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Literature Scan: Short-acting Opioids

Month/Year of Review: May 2015 **Date of Last Review: July 2013**

Current Status of PDL Class:
See **Appendix 1**.

Current Prior Authorization Criteria:
Fentanyl Buccal, Intranasal and Sublingual Products and **Opioid/non-narcotic Combinations and Excessive Dose Limits** (see **Appendix 4**).

Conclusions and Recommendations:
- Update current PA criteria for excessive dose limits on opioid/non-narcotic combination products. Propoxyphene products and combination products containing 500 mg of acetaminophen were removed, and the maximum recommended daily aspirin dose was decreased from 8 g/day to 4 g/day.
- No further review or research needed at this time. Compare drug costs in the executive session.

Previous Conclusions and Recommendations:
- Fentanyl products should only be used in opioid-tolerant patients
- Should have long acting analgesic therapy instituted
- Consider quantity limits

Methods:
A Medline OVID search was conducted with the following search terms: codeine, hydrocodone, oxycodone, hydromorphone, morphine, oxymorphone, fentanyl, buprenorphine, tramadol, tapentadol, acetaminophen, opioids, opioid analgesics, short-acting opioids, pain, pain relief, and treatment. The search was limited to English language articles of randomized control trials in humans published from 2013 to February 2015. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

A summary of potentially relevant trials are available in **Appendix 2**. Abstracts of these trials are available in **Appendix 3**.

New Systematic Reviews:
Chaparro, et al.[1] conducted a systematic review of the use of opioids and other treatments for lower back pain. The review included 15 trials lasting longer than 4 weeks comparing at least one opioid to placebo, except two trials which used celecoxib in the control arm. Tramadol was compared to placebo in five trials. There is low quality evidence that tramadol is better than placebo in improving pain [standardized mean difference (SMD) -0.55, 95% CI -0.66 to -0.44]. Two included studies compared transdermal buprenorphine to placebo, with very low quality evidence that buprenorphine is better than placebo in improving pain (SMD -2.47, 95% DI -2.69 to -2.25). There was moderate quality evidence from six trials that opioids are better than placebo in reducing pain (SMD -0.43, 95% CI -0.52 to -0.33). Patients treated with opioids had a statistically significantly higher incidence of nausea (10%, 95% CI 7% to 14%), dizziness (8%,

95% CI 5% to 11%), constipation (7%, 95% CI 4% to 11%), vomiting (7%, 95% CI 4% to 9%), somnolence (6%, 95% CI 3% to 9%) and dry mouth (6%, 95% CI 2% to 10%) than people treated with placebo. There were no head-to-head comparisons conducted in this systematic review.

An update of a systematic review and meta-analysis evaluating opioids for neuropathic pain was published.[2] 17 short-term (single dose or intravenous infusion) and 14 intermediate-term (more than a single dose but not long enough to make conclusion about chronic administration) studies were included. The short-term trials were too small to draw conclusions regarding reduction in pain. When the number of participants achieving at least 50% pain relief was analyzed in the intermediate-term trials, the overall point estimate of risk difference for opioids versus placebo was 0.17 (95% CI. 0.02 to 0.33; p=0.03). The intermediate-term studies were also of small size, short duration, and at risk of bias due to inadequate handling of dropouts. Well-conducted RCTs are needed to establish long-term efficacy, safety and quality of life estimates.

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. Chaparro, L. E. *et al.* Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev* **8,** CD004959 (2013).
2. McNicol, E. D., Midbari, A. & Eisenberg, E. Opioids for neuropathic pain. *Cochrane Database Syst Rev* **8,** CD006146 (2013).
3. Chang, A. K., Bijur, P. E., Munjal, K. G. & John Gallagher, E. Randomized clinical trial of hydrocodone/acetaminophen versus codeine/acetaminophen in the treatment of acute extremity pain after emergency department discharge. *Acad Emerg Med* **21,** 227–235 (2014).
4. Kuivalainen, A.-M., Ebeling, F. & Rosenberg, P. H. Pre-medication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy: a randomized feasibility trial. *Eur J Pain* **17,** 1357–1364 (2013).
5. Kwong, W. J. *et al.* Bowel function after tapentadol and oxycodone immediate release (IR) treatment in patients with low back or osteoarthritis pain. *Clin J Pain* **29,** 664–672 (2013).

Appendix 1: Current Status on Preferred Drug List

Route	Form	Brand	Generic	PDL
NASAL	SPRAY	BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	Y
ORAL	TABLET	CODEINE SULFATE	CODEINE SULFATE	Y
ORAL	TABLET	HYDROCODONE W/ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	VICODIN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	ANEXSIA	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	NORCO	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
ORAL	TABLET	DILAUDID	HYDROMORPHONE HCL	Y
ORAL	SOLUTION	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	TABLET	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	SOLUTION	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	ROXICODONE	OXYCODONE HCL	Y
ORAL	CAPSULE	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	PERCOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	TRAMADOL HCL	TRAMADOL HCL	Y
ORAL	TABLET	ULTRAM	TRAMADOL HCL	Y
ORAL	SUSPENSION	CAPITAL W-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	TYLENOL-CODEINE NO.3	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	TYLENOL-CODEINE NO.4	ACETAMINOPHEN WITH CODEINE	N
ORAL	ELIXIR	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	SOLUTION	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	CAPSULE	BUTALB-CAFF-ACETAMINOPH-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	FIORICET WITH CODEINE	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	ASA-BUTALB-CAFFEINE-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEINE	N
ORAL	CAPSULE	FIORINAL W/CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEINE	N
ORAL	SOLUTION	CODEINE SULFATE	CODEINE SULFATE	N
ORAL	CAPSULE	SYNALGOS-DC	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
ORAL	CAPSULE	TREZIX	DIHYDROCODEINE/APAP/CAFFEINE	N
ORAL	CAPSULE	ASPIRIN-CAFFEINE-DIHYDROCODEIN	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
ORAL	CAPSULE	SYNALGOS-DC	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
BUCCAL	LOZENGE HD	ACTIQ	FENTANYL CITRATE	N
BUCCAL	LOZENGE HD	FENTANYL CITRATE	FENTANYL CITRATE	N
NASAL	SPRAY/PUMP	LAZANDA	FENTANYL CITRATE	N
SUBLINGUAL	SPRAY	SUBSYS	FENTANYL	N
BUCCAL	TABLET EFF	FENTORA	FENTANYL CITRATE	N
SUBLINGUAL	TAB SUBL	ABSTRAL	FENTANYL CITRATE	N
ORAL	ELIXIR	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	SOLUTION	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	HYDROCODONE-IBUPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	VICOPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	REPREXAIN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	XYLON 10	HYDROCODONE/IBUPROFEN	N
ORAL	LIQUID	DILAUDID	HYDROMORPHONE HCL	N

ORAL	LIQUID	HYDROMORPHONE HCL	HYDROMORPHONE HCL	N
ORAL	SOLUTION	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	TABLET	DEMEROL	MEPERIDINE HCL	N
ORAL	TABLET	MEPERIDINE HCL	MEPERIDINE HCL	N
RECTAL	SUPP.RECT	MORPHINE SULFATE	MORPHINE SULFATE	N
ORAL	SYRINGE	MORPHINE SULFATE	MORPHINE SULFATE	N
RECTAL	SUPP.RECT	BELLADONNA-OPIUM	OPIUM/BELLADONNA ALKALOIDS	N
ORAL	CAPSULE	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	CONC SOL	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	SOLUTION	ROXICET	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	ROXICET	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	OXYCODONE HCL-ASPIRIN	OXYCODONE HCL/ASPIRIN	N
ORAL	TABLET	PERCODAN	OXYCODONE HCL/ASPIRIN	N
ORAL	TABLET	OXYCODONE HCL-IBUPROFEN	OXYCODONE/IBUPROFEN HCL	N
ORAL	TABLET	OPANA	OXYMORPHONE HCL	N
ORAL	TABLET	OXYMORPHONE HCL	OXYMORPHONE HCL	N
ORAL	TABLET	PENTAZOCINE-NALOXONE HCL	PENTAZOCINE HCL/NALOXONE HCL	N
ORAL	SOLUTION	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	TRAMADOL HCL-ACETAMINOPHEN	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	ULTRACET	TRAMADOL HCL/ACETAMINOPHEN	N

Appendix 2: New Clinical Trials

84 potentially relevant clinical trials were evaluated from the literature search. After further review, 79 trials were excluded due to wrong study design (observational), comparator (placebo), drug (long-acting opioid) or outcome (nonclinical) and were therefore excluded. The remaining 5 trials are briefly described in the table below. Full abstracts are included in Appendix 3.

Table 1. Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Chang, et al.[3]	Hydrocodone/ APAP 5/500 mg vs. Codeine/APAP 30/300 mg	Adults with acute extremity pain discharged home from the Emergency Department (n=240)	Change from baseline pain as measured by the Numeric Rating Scale	Mean decrease in pain scores were 3.9 units (hydrocodone/APAP) vs 3.5 units (codeine/APAP) (difference 0.4 units; 95% CI: -0.3 to 1.2 units). No differences found in side effects or patient satisfaction
Kuivalainen, et al.[4]	Sublingual fentanyl 200 mcg or 100 mcg or placebo	Adult patients undergoing bone marrow aspiration and/or biopsy (n=160)	Pain scores at 6 time points before, during and after the procedure	There were no differences in pain scores between either active comparison and placebo at any time point.
Kwong, et al.[5]	Tapentadol IR vs. Oxycodone IR	Adult patients with OA of the knee or hip joint	Bowel function assessed using the Bowel Movement Questionnaire (BMQ), the Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM), and laxative use	The proportions of treatment days with no or incomplete bowel movements were similar with placebo and tapentadol, but higher in the oxycodone group ($p<0.05$) after 10 days of treatment as assessed with the BMQ. When assessing bowel function with the PAC-SYM, tapentadol had significantly lower overall PAC-SYM scores and abdominal symptoms. Other differences were not statistically different.

Appendix 3: Abstracts of Clinical Trials

Chang, et al. Randomized clinical trial of hydrocodone/acetaminophen versus codeine/acetaminophen in the treatment of acute extremity pain after emergency department discharge.

OBJECTIVES: The objective was to test the hypothesis that hydrocodone/acetaminophen (Vicodin [5/500]) provides more efficacious analgesia than codeine/acetaminophen (Tylenol #3 [30/300]) in patients discharged from the emergency department (ED). Both are currently Drug Enforcement Administration (DEA) Schedule III narcotics.
METHODS: This was a prospective, randomized, double-blind, clinical trial of patients with acute extremity pain who were discharged home from the ED, comparing a 3-day supply of oral hydrocodone/acetaminophen (5 mg/500 mg) to oral codeine/acetaminophen (30 mg/300 mg). Pain was measured on a valid and reproducible verbal numeric rating scale (NRS) ranging from 0 to 10, and patients were contacted by telephone approximately 24 hours after being discharged. The primary outcome was the between-group difference in improvement in pain at 2 hours following the most recent ingestion of the study drug, relative to the time of phone contact after ED discharge. Secondary outcomes compared side-effect profiles and patient satisfaction.
RESULTS: The median time from ED discharge to follow-up was 26 hours (interquartile range [IQR] = 24 to 39 hours). The mean NRS pain score before the most recent dose of pain medication after ED discharge was 7.6 NRS units for both groups. The mean decrease in pain scores 2 hours after pain medications were taken were 3.9 NRS units in the hydrocodone/acetaminophen group versus 3.5 NRS units in the codeine/acetaminophen group, for a difference of 0.4 NRS units (95% confidence interval [CI] = -0.3 to 1.2 NRS units). No differences were found in side effects or patient satisfaction.
CONCLUSIONS: Both medications decreased NRS pain scores by approximately 50%. However, the oral hydrocodone/acetaminophen failed to provide clinically or statistically superior pain relief compared to oral codeine/acetaminophen when prescribed to patients discharged from the ED with acute extremity pain. Similarly, there were no clinically or statistically important differences in side-effect profiles or patient satisfaction. If the DEA reclassifies hydrocodone as a Schedule II narcotic, as recently recommended by its advisory board, our data suggest that the codeine/acetaminophen may be a clinically reasonable Schedule III substitute for hydrocodone/acetaminophen at ED discharge. These findings should be regarded as tentative and require independent validation in similar and other acute pain models.

Kuivalainen, et al. Pre-medication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy: a randomized feasibility trial.

BACKGROUND: Bone marrow aspiration and/or biopsy (BMAB) is often an unpleasant and painful procedure in spite of local anaesthetic infiltration. This randomized placebo-controlled trial compared the pain relieving effect of sublingual fentanyl and placebo during BMAB.
METHODS: One hundred sixty patients were randomized to receive either sublingual fentanyl 200 μg, 100 μg (patients ≥ 70 years old, weight ≤ 50 kg or in poor health) or placebo before BMAB. The grade of anxiety before the procedure and the grade of pain during local anaesthetic infiltration, aspiration, biopsy and immediately after the BMAB were assessed using the Numeral Rating Scale (0-10). Possible side effects of the study drugs were recorded.
RESULTS: Sublingual fentanyl proved inadequate in relieving pain during BMAB as no significant differences in the pain scores of the fentanyl and placebo patients were observed. However, fentanyl caused significantly more dizziness than placebo.
CONCLUSIONS: The results suggest that sublingual fentanyl in a dose of 200 μg (100 μg in infirm patients) is not a feasible preventive analgesic during BMAB. Pain scores were similar and side effects more frequent in the fentanyl group than in the placebo group.

Kwong, et al. Bowel function after tapentadol and oxycodone immediate release (IR) treatment in patients with low back or osteoarthritis pain.

OBJECTIVES: Constipation is a common side effect of opioid therapy. Tapentadol immediate release (IR) was better tolerated than oxycodone IR in 2 clinical trials involving patients with low back or osteoarthritis pain. The objective of this study was to examine patient-reported bowel function during those trials.
METHODS: Bowel function was assessed during secondary post hoc analyses using: the bowel movement questionnaire (BMQ; 10-d trial); the Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM; 90-day trial); and laxative use (both trials). Random effects maximum likelihood regressions were run to examine PAC-SYM data. BMQ data were analyzed using 1-way analyses of variance and a multinomial logistic regression. Rates of laxative use were compared using $\chi(2)$ statistics.
RESULTS: The 10- and 90-day trials consistently showed that tapentadol IR caused less impairment of bowel function than oxycodone IR. BMQ data were comparable between patients receiving tapentadol IR and placebo, and better versus oxycodone IR including: lower proportion of days where bowel movement was absent ($P<0.05$); lower risks of reporting hard stools ($P<0.001$); and moderate or severe straining ($P<0.001$). All PAC-SYM summary scores (abdominal, rectal, stool, overall) indicated fewer symptoms among patients receiving tapentadol IR versus oxycodone IR ($P<0.001$). In both trials, rates of laxative use was lower for tapentadol IR treatment groups versus oxycodone IR ($P<0.001$).
DISCUSSION: Patient-reported bowel function associated with tapentadol IR treatment was similar to that associated with placebo (10-d trial) and significantly better than that associated with oxycodone IR treatment (10- and 90-d trials).

Fentanyl Buccal, Intranasal and Sublingual Products

Goal(s):

The purpose of this prior authorization policy is to ensure that fentanyl for breakthrough pain is appropriately prescribed in accordance to FDA black box warnings:

- Short-acting fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
- Patients considered opioid-tolerant are those who are taking at least 60 mg/day morphine, 50 mcg/hour transdermal fentanyl, or an equianalgesic dose of another opioid for a week or longer.
- Because life-threatening respiratory depression can occur at any dose in patients not taking chronic opiates, transmucosal and buccal fentanyl is contraindicated in the management of acute or postoperative pain.
- This product must not be used in opioid-naïve patients. Short acting (SA) fentanyl is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable and skilled in the use of Schedule II opioids to treat cancer pain.
- When prescribing, do not convert patients from other fentanyl products on a mcg per mcg basis. Pharmacokinetic differences between products could cause fatal over-dose.
- Caution should be used when combining these agents with CYP3A4 inhibitors. Increases in fentanyl concentrations can cause fatal respiratory depression.
- Patients and their caregivers must be instructed that fentanyl products contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

Length of Authorization:

Up to 6 months (with quantity limit)

Requires PA:

- Non-preferred short-acting fentanyl buccal, intranasal and sublingual products

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria	
1. What is the diagnosis for which fentanyl is being requested?	Record ICD9 code.

Approval Criteria		
2. Is the pain diagnosis above the line or below the line? (for DMAP, short acting fentanyl is not limited to cancer pain but must be severe chronic pain)	**Above the line:** go to #3.	**Below the line:** No, Pass to RPH; Deny, (Not Covered by the OHP).
3. Is the prescriber an oncologist or pain specialist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny, (Medical Appropriateness), with message: "The described use is not consistent with the FDA labeling which SA fentanyl be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."
4. Is client tolerant to opioids (**Check profile)**, defined as chronic long-acting opioid dose of: • Morphine greater than 60 mg per day? OR • Transdermal fentanyl 50 mcg per hour? OR • Equianalgesic dose of another opioid for at least one week?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*
5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*

Approval Criteria		
6. Is the quantity >4 doses per day?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request for a quantity greater than 4 has been denied because it exceeds limits."*	**No:** Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days).

P&T / DUR Action: *5/15; 6/13; 3/10; 12/09, 9/05, 5/05*
Revision(s): *1/14 (MH), 4/10; 4/08, 6/08, 1/10*
Initiated: *9/06*

Opioid/non-narcotic Combinations and Excessive Dose Limits

Goal(s):

- Decrease risk for adverse events attributed to high doses of acetaminophen (APAP) or aspirin (ASA) when combined with an opioid product.
- Pay only for conditions funded on the OHP list of prioritized services.

Length of Authorization:

None

Requires PA:

- Non-preferred drugs.
- Prescriptions exceeding FDA recommendations of 4000 mg/day of APAP or ASA.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Pharmacy may need to adjust day's supply entry.
- Prescriber may choose a product with a higher ratio of narcotic to keep APAP or ASA within maximum limits or use a single-ingredient opioid.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does daily dose of APAP or ASA exceed the maximum daily dose?	Yes: Go to #3.	No: Instruct pharmacy to correct day's supply entry
3. Is the diagnosis funded on the OHP list of prioritized services?	Yes: Pass to RPH, DENY, (Medical Appropriateness) Review FDA maximum dose and provide alternatives.	No: Pass to RPH, DENY, (Not Covered by the OHP) Review FDA maximum dose and provide alternatives

Examples of products containing ASA:

Aspirin Combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Codeine/ASA/Caffeine/ Butalbital 30/325/40/50 mg	12 tablets	Oxycodone/ASA 4.8355/325 mg	12 tablets
Codeine/ASA/Carisoprodol 16/325/200 mg	12 tablets	Dihydrocodeine/ASA/Caffeine 16/356.4/30 mg	11 capsules

Examples of products containing APAP:

Hydrocodone/APAP combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Hydrocodone/APAP 5/300 mg	13 tablets	Hydrocodone/APAP 2.5/108 mg per 5 mL	185 mL
Hydrocodone/APAP 7.5/300 mg	13 tablets	Hydrocodone/APAP 5/217 mg per 10 mL	184 mL
Hydrocodone/APAP 10/300 mg	13 tablets	Hydrocodone/APAP 7.5/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 2.5/325 mg	12 tablets	Hydrocodone/APAP 10/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 5/325 mg	12 tablets		
Hydrocodone/APAP 7.5/325 mg	12 tablets		
Hydrocodone/APAP 10/325 mg	12 tablets		

Oxycodone/APAP combinations	
Oxycodone/APAP 5/300 mg	13 tablets
Oxycodone/APAP 7.5/300 mg	13 tablets
Oxycodone/APAP 10/300 mg	13 tablets
Oxycodone/APAP 2.5/325 mg	12 tablets
Oxycodone/APAP 5/325 mg	12 tablets
Oxycodone/APAP 7.5/325 mg	12 tablets
Oxycodone/APAP 10/325 mg	12 tablets
Oxycodone/APAP 5/325 per 5 mL	61.5 mL

Codeine/APAP combinations	
Codeine/APAP 12/120 mg per 5 mL	166.5 mL
Codeine /APAP 15/300 mg	13 tablets
Codeine /APAP 30/300 mg	13 tablets
Codeine /APAP 60/300 mg	13 tablets

Other Combinations	
Tramadol/APAP 37.5/325 mg	12 tablets
Dihydrocodeine/APAP/caffeine 16/320.5/30 mg	12 tablets

P&T / DUR Action: *5/15; 2/06; 11/99; 2/99*
Revision(s) *9/05; 5/05; 12/03; 5/03*
Initiated: