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Palladone (Hydromorphone Extended-release Capsules)

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-Please see Detail-Document #200915 for our updated opioid comparison chart-

What It Is
Palladone is a new oral extended-release hydromorphone product. It is intended for around-the-clock (ATC) administration in opioid-experienced patients requiring high potency analgesia for an extended period of time. It is the first long-acting hydromorphone product available in the U.S. Hydromorphone is a potent opioid mu receptor agonist producing analgesia as its primary therapeutic action. Other actions include anxiolysis, euphoria, and feelings of relaxation.¹

Indications
Palladone capsules are indicated for the management of persistent moderate to severe pain in patients requiring continuous ATC high-potency opioid pain relief for an extended period of time ranging from weeks to months or longer.¹,² It may be used in patients requiring a minimum total daily dose of oral opioid therapy equivalent to 12 mg of oral hydromorphone. These patients must have already received opioid therapy and demonstrated opioid tolerance. Opioid-tolerant patients are those who are taking at least one of the following:
• 60 mg of oral morphine per day,
• 30 mg of oral oxycodone per day,
• 8 mg of oral hydromorphone per day,
• or any other equianalgesic dose of another opioid for at least one week. It is not intended as initiation opioid therapy, short term use, or “as needed” therapy.¹

How Supplied - Cost
The extended-release Palladone capsules are available in 12 mg, 16 mg, 24 mg, and 32 mg strengths in bottles of 60 capsules.¹,³ The average wholesale product cost (AWP) per capsule is: $7.70/12 mg, $8.99/16 mg, $12.95/24 mg, and $16.71/32 mg.³

Product Formulation Considerations
Palladone capsules contain hydromorphone HCl in a pellet formulation which uses a controlled-release melt extrusion technology. Each pellet contains the same amount of hydromorphone with different capsule fill weights used to vary strengths. It is important to note that demonstrated dosage form proportionality on a dose-adjusted basis is three 12 mg capsules to one 32 mg capsule.¹

The terminal elimination half-life for controlled release hydromorphone is approximately 18.6 hours.¹ Palladone is formulated for once daily dosing. The capsules must not be crushed or altered in any way to assure maintenance of pellet integrity. Otherwise, rapid-release can result in hydromorphone overdose.¹

Adverse Effects
The most frequent adverse events reported in placebo-controlled clinical trials with an incidence of at least 2% were constipation, nausea, headache, somnolence, asthenia, vomiting, and pruritus.¹

Drug Interactions
As with other opioid agonists, concomitant administration of CNS depressants with Palladone may cause respiratory depression, hypotension, profound sedation, and may result in coma. Hydromorphone combined with skeletal muscle relaxants can enhance neuromuscular blockade and result in increased respiratory depression. Mixed agonist-antagonist opioid analgesics such as pentazocine, nalbuphine, and butorphanol should be administered with caution due to the potential for decreased hydromorphone analgesia and precipitation of withdrawal responses.
MAOIs should be discontinued at least 14 days prior to initiation of Palladone therapy. Palladone’s bioavailability is not significantly affected by food.\(^1\)

**Contraindications**

Palladone is contraindicated for “as needed” therapy, respiratory depression, acute or severe bronchial asthma, diagnoses of or suspected paralytic ileus, and those hypersensitive to hydromorphone or any components in Palladone.\(^1\)

**Precautions and Warnings**

Capsules must not be broken, chewed, opened, dissolved, or crushed because of the grave potential for fatal overdose. Palladone must only be used in opioid-tolerant patients. As with all CII opioid analgesics, there is increased risk and concern about misuse, abuse, addiction, and diversion. In the presence of head injury or intracranial lesions, Palladone’s respiratory depressant effects may be exaggerated and also mask neurological signs of increasing intracranial pressure. Orthostatic hypotension may occur in ambulatory patients. Cautious use of Palladone must occur in the presence of pancreatic or biliary tract disease. Palladone must not be used in patients with severe hepatic impairment and careful dosage selection is recommended for those with mild to moderate impairment. Lower dosages should be prescribed in patients with mild to moderate renal impairment. Palladone should be used with caution in patients with prior drug or alcohol abuse, adrenocortical insufficiency, debilitation, myxedema, hypothyroidism, prostatic hypertrophy, urethral stricture, and toxic psychosis.\(^3\)

**Use in Pregnancy**

Palladone is a Pregnancy Category C drug. There are no adequate and well-controlled studies in pregnant women. It should be used only if the need clearly outweighs the potential risks to the fetus.\(^1\)

**Dosage**

The dosage of Palladone is dependent on the patient’s past opioid experience, tolerance, and clinical considerations such as medical condition, co-morbidity factors, concomitant therapy, abuse history, and past pain control levels.\(^1\)

Please see Detail-Document #200915, Equianalgesic Dosing of Opioids for Pain Management,\(^4\) which has been updated to reflect Palladone dosing guidance.

Palladone extended-release capsules should be swallowed whole and are administered only once daily. All other ATC opioid products should be discontinued when initiating Palladone therapy. Patients may need immediate-release medication for breakthrough pain control or for pain prevention during certain periods of patient activity. Palladone can be administered with non-opioid analgesics or other adjuvant therapy as long as these are considered when selecting initial Palladone dosage.\(^1\)

When converting from other opioid analgesics to Palladone, monitoring for possible overdose or intolerance should occur. Monitoring for risks such as respiratory depression, altered mental status, and hypotension are essential. Because of Palladone’s prolonged elimination half-life (18 hours) overestimation of initial dose requires extended monitoring and treatment.\(^1\)

**Manufacturer**

Purdue Pharma L.P.
Stamford, CT 06901-3431
800-877-5666
www.purduepharma.com

**Commentary**

Palladone is the first extended-release hydromorphone product. Because of its release characteristics it provides dosing at 24 hour intervals and must be administered only once daily. It offers an additional choice for opioid-tolerant patients requiring ATC opioid analgesia.

Another product, Avinza, is an extended-release morphine formulation which is also administered only once daily at 24 hour intervals. Unlike Palladone, Avinza may be prescribed for opioid-naïve patients starting at the lowest dose of 30 mg once-daily.\(^5\) Equianalgesic daily doses of Palladone will cost slightly more (approximately one-third more) than Avinza.\(^3\)

Because Palladone is a potent Schedule II opioid agonist, it presents a high risk for fatal overdose and also potential abuse and diversion. Purdue Pharma with the approval of the FDA has a patient Medication Guide which must be dispensed with each Palladone prescription. It is
The following excerpts are reprinted from the September 24, 2004 FDA Talk Paper concerning FDA approval of Palladone and the development of an effective plan to reduce inappropriate use: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01315.html.

The active ingredient in Palladone, hydromorphone, is currently a Schedule II controlled substance, which is the highest level of control for drugs with a recognized medical use. Based on the risks associated with the drug, including the potential for abuse of Palladone, FDA has worked with the sponsor to develop a comprehensive risk management program (RMP).

The RMP was designed with three potential risk situations identified. These are the risks posed by improper dosing, indication, or patient selection; the risk posed by accidental pediatric exposure to the drug; and the risk posed by abuse or diversion of Palladone capsules.

As a controlled substance in Schedule II of the Controlled Substances Act (CSA), Palladone also comes under the jurisdiction of the Drug Enforcement Administration (DEA), which administers the CSA. Schedule II drugs are subject to manufacturing quotas set by DEA with input on medical need from FDA, distribution tracking, import and export controls, registration of prescribers and dispensers, and written prescriptions without refills.

In addition to the protection afforded patients through the status of Palladone as a controlled substance, the RMP includes provisions for clear and appropriate labeling, and appropriate education of healthcare professionals, patients, and caregivers. In addition, the sponsor has committed to offer appropriate training to sales representatives. To guard against the inappropriate use of the drug, the RMP also establishes a multifaceted program for monitoring and surveillance of abuse. If abuse, misuse, and diversion occur, the program includes an array of interventions.

As part of the RMP, a Medication Guide (FDA-approved patient information which is required to be dispensed with each prescription) has been written for patients prescribed Palladone. FDA requires a Medication Guide only when one or more of the following circumstances exists: (1) the drug is one for which patient labeling could help prevent serious adverse effects; (2) the drug is one that has serious risks of which patients should be made aware because information concerning the risks could affect patients’ decision to use, or continue to use the drug; and (3) the drug is important to health and patient adherence to directions for use is crucial to the drug’s effectiveness. In addition, the physician labeling for Palladone contains a “black box” warning.

FDA is also part of a larger initiative to reduce diversion and abuse of prescription drugs. On March 1, 2004, the Office of National Drug Control Policy was joined by the Surgeon General, the DEA Administrator, and the FDA Commissioner to announce the National Drug Control Strategy. The strategy emphasized new collaborative efforts at the federal, state, and local levels to prevent and reduce diversion and abuse of prescription drugs. This strategy focused on three core tactics: (1) Business Outreach and Consumer Protection, (2) Investigation and Enforcement, and (3) Protecting Safe and Effective Use of Medications. During the approval process for Palladone, FDA incorporated many of the elements of this strategy as exhibited by inclusion of the “black box” warnings on the labeling, the Medication Guide, and the implementation of a RMP.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

References
2. Anon. FDA approves new extended release pain medication: agency works with sponsor to develop an effective plan to reduce inappropriate use. FDA Talk Paper. September 24, 2004 (T04-40).
