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Charlotte,
If possible please add this research on Palladone to the supporting documents of my Citizen Petition 2005P-0076.
Thank-you,
Barbara Van Rooyan

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***Palladone* for Chronic Pain** ..... p 21

Palladone is a new long-acting formulation of the opioid agonist hydromorphone that is taken once daily for treatment of chronic pain in opioid-tolerant patients. There is no evidence that it is more effective or has fewer adverse effects than other opioids. If *Palladone* capsules are broken, dissolved, crushed or taken with alcohol, the entire 24-hour dose can be released at once and could be lethal, especially in non-opioid tolerant individuals.

• Other long-acting opioids should be tried first.

Solifenacin and Darifenacin for Overactive Bladder ..... p 23

Darifenacin (*Enablex*) and solifenacin (*VESicare*) are 2 new oral anticholinergics available for once-daily symptomatic treatment of overactive bladder. Overactive bladder is a common condition in older patients. The 5 drugs currently approved for treatment are modestly effective but also cause anticholinergic adverse effects such as dry mouth and constipation and can cause confusion in the elderly. In some experimental studies, the new drugs particularly target bladder receptors, but the clinical significance of these findings is unknown.

• No demonstrated advantage over older drugs for this indication.

IN BRIEF

Natalizumab (*Tysabri*) Withdrawn

The February 14th issue of *The Medical Letter* reviewed natalizumab (*Tysabri* – Biogen Idec), a new monoclonal antibody that was granted accelerated approval because it decreased the number of relapses in patients with multiple sclerosis. On February 28th, the FDA issued a Public Health Advisory announcing that marketing of the drug had been suspended because 2 patients who had been treated with natalizumab for more than 2 years had developed progressive multifocal leukoencephalopathy, a rare, often fatal disease (www.fda.gov).

Martin A. Rizack, M.D., Ph.D.

Martin Rizack died on March 7, 2005. He was 78 years old. Martin was an integral part of The Medical Letter for many years, beginning in 1966 as a member of our Editorial Board. He was the creator of our Drug Interactions Handbook. In recent years, Martin served as Consulting Editor. We will miss him.

Palladone for Chronic Pain

A once-daily extended-release (ER) oral formulation of the opioid analgesic hydromorphone hydrochloride (*Palladone* – Purdue Pharma) has been approved by the FDA for treatment of opioid-tolerant patients with persistent moderate to severe pain. Hydromorphone HCl, a semisynthetic congener of morphine and active metabolite of hydrocodone that has been used since the 1920s, is also available in immediate-release oral, injectable and suppository forms (*Dilaudid*, and others).

PHARMACOLOGY — With repeated dosing, the bioavailability of a once-daily dose of *Palladone* has been shown to be equivalent to that of the same total daily dose of immediate-release (IR) hydromorphone given in divided doses every 6 hours (IR hydromorphone is usually dosed q4h). Fluctuations in plasma concentrations over a 24-hour period are decreased with the extended-release formulation. The mean half-life of *Palladone* is about 18 hours, which reflects its rate of release from the dosage form (an immediate-dissolving capsule containing controlled-release pellets) and not its rate of elimination from the body.

ANALGESIC EFFICACY — Long-acting opioids are frequently prescribed for treatment of chronic pain, often in combination with adjuvant analgesics.[1] Milligram for milligram, oral hydromorphone is about 4-8 times more potent than oral morphine. Available studies suggest little difference in efficacy (or adverse effects or patient preference) between morphine and hydromorphone when they are taken in appropriate doses.[2] Studies have shown that long-acting opioids are similar in efficacy, but some patients may respond better to one opioid than to another.[3]

In 2 unpublished crossover studies, 344 patients with chronic moderate to severe pain were randomized to receive either IR hydromorphone 4 times per day or ER hydromorphone once daily. After 7 days on each treatment, pain control and use of rescue medication were similar in the two groups.[4] The efficacy of *Palladone* was established by an unpublished 4-week, randomized,

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SOME LONG-ACTING OPIOIDS FOR CHRONIC PAIN

DRUG	FORMULATIONS	APPROXIMATE EQUIANALGESIC DOSE	STARTING DOSAGE	COST[1]
Fentanyl – average generic	25-, 50-, 75-, 100-mcg transdermal patches	Formula 2	one 25-mcg/h patch q72h	$124.80
Duragesic (Alza)				156.30
Hydromorphone				
Palladone – Purdue Pharma	12-, 16-, 24-, 32-mg caps	7.5 mg	12-32 mg PO q24h[3]	208.50
Morphine				
average generic	15-, 30-, 60-, 100-, 200-mg tabs	30 mg	15-30 mg PO q8-12h	45.00
MS Contin – Purdue Pharma				55.40
Oramorph SR – Roxane	15-, 30-, 60-, 100-mg tabs			47.40
Kadian – Alpharma	20-, 30-, 50-, 60-, 100-mg caps		20 mg PO q12-24h	69.30
Avinza – Ligand	30-, 60-, 90-, 120-mg caps		30 mg PO q24h	83.10
Oxycodone				
average generic	60-mg tabs	20 mg	60 mg PO q12h[3,4]	490.20
OxyContin – Purdue Pharma	10-, 20-, 40-, 80-mg tabs		10 mg PO q12h	91.60

1. For 30 days' treatment at lowest starting dosage, according to the most recent data (January 31, 2005) from retail pharmacies nationwide available from NDCHealth, a healthcare information services company.
2. One 25-mcg/h patch is equivalent to about 45 mg/d of oral morphine.
3. For use in opioid-tolerant patients only.
4. Generic formulation is not available in lower strengths.

double-blind trial in 221 patients with chronic moderate to severe pain, described in the package insert, patients who received *Palladone* 12 mg once daily, often in addition to non-opioid medications, maintained adequate analgesia for a statistically significantly longer period of time than those given a placebo.

ADVERSE EFFECTS — The adverse effects of hydromorphone are the same as those of other opioids, including constipation, somnolence, dizziness, nausea, vomiting and pruritus. Use of alcohol (or other CNS depressants) in combination with opioids is known to lead to additive effects, but there is an additional risk with *Palladone*: alcohol acts as a solvent and can speed up absorption of hydromorphone from the pellets, possibly leading to overdose and death. As with other opioids, overdose or use in non-opioid-tolerant patients may result in hypotension, respiratory depression, cardiac arrest and death. Overdosage with intact *Palladone* capsules requires an extensive period of monitoring due to the drug's long half-life. If the integrity of the capsules is violated or they are taken with alcohol (amount and timing are unclear), a single dose can become an overdose.

DRUG DEPENDENCE AND ABUSE — Hydromorphone is a Schedule II controlled substance, the highest level of restriction for marketed drugs. Physical dependence and tolerance can develop with repeated administration. Addiction can occur, particularly in predisposed patients such as those with a history of alcoholism or drug abuse. Discontinuation of the drug in a physically dependent person without tapering the dose results in a withdrawal syndrome.

Diversion of prescription opioid pain relievers for illicit use is common in the US, particularly with *OxyContin*.[5] Abuse of oral IR tablets of hydromorphone, often by heroin addicts, has been a serious problem for decades. The tablets are usually crushed, dissolved and injected intravenously; if the contents of a *Palladone* capsule are handled in this way, or taken with possibly even small amounts of alcohol, a single dose could be fatal, especially in a non-opioid-tolerant person.

RISK MANAGEMENT — A risk management program that includes safety messages, tamper-resistant prescription pads, and a 24-hour dedicated hotline has been developed by the FDA and the manufacturer to deal with the potential for improper use, accidental exposure and abuse or diversion. In addition, a black-box warning has been included in the labeling and an FDA-approved medication guide must be distributed to patients by the pharmacist each time the drug is dispensed.

DOSAGE AND ADMINISTRATION — *Palladone* capsules should not be broken, chewed, opened, dissolved or crushed, and are recommended only for patients who are already receiving opioid therapy and have demonstrated opioid tolerance. Patients can be considered opioid-tolerant when they have been taking an opioid (a daily dose of at least 60 mg oral morphine, 30 mg oral oxycodone or 8 mg oral hydromorphone, or an equianalgesic dose of another opioid) for one week or longer. The product labeling includes dosing recommendations for switching from another opioid to *Palladone*. The dose can be titrated upward every 2 to 3 days, as necessary, increasing the total dose by 25-50% at each titration. There is no dose ceiling, except as imposed by adverse effects. In clinical trials, patients received from 12 to 500 mg per day (average 40-60 mg/day) of hydromorphone. The drug should not be given to patients with severe hepatic impairment. In patients with renal or mild to moderate hepatic impairment, careful monitoring and dose adjustment are advisable.

CONCLUSION — *Palladone* is a once-daily extended-release formulation of hydromorphone for relief of persistent moderate to severe pain in opioid-tolerant patients. There is no evidence that it is more effective than appropriate doses of other long-acting opioids, but it may be useful in patients who have not achieved adequate pain relief with other drugs. Like *OxyContin*, *Palladone* is likely to be diverted for illicit use, and if the integrity of the capsules is violated or they are taken with alcohol, fatal respiratory depression could occur. Other long-acting opioids may be safer. ☐

1. Drugs for Pain. Treat Guidel Med Lett 2004; 2:47.
2. C Quigley and PW Wilkin. A systematic review of hydromorphone in acute and chronic pain. J Pain Symptom Manage 2003; 25:169.
3. R Chou et al. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J Pain Symptom Manage 2003; 26:1026.
4. SM Weinstein et al. Two double-blind randomized trials of once-a-day controlled-release oral hydromorphone (*Palladone XL*) compared to immediate-release hydromorphone dosed qid. 18th Annual Scientific Meeting of the American Pain Society; October 21-24, 1999; Fort Lauderdale, FL., Poster #845
5. 2003 Nat'l Survey on Drug Use & Health. www.oas.samhsa.gov

Solifenacin and Darifenacin for Overactive Bladder

Solifenacin succinate (*VESIcare* – Yamanouchi and GlaxoSmithKline) and darifenacin hydrobromide (*Enablex* – Novartis) have been approved by the FDA for oral treatment of overactive bladder.

THE CONDITION — Overactive bladder is a chronic condition associated with urgency, frequency, nocturia and incontinence. It is the most common cause of incontinence in the elderly. Anticholinergic drugs are the usual treatment for symptoms, but they cause dry mouth and constipation, and can cause confusion in elderly patients. Formulations that cause less dry mouth (long-acting oral drugs, patch formulations) tend to be less effective.

MECHANISM OF ACTION — Darifenacin and solifenacin, like oxybutynin, tolterodine and trospium, are muscarinic receptor antagonists. Muscarinic receptors are involved in both smooth muscle contraction and salivary secretion. In animals, solifenacin had a higher affinity for bladder smooth muscle cells than it did for salivary gland tissue.[1] *In vitro*, darifenacin had greater affinity for M3 muscarinic receptors, which mediate effects on the bladder, GI tract, salivary gland and iris sphincter, than for M1 receptors that may mediate CNS effects.

PHARMACOLOGY

	Solifenacin	Darifenacin
Peak plasma levels[1]	3-8 hrs	7 hrs
Metabolism	Hepatic CYP3A4	Hepatic CYP3A4, 2D6[2]
Plasma half life	45-68 hrs	13-20 hrs
Excretion	Urine 70%, feces	Urine 60%, feces

1. With or without food.
2. Mostly 3A4 in 2D6 poor metabolizers.
3. 2D6 alternative metabolizers.
4. 2D6 poor metabolizers.

DRUGS FOR OVERACTIVE BLADDER

Drug	Dosage	Cost[1]
Darifenacin hydrobromide		
Enablex (Novartis) (7.5, 15 mg ER tabs)	7.5-15 mg PO once/d[2]	$91.80
Oxybutynin chloride		
Ditropan (Merrell Dow) (5 mg/5 mL syrup)	5 mg PO bid or tid	$22.80
Ditropan (Merrell Dow) (5, 10, 15 mg ER tabs)	5-30 mg PO once/d[3]	$94.20
Oxytrol (Watson) (3.9 mg/d patch for skin)	1 patch 2x/wk (3.9 mg/d)	$82.16
Solifenacin succinate		
VESIcare (GSK) (5, 10 mg tabs)	5 mg PO once/d[4]	$100.20
Tolterodine tartrate		
Detrol (Pharmacia) (1, 2 mg IR tabs)	1-2 mg PO bid[5]	$105.60
Detrol LA (2, 4 mg ER caps)	2-4 mg PO once/d[6]	$91.80
Trospium chloride		
Sanctura (Indevus/ Odyssey) (20 mg tabs)	20 mg PO bid[7]	$82.20

1. Cost of treatment for 1 month with the average recommended adult dosage, according to the most recent data (January 31, 2005) from retail pharmacies nationwide available from NDC Health, a healthcare information services company.
2. Maximum dose is 7.5 mg/d in patients taking potent 3A4 inhibitors or with moderate hepatic impairment; not recommended in patients with severe hepatic impairment.
3. Should be started at the lowest dosage and increased by 5 mg a week.
4. Maximum dose is 5 mg/d in patients taking potent 3A4 inhibitors or with severe hepatic or renal impairment (CrCl <30 mL/min).
5. Recommended dose is 1 mg bid (IR) or 2 mg once/d (ER) for patients taking potent 3A4 inhibitors or with severe hepatic or renal impairment (CrCl <30 mL/min).
6. For patients with severe renal impairment (CrCl <30 mL/min) the recommended dosage is 2 mg once a day at bedtime. For patients ≥75 years old, dosage may be titrated down to 2 mg once a day based on tolerability.

CLINICAL STUDIES — Solifenacin – A randomized, double-blind trial in 857 patients found that solifenacin decreased the average number of micturitions per 24 hours (about 12 per day at baseline) by 2.37 (5 mg) and 2.81 (10 mg), compared to a decrease of 1.59 with placebo. The drug also decreased the number of incontinence episodes (about 3 per day at baseline) by 1.63 (5 mg) and 1.57 (10 mg), compared to a decrease of 1.25 with placebo. The volume voided per micturition increased by a mean of 30.75 mL with 5 mg of the drug, by 35.99 mL with 10 mg, and by 10.67 mL with placebo.[2] In another large study that used tolterodine 2 mg twice daily as an active control, solifenacin was similarly more effective than placebo and slightly more effective than tolterodine.[3]