FDA Alert for Healthcare Professionals

Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone™)

This product is not currently available for purchase in the U.S

FDA ALERT [07/2005]: Alcohol-Palladone™ Interaction

Purdue Pharma has agreed to FDA's request that they voluntarily suspend sales and marketing of Palladone™ in the United States. At this time, the Agency has concluded that the overall risk versus benefit profile of Palladone™ is unfavorable due to a potentially fatal interaction with alcohol.

Pharmacokinetic data indicate that the co-ingestion of Palladone™ and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone. These elevated levels may be lethal, even in opioid tolerant patients.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

FDA recommends that healthcare providers who have prescribed Palladone™ contact affected patients, discuss how to use any remaining drug (that is, to use without any concomitant alcohol intake), and prescribe an appropriate substitute.

Data Summary

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

Hydropmorphone Hydrochloride Extended-Release Capsules (marketed as Palladone™)

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 Palladone™ with Different Concentrations of Alcohol (fasted state)

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

*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 has not been studied.