



# New Drug Update

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## **Invega® (paliperidone)**

**Cassie Waldorf, Pharm.D.**

**James P. Griffith, M.D., FACP**

Associate Professor, Internal Medicine/Psychiatry  
School of Medicine  
West Virginia University-Charleston

**Kristy Lucas, Pharm.D.**

Clinical Associate Professor  
Schools of Pharmacy and Medicine  
West Virginia University - Charleston

### **Introduction**

Invega® (paliperidone [pal-ee-PER-i-done]) is an atypical antipsychotic and is the extended-release form of the active metabolite of risperidone. It was approved by the FDA on December 19, 2006 for the treatment of schizophrenia in adults.

### **Therapeutic Recommendation**

**Paliperidone is approved for the treatment of schizophrenia in adults. It is the first drug in its class to use a tablet with an osmotic pressure release system to release the drug over 24 hours. This system is designed to minimize the need for dose titration, as most patients will require the starting and usual dose of 6 mg daily. Unlike risperidone, paliperidone is not extensively metabolized by the liver and therefore is associated with fewer drug interactions. In one study, time-to-recurrence of psychotic symptoms was measured and 25% of patients taking paliperidone experienced a recurrence compared to 53% of patients taking the placebo. There are no published studies comparing paliperidone to other atypical antipsychotics at this**

**time. Paliperidone has a black box warning for increased mortality for elderly patients with dementia-related psychosis, like other atypical neuroleptics.**

**Invega® (paliperidone) is simply another atypical neuroleptic that clinicians may choose from for the treatment of adult patients with schizophrenia. Once daily dosing is convenient for patients and may enhance compliance, but other atypical antipsychotics (such as quetiapine and aripiprazole) are also prescribed once-daily. Response rates would be expected to be comparable to other antipsychotic medications. It is very expensive, like most atypical antipsychotics. A study comparing paliperidone with risperidone or other antipsychotic medications would be helpful in deciding which drug to use.**

### **Dosing and Administration**

Invega® is available in a 3 mg, 6 mg, and 9 mg strength tablet. However, the recommended starting dose of paliperidone is 6 mg by mouth in the morning with or without food. Do not crush or chew the tablet. Store at room temperature and away from moisture. Some patients may see benefit at the 3 mg dose, while others may be better controlled at doses above the usual 6 mg daily dose. For patients requiring more than 6 mg daily, the dosage can be increased by 3 mg/day at intervals greater than 5 days until a maximum dose of 12 mg/day is achieved.

### **In This Issue:**

◆ **Invega® (paliperidone)**

◆ **Chantix® (varenicline tartrate)**

## Cost Comparison

Medication/Dose	Cost*		
	Rite Aid	Kroger	Fruth
Invega® 6 mg daily	374.99	418.49	375.58
Risperdal® 2 mg BID	494.99	541.00	482.37

\*Cost to patient for a 30-day supply at usual doses.

## Contraindications

Paliperidone is contraindicated in patients that have had a hypersensitivity reaction to paliperidone, risperidone, or any components of Invega®. Also, paliperidone is contraindicated in patients with AV block, bundle-branch block, cardiac arrhythmias, congenital heart diseases, QT prolongation, *torsade de pointes*, or those who are breast-feeding.

## Drug Interactions

Paliperidone is not known to affect any drugs that are metabolized by the CYP450 enzyme. However, paliperidone may block the effects of levodopa and other dopamine agonists. Vasoconstriction may be decreased when used with these medications. Because paliperidone may increase

the QT interval, it should be monitored if combined with other drugs that may act the same way.

## Common Adverse Drug Reactions

Adverse effects that occurred in >2% of patients included: dizziness, asthenia, back pain, fatigue, extrapyramidal disorder, tremor, dyspepsia, nausea, cough, orthostatic hypotension and pyrexia. Tachycardia, headache, somnolence, and anxiety were the most common.

## Special Populations

**Renal Impairment:** Patients that have a creatinine clearance < 80 ml/min should take a lower dose of paliperidone than those with normal renal function. Patients with a CrCl of 50-79 ml/min should not take more than 6 mg/day and those with a CrCl of 10-49 ml/min should not take more than 3 mg/day. Renal clearance of the drug is reduced 32% in mild (CrCl 50 to < 80 ml/min), 64% in moderate (CrCl 30 to < 50 ml/min), and 71% in severe (CrCl 10 to < 30 ml/min) renal failure.

**Hepatic Impairment:** No adjustments are required. However, there was a decrease in protein binding in studies in this group of patients.

**Geriatrics:** No adjustments are required. However, there may be a decrease in CrCl in this population.

**Pediatrics and Adolescents (less than 18):** Safety and efficacy studies have not been conducted; therefore, paliperidone is not recommended in this population.

**Gender:** No adjustments are required. In a pharmacokinetic study there were no differences found.

**Pregnancy:** Paliperidone is pregnancy category C. No studies have been done in pregnant women and it should only be used if the benefits of taking the drug outweigh the risk.

**Lactation:** Paliperidone is excreted in breast milk and therefore women who are taking the medication should not breast-feed.

**Race:** No adjustments are required. There were no differences found in a pharmacokinetic study with Japanese and Caucasian subjects.



## ...A Primary Care Physician's Guide to Newly Released Medications...

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EDITOR-IN-CHIEF - Kristy Lucas, Pharm.D.

CO-EDITOR - Greg Rosencrance, M.D.

MANAGING EDITOR - Tara White

Departments of Internal Medicine  
and Clinical Pharmacy

3110 MacCorkle Ave., SE

Charleston, WV 25304

(304) 347-1377 • Fax: (304) 347-1350

E-mail: [klucas@hsc.wvu.edu](mailto:klucas@hsc.wvu.edu)

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## Pharmacology

**Mechanism of Action:** The mechanism of action of paliperidone is unknown. However, it is thought to block central dopamine and serotonin receptors in the limbic area and mesocortical tracts and therefore decrease both the positive and negative symptoms of schizophrenia with less extrapyramidal effects than with typical antipsychotics.

**Absorption/Distribution:** The half-life of paliperidone is approximately 23 hours. Maximum concentrations are reached 24 hours after administration and steady state is reached within 4-5 days. The absolute oral bioavailability of paliperidone is 28%. The volume of distribution is 487 L. Paliperidone is 74% protein bound. The C<sub>max</sub> and AUC were decreased by 60% and 54%, respectively, when given with a meal.

**Metabolism/Excretion:** Approximately 59% of paliperidone is excreted unchanged into the urine.

### Patient Information

1. Swallow the tablet whole. Do not cut or crush the tablet.
2. It is best to take this medication at about the same time every day with water and with or without food.
3. If a dose is missed, take it as soon as possible but do not take it too close to your next dose.
4. It is important to take this medication even if you feel better and see your physician regularly.
5. Don't be alarmed if you notice part of the tablet in the stool. This is not the active drug.
6. Report any serious side effects to your doctor.

### References

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## Chantix® (varenicline tartrate)

### Norman J. Montalto, D.O.,FAAFP

Now: Medical Director, Wells Fargo TPA  
Clinician, Family Health Associates

*At the time of writing:* Professor, Family Medicine  
West Virginia University-Charleston  
Director, Freedom from Tobacco Program

### Introduction

Chantix® (varenicline tartrate [var-e-NI-kleen]) is a partial agonist of nicotinic acetylcholine receptor sub-types  $\alpha_4\beta_2$ , and is FDA approved as an aid for smoking cessation. Varenicline was approved by the FDA May 10, 2006, and is the first prescription medicine approved for smoking cessation in nearly a decade. This is the second prescription medication that is available that does not contain nicotine to reduce withdraw symptoms and cravings during cessation attempts. This agent was developed specifically for tobacco cessation.

### Therapeutic Recommendation

**Varenicline targets and has a high affinity for the acetylcholine nicotinic receptor sub-type  $\alpha_4\beta_2$ . The efficacy of varenicline is thought to be the result of the agonist activity at this receptor. The binding of this agent to the receptor also prevents binding of exogenous nicotine. Varenicline blocks the ability of nicotine to bind and activate the  $\alpha_4\beta_2$  receptors, which stimulates the central nervous system to release dopamine in the mesolimbic-dopaminergic system, which is thought to be the mechanism underlying reinforcement and reward in patients who are dependent on tobacco.**

**In clinical trials, at the end of 12 weeks, treatment with varenicline (1 mg BID) success rates were four times greater than those taking placebo and two times greater than those taking bupropion 150 mg BID. In two pivotal studies, 44% of varenicline-treated patients quit smoking by the end of the 12-week period vs. 30% who used bupropion, and 18% who used placebo.**

**The recommended dosage of varenicline (for most patients) is 0.5 mg once daily for the first three days, then twice daily to the end of the**

first week (days 4-7) followed by 1 mg twice daily from day eight through the end of treatment (12 weeks). Patients who are successful at the 12-week point may elect to continue varenicline for another 12 weeks, because data from clinical trials showed reduced relapse rates with this extended regimen. The primary side effects of this agent are similar other nicotine replacement medicines, which include nausea, abnormal dreams and insomnia.

Patients receiving varenicline also have the opportunity to access online and telephone support to improve cessation rates and reduce relapse.

## Dosing and Administration

Varenicline is available in 0.5 mg and 1 mg tablets for oral administration. In patients who are properly motivated and are willing to set a quit date, varenicline dosing should begin one week before the target quit date. It is recommended that this drug be taken after eating and with a full glass of water. The recommended dose for the first three days is 0.5 mg once daily; days four through seven 0.5 mg twice daily; and beginning on day eight 1 mg twice daily, for up to 12 weeks. For those who have successfully stopped smoking within that 12 weeks, an additional course of 12 weeks of varenicline has been shown in clinical trials to increase likelihood of longterm abstinence. Some patients will be unsuccessful in stopping smoking during the initial 12-week period or experience relapse. Strong encouragement should be provided to continue with the cessation attempt. The factors that caused the unsuccessful attempt should be identified and evaluated, and coping skills should be put in place for the subsequent attempts.

Varenicline is not recommended for use in patients under age 18, and it is not a controlled substance. It is available only by prescription.

## Contraindications

Unless an allergy is reported to some of the agents contained in the tablet, there are no cited contraindications to using varenicline. The tablets contain very small amounts of cellulose, calcium phosphate, colloidal silicon dioxide, magnesium stearate, and Opadry® White, Opadry® Blue, and Opadry® Clear.

## Cost Comparison\*

Medication/Dose	Cost <sup>^</sup>		
	<u>Kroger</u>	<u>Rite Aid</u>	<u>Walmart</u>
Chantix® (varenicline) 1 mg BID #30	74.89	82.98	67.48
Zyban® (bupropion) 150 mg BID #30	113.49	124.99	104.68
Bupropion SR (generic) 150 mg BID #30	69.29	46.99	58.68

\*Maintenance doses (usual duration 12 weeks)

## Warnings/Precautions

Use caution in patients with renal dysfunction. Renal adjustment of dose may be required. Co-administration of varenicline (1 mg BID) with transdermal nicotine (21 mg/day) resulted in a much higher incidence of side effects than for nicotine replacement therapy (NRT) alone. Rates of discontinuation using varenicline in combination with NRT were six times higher than those treated with varenicline alone. Combined use with other smoking cessation therapies is not indicated. Varenicline did not alter the steady-state pharmacokinetics of bupropion in clinical studies. The safety of this combination has not been established.

## Special Populations

**Pregnancy:** Varenicline is rated as FDA Pregnancy Category C. As with other nicotine replacements, there are no adequate and well-controlled studies in pregnant women. Varenicline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Lactation:** The safety during lactation is unknown. The decision to use in nursing mothers should be considered carefully. If the benefits of cessation are judged to outweigh the risks to the newborn this may justify the potential risk to the nursing infant.

**Pediatric:** Varenicline is not recommended for use in patients under 18 years of age as its safety and effectiveness have not been established.

**Geriatric:** In clinical trials, using 1 mg daily or twice daily, the side effect profile was similar to that of younger patients. No dosage adjustment is recommended for elderly patients.

**Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of varenicline are not well established. Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency.

**Renal Impairment:** The primary means of metabolism for varenicline is by renal elimination. Varenicline is excreted unchanged in the urine, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. In patients with severe renal impairment (creatinine clearance <30 mL/minute) varenicline should be started at 0.5 mg daily and the dose should not exceed 0.5 mg twice daily. In subjects with ESRD on hemodialysis, varenicline dose should not exceed 0.5 mg once daily.

## Drug Interactions

In clinical trials, no clinically meaningful pharmacokinetic interactions were observed. Varenicline used in combination with digoxin, warfarin, transdermal nicotine, bupropion, cimetidine and metformin revealed no clinically meaningful pharmacokinetic drug-drug interactions. However, concomitant nicotine replacement and varenicline did result in increased incidence of GI and CNS side effects (e.g., nausea, headache, dizziness). Varenicline does not inhibit nor induce the P450 enzyme systems. In addition, *in vitro* studies did not demonstrate inhibition of human renal transport proteins at therapeutic concentrations.

## Adverse Effects

In clinical trials, (1 mg BID dose), nausea was the most common adverse effect of varenicline. The nausea was described as mild or moderate and occasionally transient, but was, in pooled data, a common adverse event (30% using varenicline vs. 10% in the placebo group). The nausea was apparently dose dependant, and for that reason, the recommendation for gradual titration appears justified.

In addition, insomnia (including insomnia initially, middle, or early awakenings) was more frequent using varenicline 18-19% vs. 13% placebo; as were abnormal dreams (9-13% vs. 5% in the placebo population) and headache (15% - 19% vs. 13% with placebo).

## Pharmacology

**Mechanism of Action:** Varenicline binds selectively to the  $\alpha_4\beta_2$  neuronal nicotinic acetylcholine receptors with high affinity. This agent is thought to work at this subtype of nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to  $\alpha_4\beta_2$  receptors. Varenicline therefore blocks ability of nicotine to activate  $\alpha_4\beta_2$  receptors and appears to stimulate the central nervous mesolimbic dopamine system, which is believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

**Absorption/Distribution:** Maximum plasma concentrations of varenicline are reached within 3-4 hours after oral dosing. Steady-state conditions are reached within four days of continuous/multiple oral doses. Varenicline exhibits linear pharmacokinetics over single or repeated doses, with nearly complete absorption after oral administration and systemic availability was very high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

**Metabolism/Excretion:** The elimination half-life of varenicline is approximately 24 hours. Ninety-two percent of excreted varenicline is unchanged in the urine. The primary mechanism for elimination to the renal system is through glomerular filtration along with active tubular secretion. Caution is warranted with the use of varenicline in subjects with renal impairment (<30 mL/minute).

## Patient Information

1. Chantix® (varenicline), is a prescription medication that has been approved by the Food and Drug Administration (FDA) to assist with smoking cessation.
2. In order to use varenicline appropriately, you must be motivated to quit:
  - a. Choose a quit date.
  - b. Start taking one week (seven days) before your quit date. While the medication takes effect, you may continue smoking. However, you should try to stop smoking on your quit date.
  - c. Enroll in the free Get Quit Program. This very accessible and intensive support program will help you quit. You can use

phone, on-line and mail support that will improve your chances of quitting.

3. Varenicline is not recommended to be used with any other nicotine replacement product (gum, lozenge, patch, inhaler).
4. Do not take this medication if you are allergic to it or any components in it.
5. If you have severe kidney problems or are on dialysis, you may receive a lower dose.
6. If you are presently or are planning to become pregnant, it is not known whether varenicline will harm your unborn baby. It is best to stop smoking before you become pregnant.
7. If you are breastfeeding, you and your doctor should discuss alternative ways to feed your baby if you take this medication.
8. Take after eating, and with a full glass (8 oz.) of water.
9. Most patients will take varenicline for up to 12 weeks. If you have completely quit smoking by the end of 12 weeks, another 12 weeks of this medication may help you stay cigarette-free.
10. The most common side effects include nausea, changes in dreaming, constipation, gas, vomiting, and insomnia. Should these side

effects become significant, contact your health care provider.

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West Virginia University

Robert C. Byrd Health Sciences Center  
Charleston Division

Departments of Internal Medicine  
and Clinical Pharmacy  
3110 MacCorkle Ave., SE  
Charleston, WV 25304

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