HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PALLADONE safely and effectively. See full prescribing information for PALLADONE.

PALLADONE (hydromorphone HCl) extended-release capsule, for oral use, CII
Initial U.S. Approval: 1984

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- **PALLADONE exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow PALLADONE capsules whole to avoid exposure to a potentially fatal dose of hydromorphone. (5.2)**
- **Accidental consumption of PALLADONE, especially in children, can result in fatal overdose of hydromorphone. (5.2)**
- **Prolonged use of PALLADONE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking PALLADONE because co-ingestion can result in fatal plasma hydromorphone levels. (5.4)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	04/2014
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

----------INDICATIONS AND USAGE----------

PALLADONE is indicated for the management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid.

Limitations of Use (1)

- 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 PALLADONE 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.
- PALLADONE is not indicated as an as-needed (prn) analgesic.

----------DOSAGE AND ADMINISTRATION----------

- For once daily administration (2.1)
- Instruct patients to swallow PALLADONE capsules intact. (2.6)
- Do not abruptly discontinue PALLADONE. (2.3, 5.12)
- To convert to PALLADONE from another opioid, use available conversion factors to obtain estimated dose. (2.1)
- Dose can be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.(2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release capsules: 12 mg, 16 mg, 24 mg, and 32 mg (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients (4)
- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Narrowed or obstructed gastrointestinal tract (4)
- Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites (4)

----------WARNINGS AND PRECAUTIONS----------

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5)
- Hypotensive effect: Monitor during dose initiation and titration (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of PALLADONE in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions seen on initiation of therapy are: constipation, nausea, vomiting, somnolence, headache, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rhodes Pharmaceuticals L.P. at (1-888-827-0616); or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CNS depressants: Avoid use of PALLADONE with other drugs or substances having increased risk of respiratory depression. (7.2) Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with PALLADONE because they may reduce analgesic effect of PALLADONE or precipitate withdrawal symptoms. (5.12, 7.3)
- Monoamine oxidase inhibitors (MAOIs): Avoid use of PALLADONE in patients taking MAOIs or within 14 days of stopping such treatment. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: PALLADONE is not recommended. Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: PALLADONE is not recommended. Hydromorphone has been detected in human milk. Closely monitor infants of nursing women receiving PALLADONE. (8.3)
- Hepatic or renal impairment: Administer a reduced dose of PALLADONE in patients with moderate hepatic (8.6) and moderate renal impairment (8.7). Consider use of an alternate analgesic in patients with severe hepatic (8.6) and renal impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

Addiction, Abuse, and Misuse

PALLADONE exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing PALLADONE, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of PALLADONE. Monitor for respiratory depression, especially during initiation of PALLADONE or following a dose increase. Instruct patients to swallow PALLADONE capsules whole; crushing, chewing, or dissolving PALLADONE capsules can cause rapid release and absorption of a potentially fatal dose of hydromorphone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of PALLADONE, especially by children, can result in a fatal overdose of hydromorphone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PALLADONE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking PALLADONE. The co-ingestion of alcohol with PALLADONE may result in increased plasma levels and a potentially fatal overdose of hydromorphone *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

PALLADONE is indicated for the management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid.

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 PALLADONE 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.
- PALLADONE is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

PALLADONE should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Due to the risk of respiratory depression, PALLADONE is only indicated for use in patients who are already opioid-tolerant. Discontinue or taper all other extended-release opioids when beginning PALLADONE therapy. As PALLADONE is only for use in opioid-tolerant patients, do not begin any patient on PALLADONE as the first opioid.

Patients considered opioid-tolerant are those who are taking at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Initiate the dosing regimen for each patient individually; taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with PALLADONE *[see Warnings and Precautions (5.2)]*.

PALLADONE extended-release capsules must be taken whole. Crushing, chewing, or dissolving PALLADONE capsules will result in uncontrolled delivery of hydromorphone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Conversion from Other Oral Opioids to PALLADONE

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

While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient’s 24-hour oral hydromorphone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydromorphone requirements which could result in adverse reaction.

In a PALLADONE clinical trial with an open-label titration period, patients were converted from their prior opioid to PALLADONE using the Table 1 as a guide for the initial PALLADONE dose. The recommended starting dose of PALLADONE is 50% of the calculated estimate of daily hydromorphone requirement. Calculate the estimated daily hydromorphone requirement using **Table 1**.

Consider the following when using the information in **Table 1**:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** PALLADONE.
- The table **cannot** be used to convert **from** PALLADONE to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

Table 1.
Conversion Factors to PALLADONE[*]

Prior Oral Opioid	Approximate Oral Conversion Factor
Hydromorphone	1.00
Codeine	0.04
Hydrocodone	0.22
Methadone[†]	0.38
Morphine	0.12
Oxycodone	0.25

To calculate the estimated PALLADONE dose using Table 1:

- For patients on a single opioid, 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 hydromorphone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydromorphone dose for each opioid and sum the totals to obtain the approximate total hydromorphone daily dose.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate PALLADONE strength(s) available.

Example conversion from a single opioid to PALLADONE:

Step 1: Sum the total daily dose of the opioid
- 30 mg of oxycodone 2 times = 60 mg total daily dose of oxycodone

Step 2: Calculate the approximate equivalent dose of oral hydromorphone based on the total daily dose of the current opioid using Table 1
- 60 mg total daily dose of oxycodone x Conversion Factor of 0.25 =15 mg of oral hydromorphone daily

Step 3: Calculate the approximate starting dose of PALLADONE to be given every 24 hours, which is 50% of the calculated oral hydromorphone dose. Round down, if necessary, to the appropriate PALLADONE capsule strengths available.
- 50 % of 15 mg is an initial dose of 6 mg of PALLADONE once daily
- Adjust individually for each patient

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to PALLADONE.

Conversion from Transdermal Fentanyl to PALLADONE

Eighteen hours following the removal of the transdermal fentanyl patch, PALLADONE treatment can be initiated. To calculate the 24-hour PALLADONE dose, use a conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of PALLADONE. Then reduce the PALLADONE dose by 50%.

For example:

Step 1: Identify the dose of transdermal fentanyl.

- 75 mg of transdermal fentanyl

Step 2: Use the conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of PALLADONE.

- 75 mg of transdermal fentanyl : 36 mg total daily dose of PALLADONE

Step 3: Calculate the approximate starting dose of PALLADONE to be given every 24 hours, which is 50% of the converted dose. Round down, if necessary, to the appropriate PALLADONE tablet strengths available.

- 50% of 36 mg results in an initial dose of 18 mg, which would be rounded down to 16 mg of PALLADONE once daily
- Adjust individually for each patient

Conversion from Methadone to PALLADONE

Close monitoring is of particular importance 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 can accumulate in the plasma.

2.2 Titration and Maintenance of Therapy

Individually titrate PALLADONE to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving PALLADONE to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

Plasma levels of PALLADONE are sustained for 18 to 24 hours. Dosage adjustments of PALLADONE may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.

Patients who experience breakthrough pain may require a dose increase of PALLADONE, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the PALLADONE dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Discontinuation of PALLADONE

When a patient no longer requires therapy with PALLADONE, taper doses gradually, by 25% to 50% every 2 or 3 days down to a dose of 12 mg before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the opioid-tolerant patient.

To dispose of unused PALLADONE flush all remaining capsules down the toilet or remit to authorities at a certified drug take-back program.

2.4 Hepatic Impairment

Start patients with moderate hepatic impairment on 25% of the PALLADONE dose that would be prescribed for patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with PALLADONE and during dose titration. Use of alternate analgesics is recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.5 Renal Impairment

Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the PALLADONE dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with PALLADONE and during dose titration. As PALLADONE is only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment *[see Use in Specific Populations (8.7)]*.

2.6 Administration of PALLADONE

Instruct patients to swallow PALLADONE capsules intact. The capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of hydromorphone *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

PALLADONE extended-release capsules are available in 12 mg, 16 mg, 24 mg or 32 mg dosage strengths.

The 12 mg extended-release capsules are cinnamon-colored capsules imprinted with “P-XL” on the cap and “12 mg” on the body.

The 16 mg extended-release capsules are pink, imprinted with "P-XL" on the cap and 16 mg on the body.

The 24 mg extended-release capsules are blue, imprinted with "P-XL" on the cap and 24 mg on the body.

The 32 mg extended-release capsules are white, imprinted with "P-XL" on the cap and 32 mg on the body.

4 CONTRAINDICATIONS

PALLADONE is contraindicated in:

- Opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant.
- Patients with significant respiratory depression
- Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Patients with known or suspected paralytic ileus
- Patients who have had surgical procedures and/or underlying disease resulting in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction.
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite-containing medications *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

PALLADONE contains hydromorphone, a Schedule II controlled substance. As an opioid, PALLADONE exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as PALLADONE deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydromorphone present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed PALLADONE and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing PALLADONE, and monitor all patients receiving PALLADONE for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of PALLADONE for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as PALLADONE,

but use in such patients necessitates intensive counseling about the risks and proper use of PALLADONE along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of PALLADONE by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of hydromorphone and can result in overdose and death *[see Overdosage (10)]*.

Opioid agonists such as PALLADONE are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing PALLADONE. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of PALLADONE, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with PALLADONE and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of PALLADONE are essential *[see Dosage and Administration (2)]*. Overestimating the PALLADONE dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of PALLADONE, especially by children, can result in respiratory depression and death due to an overdose of hydromorphone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of PALLADONE during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if PALLADONE is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of PALLADONE in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin PALLADONE is made, start with 1/3 to ½ the calculated starting dose of PALLADONE, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*.

5.5 Use In Ederly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating PALLADONE and when PALLADONE is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2*) and (5.5)].

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with PALLADONE, as in these patients, even usual therapeutic doses of PALLADONE may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Hypotensive Effect

PALLADONE may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7.2)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of PALLADONE.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking PALLADONE who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with PALLADONE. PALLADONE may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of PALLADONE in patients with impaired consciousness or coma.

5.9 Use In Patients with Gastrointestinal Conditions

PALLADONE is contraindicated in patients with paralytic ileus. Avoid the use of PALLADONE in patients with other GI obstruction.

Because the PALLADONE capsule is nondeformable and does not appreciably change in shape in the GI tract, PALLADONE is contraindicated in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel’s diverticulum). There have been reports of obstructive symptoms in patients with known strictures or risk of strictures, such as previous GI surgery, in association with the ingestion of drugs in nondeformable extended-release formulations.

It is possible that PALLADONE capsules may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

The hydromorphone in PALLADONE may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.10 Sulfites

PALLADONE contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.11 Use in Patients with Convulsive or Seizure Disorders

The hydromorphone in PALLADONE may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during PALLADONE therapy.

5.12 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonists (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including PALLADONE. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7.3)]*.

When discontinuing PALLADONE, gradually taper the dose *[see Dosage and Administration (2.3)]*. Do not abruptly discontinue PALLADONE.

5.13 Driving and Operating Machinery

PALLADONE may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of PALLADONE and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive Effect *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trial Experience

The safety of PALLADONE was evaluated in double-blind clinical trials involving 612 patients with moderate to severe pain. An open-label extension study involving 143 patients with cancer pain was conducted to evaluate the safety of PALLADONE when used for longer periods of time in higher doses than in the controlled trials. Patients were treated with doses averaging 40 to 50 mg of PALLADONE per day (ranging between 12 and 500 mg/day) for several months (range 1 to $\geq$ 52 weeks).

Serious adverse reactions which may be associated with PALLADONE therapy in clinical use are similar to those of other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and to a lesser degree, circulatory depression, hypotension, shock or cardiac arrest *[see Overdosage (10)]*.

Adverse Events Reported in Controlled Trials

Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in the placebo-controlled trials for which the rate of occurrence was greater for those treated with PALLADONE 12 mg capsules than those treated with placebo.

Table 2. Adverse Events Reported in the Placebo-Controlled Clinical Trials with Incidence ≥2% in Patients Receiving PALLADONE Capsules for Nonmalignant Pain

Body System / Adverse Event (COSTART Terminology)	Placebo* (N=191) Double-blind %	PALLADONE* (N=190) Double-blind %
Total percentage of patients with AEs	**35.1%**	**49.5%**
Body as a Whole	15.7%	18.4%
Headache	2.1%	4.7%
Asthenia	0.5%	3.2%
Infection	5.8%	5.3%
Digestive System	**13.1%**	**27.9%**
Constipation	1.0%	15.8%
Nausea	6.3%	10.5%
Vomiting	1.6%	3.2%
Nervous System	**13.1%**	**11.6%**
Somnolence	1.6%	4.7%
Skin	**5.2%**	**4.7%**
Pruritus	1.0%	2.6%

*** Average exposure was 21 days for** PALLADONE and 15 days for placebo.

Adverse Events Observed in Clinical Trials

PALLADONE has been administered to 785 individuals during completed clinical trials. The conditions and duration of exposure to PALLADONE varied greatly, and included open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing.

These categories are used in the listing below. The frequencies represent the proportion of 785 patients from these trials who experienced that event while receiving PALLADONE. All adverse events included in this tabulation occurred in at least one patient. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; adverse events occurring with an incidence less than 1% are considered infrequent. These adverse events are not necessarily related to PALLADONE treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Frequent Adverse Events

*Body as a Whole***:** headache, asthenia, pain, abdominal pain, fever, chest pain, infection, chills, malaise, neck pain, carcinoma, accidental injury

*Cardiovascular System***:** vasodilatation, tachycardia, migraine

*Digestive System***:** nausea, constipation, vomiting, diarrhea, dyspepsia, anorexia, dry mouth, nausea and vomiting, dysphagia, flatulence

Hemic and Lymphatic System: anemia, leukopenia

*Metabolic and Nutritional Disorders***:** peripheral edema, dehydration, edema, generalized edema, hypokalemia, weight loss

*Musculoskeletal***:** arthralgia, bone pain, leg cramps, myalgia

*Nervous System***:** somnolence, dizziness, nervousness, confusion, insomnia, anxiety, depression, hypertonia, hypesthesia, paresthesia, tremor, thinking abnormal, hallucinations, speech disorder, agitation, amnesia, tinnitus, abnormal gait

*Respiratory System***:** dyspnea, cough increased, rhinitis, pharyngitis, pneumonia, epistaxis, hiccup, hypoxia, pleural effusion

*Skin and Appendages***:** pruritus, sweating, rash

*Special Senses***:** amblyopia, taste perversion

*Urogenital System***:** dysuria, urinary incontinence

Infrequent Adverse Events

*Body as a Whole***:** face edema, ascites, allergic reaction, cellulitis, overdose, hypothermia, neoplasm, photosensitivity reaction, sepsis, flank pain

*Cardiovascular System***:** hypertension, hypotension, syncope, deep thrombophlebitis, arrhythmia, postural hypotension, atrial fibrillation, pallor, bradycardia, electrocardiogram abnormal, myocardial infarction, palpitation, angina pectoris, congestive heart failure, QT interval prolonged, supraventricular tachycardia, thrombosis, cardiomegaly, hemorrhage

*Digestive System***:** fecal impaction, intestinal obstruction, abnormal stools, fecal incontinence, hepatic failure, increased appetite, cholangitis, cholecystitis, colitis, enterocolitis, hepatomegaly, jaundice, liver function tests abnormal, biliary spasm, ileus, eructation, rectal hemorrhage, esophagitis, glossitis, melena, mouth ulceration, gastrointestinal hemorrhage, tongue edema

Endocrine: adrenal cortex insufficiency

Hemic and Lymphatic System: ecchymosis, thrombocytopenia, leukocytosis, lymphadenopathy, agranulocytosis, lymphoma like reaction, pancytopenia, petechia

*Metabolic and Nutritional Disorders***:** hyperglycemia, hyponatremia, cachexia, hypercalcemia, hypomagnesemia, cyanosis, diabetes mellitus, gout, respiratory acidosis, elevated liver enzymes, thirst

*Musculoskeletal***:** myasthenia

*Nervous System***:** abnormal dreams, emotional lability, paranoid reaction, sleep disorder euphoria, incoordination, stupor, ataxia, convulsion, hallucination, hostility, myoclonus, psychosis, vertigo, withdrawal syndrome, apathy, delirium, dementia, drug dependence, nystagmus, twitching, depersonalization, aphasia, cerebrovascular accident, circumoral parasthesia, seizure, hyperkinesia, hypotonia, increased salivation, neuralgia

*Respiratory System***:** hypoventilation, apnea, atelectasis, hemoptysis, asthma, hyperventilation, pulmonary embolus, laryngismus

*Skin and Appendages***:** urticaria, maculopapular rash, alopecia

Special Senses: abnormal vision, diplopia, dry eyes, lacrimation disorder, hyperacusis

Urogenital: urinary retention, hematuria, impotence, urinary frequency, urination impaired, dysmenorrhea, creatinine increased, urinary urgency

Additional Adverse Events From Non-U.S. Experience

Addiction, blurred vision, drowsiness, dysphoria, sedation, seizure, physical dependence, biliary spasm, and ileus

7 DRUG INTERACTIONS

7.1 Alcohol

Concomitant use of alcohol with PALLADONE can result in an increase of hydromorphone plasma levels and potentially fatal overdose of hydromorphone. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on PALLADONE therapy *[see Clinical Pharmacology (12.3)]*.

7.2 CNS Depressants

The concomitant use of PALLADONE with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and PALLADONE for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2)* and *Warnings and Precautions (5.4*)].

7.3 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of PALLADONE and/or may precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist analgesics in patients receiving PALLADONE.

7.4 Monoamine Oxidase Inhibitors (MAOIs)

The effects of opioid analgesics may be potentiated by MAOIs. PALLADONE is not recommended for use in patients who have received MAOIs within 14 days. If concurrent therapy with an MAOI and PALLADONE is unavoidable, monitor patients for increased respiratory and central nervous system depression.

7.5 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with PALLADONE 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 or reduced gastric motility when PALLADONE is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Teratogenic Effects - Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. PALLADONE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydromorphone was not teratogenic in female rats given oral doses up to 10 mg/kg or female rabbits given oral doses up to 50 mg/kg during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 3-fold and 6-fold higher than a 32 mg human daily oral dose based on exposure ($AUC_{0\text{-}24h}$).

Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenicity likely the result of maternal toxicity associated with sedation and hypoxia. In Syrian hamsters given single subcutaneous doses from 14 to 278 mg/kg during organogenesis (gestation days 8 to10), doses ≥ 19 mg/kg hydromorphone produced skull malformations (exencephaly and cranioschisis). Continuous infusion of hydromorphone (5 mg/kg, s.c.) via implanted osmotic mini pumps during organogenesis (gestation days 7 to10) produced soft tissue malformations (cryptorchidism, cleft palate, malformed ventricals and retina), and skeletal variations (supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were at doses approximately 3-fold higher and <1-fold lower, respectively, than a 32 mg human daily oral dose on a body surface area basis.

Nonteratogenic Effect

In a rat pre- and post-natal study, an increase in pup mortality and a decrease in pup body weight which was associated with maternal toxicity was observed at doses of 2 and 5 mg/kg/day. The maternal no effect level for hydromorphone was 0.5 mg/kg/day which is <1-fold lower than a 32 mg human daily oral dose on a body surface area. Hydromorphone had no effect on pup development or reproduction when given to female rats during the pre-natal and postnatal periods up to a dose of 5 mg/kg which is equivalent to a 32 mg human daily oral dose on a body surface area basis.

Neonates born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Approaches to the treatment of the syndrome have included supportive care and, if indicated, drugs such as paregoric or phenobarbital.

8.2 Labor and Delivery

PALLADONE is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate [*see Indications and Usage (1)]*. Occasionally, opioid analgesics may prolong labor by temporarily reducing the strength, duration, and frequency of uterine contractions. However, these effects are not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. An opioid antagonist, such as naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate in such situations.

8.3 Nursing Mothers

Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Nursing should not be undertaken while a patient is receiving PALLADONE since hydromorphone is excreted in the milk.

8.4 Pediatric Use

The safety and effectiveness of PALLADONE in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

Elderly patients have been shown to be more sensitive to the adverse effects of opioids compared to the younger population. Of the total number of subjects in clinical studies of Palladone, 22% were 65 and over, and 6% were 75 and over. Dosages should be adjusted according to the clinical situation. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. Therefore, closely monitor elderly patients for respiratory and central nervous system depression when prescribing PALLADONE, particularly during initiation and titration.

8.6 Hepatic Impairment

PALLADONE was not studied in patients with severe hepatic impairment and are not recommended for use in such patients. Care in initial dose selection and careful observation are recommended in patients with evidence of mild to moderate hepatic impairment.

8.7 Renal Impairment

In patients with mild to moderate renal impairment, based on calculated creatinine clearance, the concentrations of hydromorphone in plasma were slightly higher than in subjects with normal renal function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

PALLADONE contains hydromorphone, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. PALLADONE can be abused and is subject to misuse, abuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

PALLADONE, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of PALLADONE

PALLADONE is intended for oral use only. Abuse of PALLADONE poses a risk of overdose and death. This risk is increased with concurrent abuse of PALLADONE with alcohol and other substances.

Taking cut, broken, chewed, crushed, or dissolved PALLADONE poses a hazard of overdose and death.

With intravenous abuse, the capsule excipients, especially polyethylene oxide, can be expected to result in necrosis and inflammation of cardiac tissues. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid

antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine) or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

PALLADONE should not be abruptly discontinued *[see Dosage and Administration (2.3)]*. If PALLADONE is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1, 8.2)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes pulmonary edema, bradycardia, hypotension and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, such as naloxone and naltrexone, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. Such agents should be administered cautiously to patients who are known, or suspected to be, physically dependent on PALLADONE. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

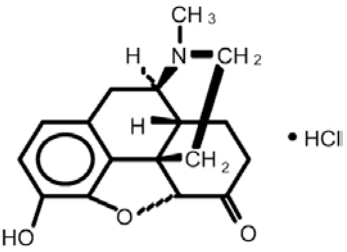
Because the duration of reversal would be expected to be less than the duration of action of hydromorphone in PALLADONE, carefully monitor the patient until spontaneous respiration is reliably re-established. PALLADONE will continue to release hydromorphone adding to the hydromorphone load for up to 24 hours after administration, necessitating prolonged monitoring for at least 24 to 48 hours beyond the overdose. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

PALLADONE extended-release capsules are for oral use and contain hydromorphone hydrochloride, a mu-opioid.

Hydromorphone hydrochloride USP is 4,5α-epoxy-3-hydroxy-17-methlymorphinan-6-one hydrochloride. Hydromorphone hydrochloride is a white or almost white crystalline powder that is freely soluble in water, very slightly soluble in ethanol (96%), and practically insoluble in methylene chloride. Its empirical formula is $C_{17}H_{19}NO_3$•HCl. The compound has the following structural formula:



($C_{17}H_{19}NO_3$•HCl) MW 321.80

PALLADONE also contains the following inactive ingredients: ammonio methacrylate copolymer type B, ethylcellulose, and stearyl alcohol, synthetic black iron oxide, gelatin, red iron oxide (12 mg & 16 mg only), FD&C Blue No. 2 (24 mg only), and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine. Hydromorphone is principally an agonist of mu-receptors, showing a weak affinity for κ-receptors. Comparing relative binding affinity for mu- and κ-opioid receptors, hydromorphone binds more specifically to mu- receptors than structurally related morphine. As an opioid agonist, the principle therapeutic action of hydromorphone is analgesia. The precise mechanism of action of opioid analgesics is not known but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS). Interaction with the mu-opioid receptor subtype is believed to be responsible for most of hydromorphone's clinical effects. There is no intrinsic limit to the analgesic effect of hydromorphone. Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, sedation, nausea, and vomiting, which can result from high doses.

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction
Additive pharmacodynamic effects may be expected when PALLADONE is used in conjunction with alcohol, other opioids, legal or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System
Hydromorphone produces dose-related respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Hydromorphone depresses the cough reflex by direct effect on the cough center in the medulla.

Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic. Marked mydriasis, rather than miosis, may be seen due to severe hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Gastric, biliary and pancreatic secretions are decreased by hydromorphone. Hydromorphone causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm. The end result is constipation. Hydromorphone also can cause an increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects on the Cardiovascular System
Hydromorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by hydromorphone and can contribute to opioid-induced hypotension.

Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

Effects on the Endocrine System
Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

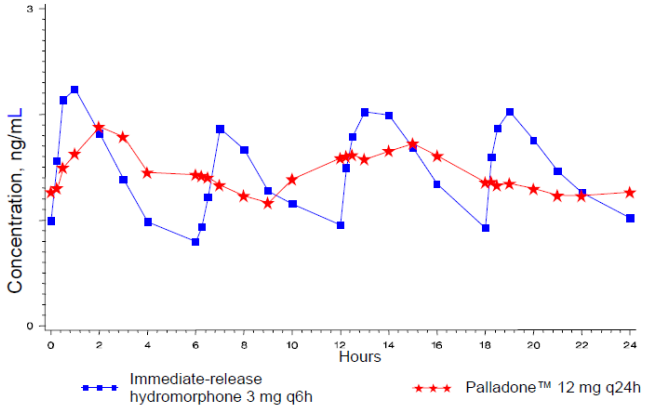
Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

12.3 Pharmacokinetics

Absorption
PALLADONE is an extended-release formulation of hydromorphone. Administration of a single PALLADONE dose is characterized by biphasic absorption, a relatively rapid rise to an initial peak concentration, followed by a second broader peak with therapeutic plasma concentrations maintained over the 24-hour dosing interval. The absolute bioavailability of hydromorphone from PALLADONE has not been determined. Under conditions of multiple dosing, the bioavailability of a once-daily dose of PALLADONE is equivalent to the same total daily dose of immediate-release hydromorphone given in divided doses every 6 hours. Dose proportionality has been established in terms of C_{max} and AUC for the 12 mg and 24 mg dosage strengths. Dosage form proportionality on a dose-adjusted basis has been demonstrated for three 12 mg capsules to one 32 mg capsule.

In a study comparing 12 mg PALLADONE dosed every 24 hours to 3 mg of immediate-release hydromorphone dosed every 6 hours in healthy human subjects, the two treatments were found to be equivalent in terms of extent of absorption (AUC) (see Figure 1). The extended-release characteristics of PALLADONE resulted in lower steady-state peak levels (C_{max}), higher trough levels (C_{min}), and an approximately twofold to threefold reduction in the fluctuation seen with the immediate-release hydromorphone tablets.

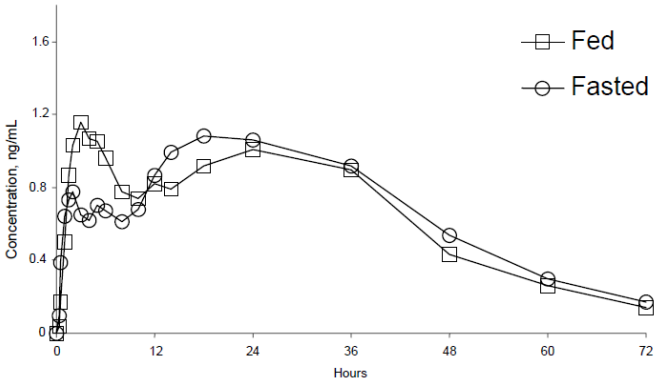
FIGURE 1. Steady-State Plasma Hydromorphone Concentration-Time Curves



Steady-state plasma concentrations with PALLADONE were achieved within 2 to 3 days after initiation of dosing. This is consistent with the mean apparent terminal elimination half-life for PALLADONE of approximately 18.6 hours. Hydromorphone did not accumulate significantly after multiple dosing with once-daily administration.

Food had no significant effect on the peak (C_{max}), AUC or the elimination of hydromorphone from PALLADONE (see Figure 2).

FIGURE 2. Single-Dose Palladone™ Pharmacokinetic Profiles



Food Effect
The pharmacokinetics of PALLADONE is not affected by food as indicated by bioequivalence when administered under fed and fasting conditions. Therefore, PALLADONE may be administered without regard to meals.

Distribution
Following intravenous administration of hydromorphone, the reported volume of distribution is 295 L (4 L/kg). Hydromorphone is approximately 20% bound to human plasma proteins.

Metabolism
Hydromorphone is metabolized by direct conjugation, or by 6-keto reduction followed by conjugation. Following absorption, hydromorphone is metabolized to the major metabolites hydromorphone-3-glucuronide, hydromorphone-3-glucoside and dihydroisomorphine-6-glucuronide. Also observed were the less prevalent metabolites, dihydroisomorphine-6-glucoside, dihydromorphine and dihydroisomorphine.

Hydromorphone metabolites have been found in plasma, urine and in human hepatocyte test systems. However, it is not known whether hydromorphone is metabolized by the cytochrome P450 enzyme system. Hydromorphone is a poor inhibitor of human recombinant CYP isoforms including CYP1A2, 2A6, 2C8, 2D6, and 3A4 with an IC50 > 50 µM. Therefore, hydromorphone is not expected to inhibit the metabolism of other drugs metabolized by these CYP isoforms.

Specific Populations

Geriatric Patients
Age-related increases in exposure in clinical studies were observed between geriatric and younger adult subjects. Greater sensitivity of some older individuals cannot be excluded. Dosages should be adjusted according to the clinical situation.

Pediatric Patients
The safety and effectiveness of PALLADONE have not been established in patients below the age of 18.

Gender
Pharmacokinetics of hydromorphone from PALLADONE is comparable in men and women.

Race
The pharmacokinetics of hydromorphone in African Americans and Caucasians in the clinical population were comparable.

Hepatic Impairment

PALLADONE was not studied in patients with severe hepatic insufficiency and is not recommended for use in such patients. Start patients with moderate hepatic impairment on 25% of the usual dose of PALLADONE and closely monitor for respiratory and central nervous system depression during dose titration. Consider alternate analgesic therapy for patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Specific Populations (8.6)]*.

Renal Impairment

In patients with mild renal impairment, based on calculated creatinine clearance, the concentrations of hydromorphone in plasma were slightly higher than in subjects with normal renal function. Start patients with moderate renal impairment on 50% of the usual PALLADONE dose for patients with normal renal function and closely monitor for respiratory and central nervous system depression during dose titration. As PALLADONE is only intended for once-daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Drug Interaction/Alcohol Interaction

A pharmacokinetic study in healthy subjects showed that co-ingestion of a 12 mg PALLADONE capsule with 240 mL (8 ounces) of 40% (80 proof) alcohol resulted in an average peak hydromorphone concentration approximately six times greater than when taken with water. One subject in this study experienced a 16-fold increase when the drug was ingested with 40% alcohol compared with water. In certain subjects, 8 ounces of 4% alcohol (equivalent to 2/3 of a typical serving of beer) resulted in almost twice the peak plasma hydromorphone concentration than when the drug was ingested with water.

This pharmacokinetic study was an open-label, four-arm, crossover design study and included twenty-four healthy adult subjects who were tested under fasted conditions and 24 healthy adult subjects who were tested under standardized fed conditions. Subjects were pretreated with naltrexone to block the opiate effects, and then administered one of the following four treatments:

Group A PALLADONE, 12 mg + 240 mL of 40% ethanol
Group B PALLADONE, 12 mg + 240 mL of 20% ethanol
Group C PALLADONE, 12 mg + 240 mL of 4% ethanol
Group D PALLADONE, 12 mg + 240 mL of water

Plasma was sampled and analyzed for hydromorphone concentration at appropriate intervals. Each subject received each of the four treatments, thereby acting as his or her own control (Group D).

The effects of alcohol co-ingestion were more marked in the fasted state and are summarized below.

Pharmacokinetic Outcomes Resulting from Co-ingestion of PALLDONE with Different Concentrations of Alcohol (fasted state)

		Ratio 40*	Ratio 20**	Ratio 4†
C_{max}‡	Mean	6	2	1
	Range	1 to 16	1 to 6	1 to 2
AUC***	Mean	1.3	1	1
	Range	0.6 to 3.4	0.4 to 1.5	0.5 to 1.9

*Ratio of values when co-ingested with 240 mL of 40% ethanol compared to co-ingestion with 240 mL of water, i.e. if the peak plasma concentration was 6 ng/mL when administered with alcohol and 1 ng/mL when administered with water, this ratio would be 6
**Ratio of values (as above) when co-ingested with 240 mL of 20% ethanol compared to co-ingestion with 240 mL of water
†Ratio of values (as above) when co-ingested with 240 mL of 4% ethanol compared to co-ingestion with 240 mL of water
‡Peak plasma concentration
***Measure of total drug exposure

In the fed state, the mean peak plasma concentration ratio (40% alcohol:water) was 3.5 with a maximum of 6.

In summary, the study showed that ingesting PALLADONE with alcohol in clinically relevant amounts results in significantly higher peak plasma concentrations of hydromorphone. The effect is more pronounced with increasing concentrations of alcohol and in a fasted state.

The effects of co-ingestion of smaller volumes and with other concentrations of alcohol have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No carcinogenicity studies have been conducted in animals.

Hydromorphone was negative in the *in vitro* bacterial reverse mutation assay and in the *in vivo* mouse micronucleus assay. Hydromorphone was negative in the mouse lymphoma assay in the absence of metabolic activation, but was positive in the mouse lymphoma assay in the presence of metabolic activation. Morphinone, an impurity, tested as a besylate salt was negative in the *in vitro* bacterial reverse mutation assay and negative in the *in vivo* mouse micronucleus assay. Morphinone was positive in the Chinese Hamster Ovary Cell Chromosomal Aberration test in the absence and presence of metabolic activation.

Hydromorphone did not affect fertility in rats at oral doses up to 5 mg/kg which is equivalent to a 32 mg human daily oral dose on a body surface area basis.

Mutagenesis: Hydromorphone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the *in vitro* human lymphocyte chromosome aberration assay or the *in vivo* mouse micronucleus assay.

Impairment of Fertility: Hydromorphone given orally to rats during the mating period caused a slight but statistically significant reduction in implantations at 6.25 mg/kg/day (~1.2 times the human exposure following to 32 mg/day).

14 CLINICAL STUDIES

The efficacy of PALLADONE was established in a double-blind, randomized, parallel group, multicenter, placebo-controlled, four-week trial of patients with pain that was present for at least one month. The majority of these patients experienced moderate to severe pain due to musculoskeletal disorders while maintained on one or more opioid analgesics, often in addition to non-opioid analgesics. Two hundred twenty-one patients with chronic moderate to severe pain were randomized to receive once daily 12 mg PALLADONE capsule or placebo after they had demonstrated that they needed approximately 12 mg of immediate-release hydromorphone (in addition to non-opioid medication) around-the-clock to improve their pain control. Patients randomized to PALLADONE maintained adequate analgesia for a significantly longer period of time ($P<0.0001$) than patients randomized to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

PALLADONE (hydromorphone hydrochloride) extended-release capsules are supplied as follows:

12 mg: cinnamon-colored capsules imprinted with "P-XL" on the cap and "12 mg" on the body and available as follows:

60 capsules, opaque plastic bottle .....…….	**NDC** 42858-008-06
20 capsules, Unit Dose (2 X 10) .....…….	**NDC** 42858-008-11

16 mg: pink-colored capsules imprinted with "P-XL" on the cap and "16 mg" on the body and available as follows:

60 capsules, opaque plastic bottle .....…….	**NDC** 42858-027-06
20 capsules, Unit Dose (2 X 10) .....…….	**NDC** 42858-027-11

24 mg: blue-colored capsules imprinted with "P-XL" on the cap and "24 mg" on the body and available as follows:

60 capsules, opaque plastic bottle .....……. **NDC** 42858-039-06

20 capsules, Unit Dose (2 X 10) .....……. **NDC** 42858-039-11

32 mg: white capsules imprinted with "P-XL" on the cap and "32 mg" on the body and available as follows:

60 capsules, opaque plastic bottle .....……. **NDC** 42858-204-06

20 capsules, Unit Dose (2 X 10) .....……. **NDC** 42858-204-11

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Avoid temperatures above 40°C (104°F) [See USP Excessive Heat]

Dispense in a tight, light-resistant container.

CAUTION

DEA ORDER FORM REQUIRED.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of PALLADONE, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share PALLADONE with others and to take steps to protect PALLADONE from theft or misuse.

Life-threatening Respiratory Depression

Inform patients of the risk of life-threatening of respiratory depression, including information that the risk is greatest when starting PALLADONE or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store PALLADONE securely and to dispose of unused PALLADONE by flushing the capsules down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of PALLADONE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if PALLADONE is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take PALLADONE, including the following:

- Swallowing PALLADONE whole
- Not crushing, chewing, splitting or dissolving the capsule
- Using PALLADONE exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing PALLADONE without first discussing the need for a tapering regimen with the prescriber

Gastrointestinal Blockage

Advise patients that people with certain stomach or intestinal problems such as narrowing of the intestines or previous surgery may be at higher risk of developing a blockage. Symptoms include abdominal distension, abdominal pain, severe constipation, or vomiting. Instruct patients to contact their healthcare provider immediately if they develop these symptoms.

Hypotension

Inform patients that PALLADONE may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that PALLADONE may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in PALLADONE. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that PALLADONE can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Disposal

Advise patients to flush the unused capsules down the toilet when PALLADONE is no longer needed.

Marketed by:
Rhodes Pharmaceuticals L.P.
Coventry, RI 02816

Manufactured by:
The PF Laboratories Inc.
Totowa, New Jersey, 07512

U.S. Patent Numbers 5,958,452; 5,965,161; 5,968,551, 6,294,195, 6,335,033; 6,706,281

303260-0A

Revision: March 2014

Medication Guide
PALLADONE (pal-a-d-own) (hydromorphone hydrochloride) extended-release capsules, CII

PALLADONE is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, in people who are already regularly using opioid pain medicine, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about PALLADONE:

- **Get emergency help right away if you take too much PALLADONE (overdose).** When you first start taking PALLADONE, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
- Never give anyone your PALLADONE. They could die from taking it. Store PALLADONE away from children and in a safe place to prevent stealing or abuse. Selling or giving away PALLADONE is against the law.

Do not take PALLADONE if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking PALLADONE, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- allergy to sulfites
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of PALLADONE during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding**. PALLADONE passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking PALLADONE with certain other medicines can cause serious side effects.

When taking PALLADONE:

- Do not change your dose. Take PALLADONE exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow PALLADONE whole. Do not cut, break, chew, crush, dissolve, snort, or inject PALLADONE because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking PALLADONE without talking to your healthcare provider.**
- After you stop taking PALLADONE, flush any unused tablets down the toilet.

While taking PALLADONE DO NOT:

- Drive or operate heavy machinery until you know how PALLADONE affects you. PALLADONE can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with PALLADONE may cause you to overdose and die.

The possible side effects of PALLADONE are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of PALLADONE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured for: Rhodes Pharmaceuticals L.P., or call 1-888-827-0616