

**Controlled Substance Staff (CSS) Abuse Liability Analysis of  
Palladone (hydromorphone hydrochloride extended release capsules)  
12 mg, 16 mg, 24 mg and 32 mg**

Hydromorphone hydrochloride has been marketed in an immediate release tablet formulation, Dilaudid, in the United States for many years. Dilaudid, available in 2mg, 4mg and 8-mg strengths, is indicated for the treatment of moderate to severe pain. Palladone represents a new extended release formulation of hydromorphone which is under review by the FDA for the management of chronic moderate to severe pain in patients requiring continuous around-the-clock opioid analgesia for an extended period of time. The sponsor proposes capsules containing 12 mg, 16 mg, 24 mg and 32 mg to release hydromorphone over 24 hours and to be administered once per day. The proposed label specifies that Palladone is to be administered in opioid-tolerant patients only.

Palladone SR, hydromorphone hydrochloride modified release capsules (2 mg, 4 mg, 8 mg, 16 mg and 24 mg) are approved in the United Kingdom for the "treatment of severe pain in cancer patients." In Canada, Palladone XL controlled release capsules are available in 12 mg, 16 mg, 24 mg and 32 mg strengths and approved for "the relief of severe pain requiring the prolonged use of an oral opioid formulation." (See attached labels)

Hydromorphone shares potent mu opioid agonist properties with oxycodone and morphine and is similarly controlled under Schedule II of the Controlled Substances Act (CSA) the highest level of control for an approved drug. Hydromorphone however is significantly more potent and has pharmacologic properties that imbue it with greater abuse liability than morphine and oxycodone.

Abuse liability is a widely used, albeit poorly defined concept. Generally, abuse liability encompasses an array of factors in addition to the specific pharmacological properties of the drug. These typically include social and cultural determinants, such as drug availability, fads, diversion history, as well as chemical properties such as extractability and ease of synthesis.

The abuse liability assessment encompasses all of the drug properties including evaluation of chemistry, pharmacology (preclinical and clinical), pharmacokinetic and pharmacodynamic profiles, adverse events observed in clinical trials, as well as epidemiological data and actual experience in the community.

Abuse liability puts the narrower concept of abuse potential into a broader social and public health context. Abuse potential, as defined by the legislative history of the CSA, refers to the tendency of a central nervous system-active drug to produce a positive psychic effect, which is viewed as correlated with or predictive of abuse and addiction.

The actual abuse patterns of a drug at a particular point in time or community depend upon a multitude of factors that are difficult to predict. These unpredictable factors include availability, knowledge of the drug's actions, fads, available formulations of the drug, prescribing, attitudes, state laws, local controls and social environment.

## I. PHARMACOLOGY OF HYDROMORPHONE

Hydromorphone, oxycodone, and morphine share mu-opioid properties but exhibit different relative analgesic and subjective effect potencies. Hydromorphone is significantly more potent than morphine and oxycodone. At equianalgesic doses, oral hydromorphone is approximately **four** times more potent than oral oxycodone and morphine when physiological opioid effects (miosis, hypotension) are compared, while hydromorphone is **ten** times more potent than morphine when subjective effects of liking and euphoria are measured.

The lowest dose 12-mg Palladone capsule is equivalent in its opioid effects of analgesia, miosis, and respiratory depression to 48 mg of oral oxycodone, and 48 mg of oral morphine. The highest Palladone dose, 32-mg capsule, is equivalent in opioid analgesic and physiological effects (miosis and respiratory depression) to approximately 130 mg of oral oxycodone or morphine.

Hydromorphone administered parenterally is **6-7** times as potent as intravenously administered morphine when equianalgesic effects are compared. Thus, injection of 32 mg of "extracted" Palladone is approximately equivalent in analgesic and opioid effects to 214 mg of parenteral morphine.

When euphoria and reinforcing effects of oral or intravenous hydromorphone are compared to those of oral or intravenous morphine, **hydromorphone** is **ten** times as potent as morphine in drug abusing subjects and in normal volunteers (Jasinski *et al.*, 1977; Hill and Zacny, 2000). Thus, 12 mg of Palladone produces a psychic effect equivalent to 120 mg of morphine while 32 mg is equipotent to 320 mg of morphine.

When comparing currently available OxyContin tablet strengths to hydromorphone and morphine, the 40-mg OxyContin tablet is approximately equivalent to 10 mg of hydromorphone, 40 mg of oral morphine, and 27 mg of methadone.

## II. PHARMACOKINETICS

Administration of the once a day, controlled release Palladone formulation yields approximately 25% lower peak levels compared to an equivalent total daily dose of immediate release formulation administered four times a day. The 12-mg Palladone capsule produces a constant plasma hydromorphone level, comparable to that achieved by administration of the 3mg immediate release tablet, administered every 6 hours.

## III. HISTORY OF HYDROMORPHONE ABUSE

Hydromorphone has a well-documented history of abuse in the United States dating back to the 1970s and has been subject to special DEA task force attention. Hydromorphone was historically the drug of choice among opiate abusers who often administered the drug intravenously after crushing and dissolving the 4-mg (immediate release) Dilaudid tablets. Dilaudid has a reported street value up to \$50 per tablet and continues to be diverted and abused.

**IV. EPIDEMIOLOGY OF OPIOID ANALGESIC ABUSE**

**- Prescription data**

Prescription data from IMS Heath, National Prescription Audit *Plus*<sup>TM</sup>, are displayed in **Table 1** to provide a context for the interpretation of the drug abuse data provided by the National Survey on Drug Use and Health and the Drug Abuse Warning Network (DAWN) that follows.

The National Prescription Audit *Plus* database from IMS Health tracks the projected total number of prescriptions (new and refill) dispensed by U.S. retail pharmacies (chain, independent and food stores) including mail orders and long term care facilities. These values are used as a crude denominator to calculate the frequency of abuse related indicators relative to the total number of dispensed prescriptions (**Table 1**).

**Table 1.** Drug Utilization Values Reported as Annual Prescriptions Dispensed in the U.S.A. (In for Hydromorphone, Oxycodone single drug, and Hydrocodone/combinations (1999-2002).

DRUGS	PROJECTED TOTAL PRESCRIPTIONS IN			
	1999	2000	2001	2002
HYDROMORPHONE				
OXYCODONE/ SINGLE <sup>1</sup>				
OXYCODONE TOTAL				
HYDROCODONE/COMB.				
FENTANYL <sup>2</sup>				
MORPHINE <sup>3</sup>				
METHADONE				

<sup>a</sup> Source: IMS Health, National Prescription Audit *Plus*<sup>TM</sup>.

<sup>1</sup>OxyContin products represent approximately 75% (2002) and 80 % (1999) of the oxycodone/single entity prescriptions.

<sup>2</sup>Duragesic transdermal products represent approximately 96% (2002) and 99% (1999) of the fentanyl prescriptions.

<sup>3</sup>Morphine sustained release products, including all strengths of MS Contin, Avinza, Kadian and Oramorph, represented 27% (2002) and 48% (1999) of all morphine prescriptions.

**- National Survey on Drug Use and Health (NSDUH). Office of Applied Studies, Substance Abuse and Mental Health Services Administration. - Prevalence of Prescription Drug Abuse: Analgesics**

This section highlights key findings on the non-medical use of prescription analgesics from the National Survey on Drug Use and Health (NSDUH). For a complete description of this database and data analysis, please see "Non-medical Pain Reliever Use: Data from the National Survey on

Drug Use and Health," Tab 5, provided by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA).

The 2001 survey reported an estimated 3.5 million persons used pain relievers non-medically. This represents a significant increase from 2000, when the estimate was 2.8 million.

In 2001, an estimated 2.8 million persons reported some lifetime use of non-medical hydrocodone. This represents a significant increase over the 1.6 million persons in 1999 and 1.8 million in 2000 who reported lifetime use.

In 2001, approximately 957,000 persons (aged 12 or older) reported using OxyContin non-medically in their lifetime. This represents a four-fold increase from 1999 when 221,000 persons reported non-medical lifetime use of OxyContin and more than double the number of persons using OxyContin in 2000 (399,000).

The estimated number of persons with lifetime non-medical use of Dilaudid remains high between 1999 (680,000) and 2001 (837,000).

**Non-medical first time** use of pain relievers has increased steadily since the mid-1980s when there were approximately 400,000 initiates annually. The number of initiates reached 2.0 million in 2000, significantly more than in 1999 (1.7 million) and 1998 (1.5 million). During the period 1998 through 2000, there were significantly more new users among those aged 12 to 17 years old than among those aged 18 to 25 years old.

#### **- Drug Abuse Warning Network (DAWN)- Office of Applied Studies, SAMHSA**

Key findings highlight some important facts from the Drug Abuse Warning Network (DAWN). For a complete report see Tab 5, provided by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA).

The DAWN system provides active surveillance data annually from Emergency Departments and Medical Examiners on the health consequences of drug use in the United States. DAWN captures drug-related visits to emergency departments -ED episodes- for the non-medical use of a substance for psychic effects, dependence, or suicide attempt.

#### **- Drug Abuse Related Deaths- DAWN**

For the 1999-2001 period, 1,272 deaths were related to oxycodone, 132 related to hydromorphone, and 1,593 for hydrocodone/combination products (**Table 2**).

Oxycodone-related deaths increased from 262 in 1999 to 555 in 2001, representing a greater than 100% increase. The number of hydromorphone related deaths remains constant for 1999 to 2001. The death rate adjusted for total retail prescriptions gave an estimate of one death per \_\_\_\_\_ hydromorphone prescriptions, one death per \_\_\_\_\_ oxycodone prescriptions and one death per \_\_\_\_\_ hydrocodone prescriptions for 1999-2001. The death rates expressed as number of deaths per one hundred thousand prescriptions, are \_\_\_\_\_ for hydromorphone, \_\_\_\_\_ for oxycodone and \_\_\_\_\_ for hydrocodone (**Table 2**).

**Table 2.** DAWN Medical Examiner (ME) Deaths Relative to Availability (IMS Health, National Prescription Audit *Plus*<sup>TM</sup>) for Hydromorphone, Oxycodone and Hydrocodone Drugs (1999-2001).

DRUG	DAWN ME'S REPORTED DEATHS	NUMBER OF PRESCRIPTIONS	DAWN DEATHS PER PRESCRIPTIONS <sup>a</sup>
	1999-2001	1999-2001	
HYDROMORPHONE	132 <sup>b</sup>	—	—
OXYCODONE	1,272 <sup>b</sup>	—	—
HYDROCODONE	1,593 <sup>b</sup>	—	—

<sup>a</sup>. The above ratios may be considered “crude” estimates because ME reports are not national estimates whereas the sales data represent the whole U.S. market.

<sup>b</sup>. Total mentions for drugs in combination and taken alone.

**V. RISKS OF PALLADONE**

1. Palladone, high dose and potent hydromorphone capsules, poses significant risks of overdose (intentional and unintentional), death, abuse, misuse, and addiction.
2. Experience with OxyContin and other related products, has demonstrated that extended release analgesic properties are readily altered, delivering a high and potentially fatal dose of the opioid drug.
3. High prevalence of ongoing abuse and overdose deaths associated with immediate release hydromorphone, strongly suggests that Palladone formulations will be associated with high levels of abuse, misuse, overdose, and death.
4. The CSA regulates importation, manufacture and distribution of controlled substances. It licenses prescribers and dispensers. It does not provide active surveillance nor does it address education for prescribers and patients.