combination oxycodone and acetaminophen products in order to avoid exceeding the safe daily limit of acetaminophen. These product specifications, in addition to its acute pain indication, led the FDA to conclude that the safety profile of OXY/APAP XR was consistent with currently approved IR formulations of oxycodone/acetaminophen and a that REMS would not be required.

Pharmacokinetic Considerations: Bioavailability of OXY and APAP following single- and multiple-doses of OXY/APAP XR tablets are comparable to IR products containing either drug alone or in combination. Steady state concentrations of OXY and APAP are reached within 24 hours of product initiation. See the approved labeling for an in depth discussion of the pharmacokinetics of OXY/APAP XR.

Patient Satisfaction Assessment: Patient satisfaction was assessed in the 14 day open label extension safety evaluation. At the day 7 visit, ≥ 88.9% of 144 patients and at the day 14 visit ≥ 83.3% of patients indicated they were satisfied on each of the 5 measures (ease of administration, dosing frequency, number of tablets taken, time for medication to work, and level of pain relief). The authors noted that the ‘level of pain relief by pain medicine’ questionnaire utilized is not a validated scale.

Special Populations

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Elderly ≥ 65 years</th>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
<th>Pharmacogenetics/genomics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No untoward or unexpected adverse reactions were seen in the elderly patients who received OXY/APAP XR tablets in the phase II trials (10.3% of the 607 patients were &gt; 65 years old; 1.6% were &gt; 75).</td>
<td>Pregnancy Category C. No adequate and well-controlled studies in pregnant women. Use OXY/APAP XR during pregnancy only if the potential benefits justify the potential risk to the fetus. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. OXY/APAP XR should not be used in women during and immediately prior to labor, when short-acting opioids or other analgesic techniques are more appropriate.</td>
<td>Oxycodone is present in human milk and there is potential for accumulation and toxicities such as sedation and respiratory depression. Acetaminophen is also present in human milk in small quantities. Because of the potential for serious adverse reactions in nursing infants from OXY/APAP XR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.</td>
<td>Patients with renal impairment (creatinine clearance &lt;60 mL/min) have higher plasma concentrations of oxycodone than subjects with normal renal function. In patients with renal impairment start with one tablet and adjust the dosage as needed. Monitor closely for respiratory depression.</td>
<td>OXY/APAP XR contains both oxycodone and acetaminophen, which are extensively metabolized in the liver. In patients with hepatic impairment start with one tablet and adjust the dosage as needed. Monitor closely for respiratory depression.</td>
<td>There are no data identified in the FDA approved labeling or at this site: <a href="http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm">http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm</a> (accessed August 3, 2015).</td>
<td></td>
</tr>
</tbody>
</table>
**Projected Place in Therapy**

- There is good quality evidence for the short-term (48 hour) analgesic efficacy of OXY/APAP XR compared to placebo; however, long term efficacy data for OXY/APAP XR are lacking and there are no trials comparing the analgesic efficacy of OXY/APAP XR to any other analgesic agent.
- A trial of OXY/APAP XR for treatment of acute pain should be reserved for patients who have had an inadequate response to alternative pain therapies and who have pain severe enough to require opioid treatment.
- OXY/APAP XR is the first extended-release opioid combination product to carry an acute pain indication; relative to IR combinations, the ability to dose every 12 hours may increase ease of administration for patients and healthcare personnel.

**References**


7. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Xartemis XR (oxycodone and acetaminophen) NDA 204-031 Cross Discipline Team Leader Review, November 7, 2013 (Reference ID: 3403487).

