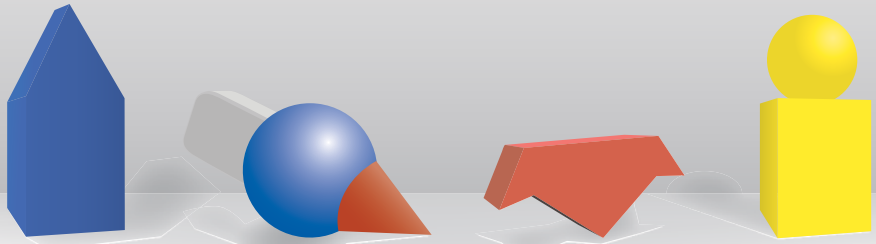
A Pocket Guide to Atypical Antipsychotics

Dosing, switching, and other practical information

by

Stephen M. Stahl



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Indications and Usage[1]

Amisulpride is an atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in adults with:
   - positive symptoms such as delusions, hallucinations, thought disorders, hostility, suspiciousness
   - negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal

Mechanism of Action[1, 2, 3]

The therapeutic activity of amisulpride is mediated through a combination of D_2 and D_3 dopamine receptor antagonism. Unlike classical and atypical neuroleptics, amisulpride displays low affinity for serotonergic, α-adrenergic, histaminergic receptor subtypes, and muscarinic receptors and sigma sites. Amisulpride is also an antagonist at $5HT_7$ receptors.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

Indication	Initial Dose	Titration	Maximum Dose
Schizophrenia in Adults	400–800 mg/day*	No Titration Required	1200 mg/day
Schizophrenia with Predominant Negative Symptoms	50–300 mg/day	No Titration Required	300 mg/day

*Amisulpride should be administered twice daily for doses above 300 mg. Doses above 800 mg/day have shown no significant improvement over lower doses.

Special Considerations[1]

Amisulpride induces a dose-dependent prolongation of QT interval, which potentiates the risk of serious ventricular arrhythmias such as torsades de pointes.

The following factors could favor the occurrence of this rhythm disorder:

- bradycardia < 55 bpm
- cardiac disease or family history of sudden death or QT prolongation
- electrolyte imbalance, in particular hypokalaemia
- congenital prolonation of the QT interval
- on-going treatment with a medicinal production likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval

The dose of amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500 ms.

Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during intercurrent illness.

Concomitant antipsychotics should be avoided.

Caution should be also exercised when prescribing amisulpride to patients with Parkinson's disease since it may cause worsening of the disease. Amisulpride should be used only if antipsychotic treatment cannot be avoided.

Amisulpride may lower the seizure threshold. Therefore patients with a history of epilepsy should be closely monitored during amisulpride therapy.

Pharmacokinetics[1]

Time to Peak Plasma Concentration	Mean Elimination Half-Life	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
3–4 hrs	12 hrs	48–60 hrs	50 %	—

CYP450 = Cytochrome P450

Pharmacokinetics in Special Populations[1]

Renal Impairment

Use with caution in patients with renal insufficiency. Amisulpride is renally eliminated, and in patients with renal insufficiency, systemic clearance is reduced by a factor of 2.5 to 3. The AUC in mild renal failure is increased two-fold and almost tenfold in moderate renal failure.

Although there is no data to support clearance and AUC alterations for doses above 50 mg/day in patients with renal impairment, it is recommended to adjust dosage as follows:

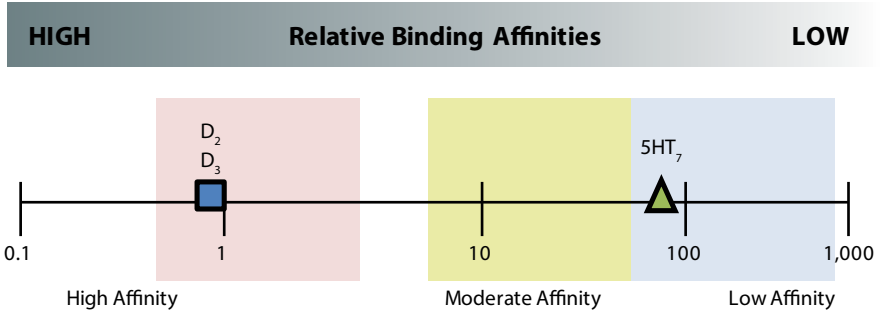
- In patients with creatinine clearance $30 \geq CL_{cr} \leq 60$ mL/min, use half of the recommended dose
- In patients with creatinine clearance $10 \geq CL_{cr} \leq 30$ mL/min, use one third of the recommended dose
- Amisulpride should not be used in patients with severe renal impairment ($CL_{cr} < 10$ ml/min)

Hepatic Impairment

No dose adjustment required for patients with hepatic impairment.

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve

Pharmacodynamics[1, 2, 3]



Efficacy[4]

The efficacy of amisulpride in the treatment of schizophrenia was established in four short-term controlled trials of inpatients who met DSM-III-R or DSM-IV criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression (CGI).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R or DSM-IV criteria for schizophrenia	100 mg/day 400 mg/day 800 mg/day 1200 mg/day	4 wks	PANSS, BPRS, CGI	✓ 400 and 800 mg/day superior to lower doses; all doses were as effective as the comparative treatment (haloperidol 16 mg/day)
	800 mg/day			✓ equivalent to comparative treatment in efficacy (20 mg/day haloperidol); improved response rate with CGI vs. haloperidol
	1000 mg/day			✓ equivalent to comparative treatment in efficacy (25 mg/day flupenthixol)
	800 mg/day			✓ equivalent to comparative treatment in efficacy (8 mg/day risperidone)

Efficacy[4]

Three trials were conducted versus placebo in schizophrenic patients with predominant negative symptoms according to DSM-III and DSM-III-R, showing that low doses of amisulpride are active against negative symptoms. Psychiatric signs and symptoms were assessed using the Clinical Global Impression (CGI), Scale for the Assessment of Negative Symptoms (SANS), Montgomery–Åsberg Depression Rating Scale (MADRS), and Global Assessment of Functioning (GAF).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R or DSM-III criteria for schizophrenia	100 mg/day 300 mg/day	6 wks	SANS	✓ 100 and 300 mg/day vs. placebo
	50 mg/day 100 mg/day	3 months	CGI, MADRS	✓ 50 and 100 mg/day vs. placebo
	100 mg/day	6–12 months	CGI, SANS, GAF	✓ 100 mg/day maintained improvement of negative symptoms and prevented recurrence of positive symptoms vs. placebo

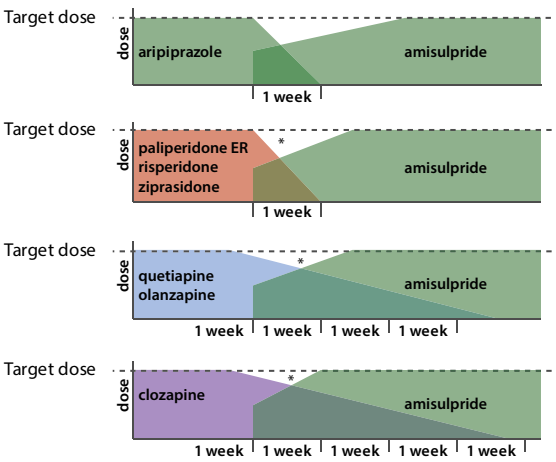
Safety and Tolerability[4]

	Percent of Patients Reporting	
	Placebo (n=202)	Amisulpride (n=921)
Extrapyramidal disorder	2	11
Insomnia	7	10
Anxiety	5	7
Weight increase	5	6
Agitation	3	5

Adverse reactions reported by ≥ 5% of patients treated with amisulpride in a 6-week, double-blind, placebo-controlled trial.

Switching[2]

Switching from Oral Antipsychotics to Amisulpride



Begin amisulpride at middle dose.

It is advisable to begin amisulpride at an intermediate dose and build the dose rapidly over 3-7 days.

Clinical experience has shown that quetiapine and olanzapine should be tapered off slowly over a period of 3-4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors.

Clozapine should always be tapered off slowly, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis.

References

1. Amisulpride prescribing information, electronic Medicines Compendium, July 31, 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422, 431–436.
3. Abbas AI et al. Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo, 2009, *Psychopharmacology*, 205:119–128.
4. SOLIAN prescribing information, Sanofi-Aventis Pharmaceuticals, Ltd. June 2012.

Indications and Usage[1]

Aripiprazole is an atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in:
   - adults
   - adolescents above 15 years of age
2. The treatment of symptoms of bipolar I disorder, including:
   - moderate to severe manic episodes
   - prevention of recurrence of manic episodes

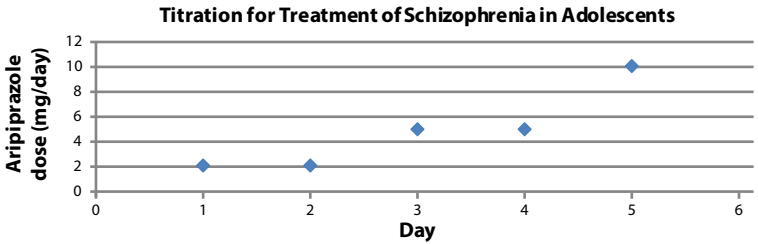
Mechanism of Action[1, 2]

The therapeutic activity of aripiprazole is mediated through a combination of $5HT_{2A}$, $5HT_{2C}$, and $5HT_7$ serotonin, D_3 and D_4 dopamine, H_1 histamine, and α_1-adrenergic receptor antagonism. Aripiprazole also acts as a partial agonist for D_2 dopamine, and $5HT_{1A}$ serotonin receptor.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

Indication	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia in Adults	10 or 15 mg/day	—	10–15 mg/day*	10–30 mg/day*
Schizophrenia in Adolescents	2 mg/day	2 mg/day for 2 days 5 mg/day for 2 days	10 mg/day**	10–30 mg/day**
Bipolar disorder manic episodes	15 mg/day		15 mg/day	15–30 mg/day*



*Doses above 15 mg given once daily demonstrated no significant improvement over lower doses, although some patients may do better on higher dose. Do not exceed 30 mg/day.

**Doses above 10 mg demonstrated no significant improvement in adolescent patients, although some patients may benefit from higher doses.

When appropriate, increases in dosage should be made in increments of 5 mg/day. Do not exceed 30 mg/day.

Pharmacokinetics[1]

Time to Peak Plasma Concentration	Mean Elimination Half-Life	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
3–5 hrs	75 hrs	14 days	18%	CYP2D6 CYP3A4

CYP450 = Cytochrome P450

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced.

When the concomitant administration of CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased.

When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose.

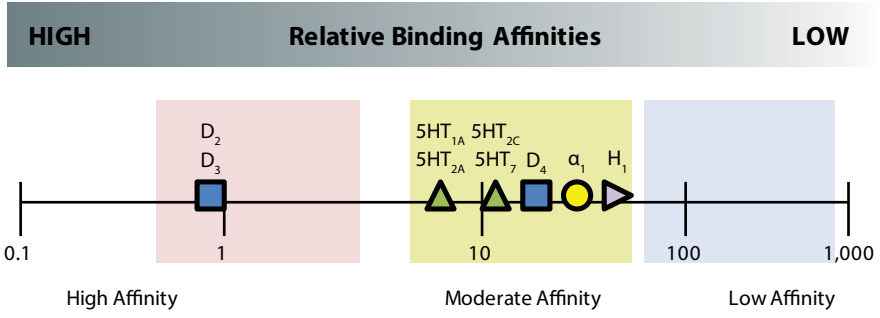
Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Increase in AUC	Recommended Initial Dose	Titration	Max Dosage
Mild	No dose adjustment needed for renal impairment.					
Moderate						
Severe						

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment. Use 30 mg/day dose with caution in patients with severe hepatic impairment. (There is insufficient data to establish dose recommendations for these patients.)

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve

Pharmacodynamics[1, 2, 3, 4]



Efficacy[3]

The efficacy of aripiprazole in the treatment of schizophrenia was established in five short-term controlled trials of inpatients who met DSM-III-R or DSM-IV criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R or DSM-IV criteria for schizophrenia	15 mg/day 30 mg/day	4 wks	PANSS, CGI	✓ 15 and 30* mg/day vs. placebo
	20 mg/day 30 mg/day	4 wks	PANSS, CGI	✓ 20 and 30 mg/day vs. placebo
	10 mg/day 15 mg/day 20 mg/day	6 wks	PANSS	✓ 10, 15, and 20* mg/day vs. placebo
	2 mg/day 5 mg/day 10 mg/day	6 wks	PANSS	✓ 10 mg/day vs. placebo
	5–30 mg/day	4 wks	CGI	✓ All doses superior to placebo*

*Across studies, higher doses did not demonstrate superior efficacy compared to lower doses.

Efficacy[3]

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, based on medical history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to 15 mg/day aripiprazole or placebo for up to 26 weeks of observation for relapse.

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-IV criteria for schizophrenia	15 mg/day	26 wks	PANSS, CGI	✓ 15 mg/day demonstrated longer time to relapse compared to placebo

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia.

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adolescent DSM-IV criteria for schizophrenia	10 mg/day 30 mg/day	6 wks	PANSS	✓ 10 and 30 mg/day vs. placebo; no significant advantage of 30 mg/day compared to 10 mg/day

Safety and Tolerability[3]

	Percent of Patients Reporting			Percent of Patients Reporting	
	Placebo (n=1166)	Aripiprazole (n=1843)		Placebo (n=1166)	Aripiprazole (n=1843)
Headache	23	27	Dyspepsia	4	7
Agitation	17	19	Fatigue	4	6
Insomnia	13	18	Dry mouth	4	5
Anxiety	13	17	Extrapyramidal sypmtoms	3	5
Nausea	11	15	Somnolence	3	5
Constipation	7	11	Restlessness	3	5
Vomiting	6	11	Tremor	3	5
Dizziness	7	10			
Akasthisia	4	10			

Adverse reactions reported by ≥ 5% among patients treated with aripiprazole in a 6-week, double-blind, placebo-controlled trial.

Safety and Tolerability in Adolescents[3]

	Percent of Patients Reporting	
	Placebo (n=97)	Aripiprazole (n=197)
Somnolence	3	23
Extrapyramidal disorder	3	20
Fatigue	4	11
Nausea	4	11
Akathisia	2	10
Blurred vision	0	8
Salivary hypersecretion	0	6
Dizziness	1	5

The following findings are based on one 6-week, placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day. This table represents adverse reactions reported by ≥ 5% of aripiprazole-treated adolescent patients (13–17 years of age) with schizophrenia.

Special Considerations[1]

Aripiprazole should be used with caution in patients with :

- known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities)
- cerebrovascular disease
- conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products)

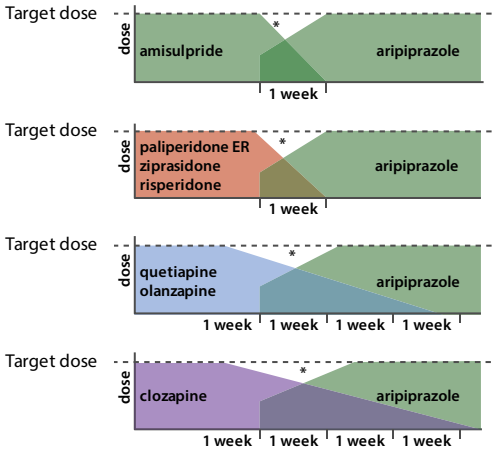
  or

- hypertension, including accelerated or malignant

Aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Switching[2]

Switching from Oral Antipsychotics to Aripiprazole



It is advisable to begin aripiprazole at an intermediate dose and build the dose rapidly over 3–7 days.

Clinical experience has shown that olanzapine and quetiapine should be tapered off over a period of 3–4 weeks due to the risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha–1 receptor blocking.

Clozapine should always be tapered off gradually, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis.

References

1. ABILIFY prescribing information, Otsuka Pharmaceuticals Europe Ltd., European Medicines Agency, http://www.ema.europa.eu/
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408-422, 431-436.
3. ABILIFY prescribing information, Otsuka Pharmaceuticals Co., Ltd, February 2012.
4. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics, 2010, *European Psychiatry*, 25, S12-S21.

Indications and Usage[1]

Clozapine is an atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in:
   - Patients who have severe, untreatable, neurological adverse reactions to other antipsychotic agents
   - Treatment-resistant patients
2. Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Mechanism of Action[1, 2, 3]

The therapeutic activity of clozapine is mediated through a combination of $5HT_1$, $5HT_2$, $5HT_3$, $5HT_6$, $5HT_7$ serotonin, D_4 dopamine, M_1 muscarinic, H_1 histamine, and α_1-adrenergic receptor antagonism. It also has weak D_2 blocking properties.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

Indications	Initial Dose Day 1	Second Dose Day 2	Titration	Target dose	Dose Range	Maximum Dose
Schizophrenia (Adults)	12.5 mg administered once or twice	25 mg administered once or twice	25–50 mg/day over 2–3 weeks	300 mg/day within 2–3 weeks of initial dose	200–450 mg/day *may be given in divided doses with larger dose given at bedtime*	900 mg/day*

*Daily dose may be increased to maximum after achieving target dose. Increase in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals. Increased adverse reactions (in particular seizures) are possible at doses over 450 mg/day.

Maintenance Dosing:

- After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses.
- Careful downward titration is recommended when reducing dose.
- For effective doses < 200 mg/day, once-daily administration in evening may be appropriate.

Use in Elderly:

- Initiation of treatment is recommended at 12.5 mg once daily, with subsequent dose increments restricted to 25 mg/day.

Special Considerations[1]

WBC and differential blood counts must be performed within 10 days prior to initiating clozapine treatment.

Only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm^3 (3.5x10^9/l) and ANC ≥ 2000/mm^3 (2.0x10^9/l)) should receive clozapine.

After the start of clozapine treatment, the WBC count and ANC must be monitored weekly for the first 18 weeks, and at least four-week intervals thereafter.

Seizures have been associated with the use of clozapine with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors.

Cardiovascular and respiratory effects include myocarditis, orthostatic hypotension, respiratory and/or cardiac arrest, especially when clozapine is administered with benzodiazepines or other psychotropic drugs. Orthostatic hypotension is more likely to occur during initial titration.

Pharmacokinetics[1]

Time to Peak Plasma Concentration (Hours)	Time to Steady-State Concentration (Days)	Mean Elimination Half-Life (Hours)
2.5	8–10*	12

Oral Bioavailability	Bioavailability with Food	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
27%	27%	50%	**CYP1A2**, CYP2D6, CYP3A4

CYP450 = Cytochrome P450

*Time to reach clozapine steady state concentrations exceeds 4-5 half-lives because of required titration.

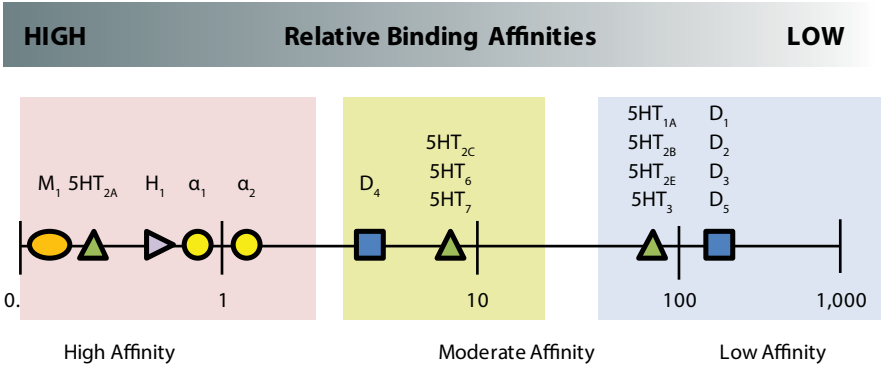
Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Recommended Initial Dose (mg/day)	Maximum Recommended Dose (mg/day)
Mild	No significant reduction in clearance (Bennett 1997). Use with caution, due to possibility of interstitial nephritis.					
Moderate						
Severe	Not recommended					

Hepatic Impairment
Caution is advised in patients using clozapine who have concurrent hepatic disease.
Hepatitis has been reported in both patients with normal and preexisting liver function abnormalities.
In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Pharmacodynamics[1, 2, 3, 4]



Efficacy: Treatment-Resistant Schizophrenia[5]

The effectiveness of clozapine in a treatment-resistant schizophrenic population was demonstrated in a 6-week study comparing clozapine and chlorpromazine.

Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open prospective treatment with haloperidol before entering into the double-blind phase of the study.

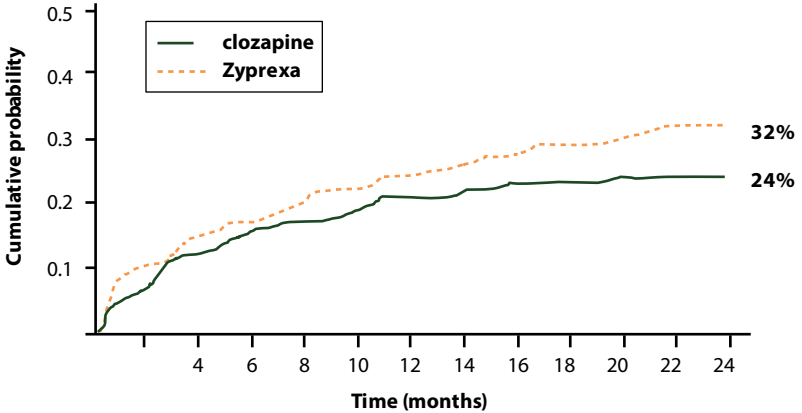
Efficacy was evaluated using the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression Scale (CGI).

	clozapine 500 mg/day (n=126)	chlorpromazine 1000 mg/day* (n=139)	*p*-value[b]
Kane et al. 1988			
BPRS Baseline Score[a]	61 (12)	61 (11)	
BPRS End Point Score[a]	45 (13)	56 (12)	< 0.001
CGI Scale Baseline Score[a]	5.6 (0.7)	5.7 (0.7)	
CGI Scale End Point Score[a]	4.4 (1.1)	5.3 (0.8)	< 0.001

[a]Mean (Standard Deviation), [b]Based on two-tailed analysis of covariance model with criterion variables and drug as covariates, demonstrating superiority of clozapine over chlorpromazine. *Plus 6 mg/day benztropine mesylate.

Efficacy: Suicide Prevention[6]

The International Suicide Prevention Trial (InterSePT) was a randomized, international, parallel-group comparison of clozapine vs. Zyprexa in reducing the risk of recurrent suicidal behavior in patients diagnosed with schizophrenia (62% of patients) or schizoaffective disorder (28% of patients) (n = 980)*.



Kaplan-Meier Estimates of Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide

*27% of patients in this study were considered resistant to standard antipsychotic drug treatment

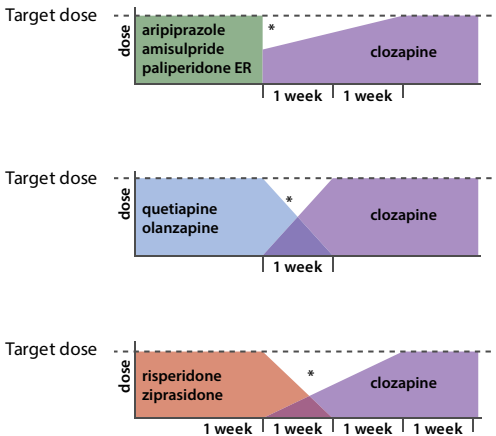
Safety and Tolerability[6]

	Percent of Patients Reporting (n=842)		Percent of Patients Reporting (n=842)
Drowsiness/Sedation	39	Tremor	6
Salivation	31	Syncope	6
Tachycardia	25	Sweating	6
Dizziness/vertigo	19	Dry mouth	6
Constipation	14	Nausea	5
Hypotension	9	Visual disturbances	5
Headache	7	Fever	5

Adverse reactions reported by ≥ 5% of clozapine-treated adult subjects with schizophrenia in premarket clinical trials. These rates are not adjusted for duration of exposure.

Switching[2]

Switching from Oral Antipsychotics to Clozapine



Immediate stop possible, begin clozapine at middle dose.

Begin clozapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect.

* Benzodiazepine or anticholinergic medication administered during reduction of olanzapine, quetiapine, and clozapine can alleviate side effects such as insomnia, anxiety, agitation, and/or psychosis.

References

1. CLOZARIL 25 mg and 100 mg Tablets, Novartis Pharmaceuticals, electronic Medicines Compendium, August 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422, 431–436.
3. Nasrallah HA, Atypical Antipsychotic-Induced Metabolic Side Effects: Insights from Receptor-Binding Profiles, 2008, *Molecular Psychiatry*, 13, 27–35.
4. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics, 2010, *European Psychiatry*, 25, S12-S21.
5. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine, 1988, *Arch Gen Psychiatry*, 45, 789–796.
6. CLOZARIL Prescribing Information, Novartis Pharmaceuticals Corporation, October 2011.

Indications and Usage[1]

Olanzapine is an atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in adults.
2. Maintaining clinical improvement during continuation therapy in adult patients with schizophrenia who have shown an initial treatment response.
3. The treatment of symptoms of bipolar I disorder in adults, including:
   - Moderate to severe manic episodes
   - Prevention of recurrence of manic episode

*Licenses differ between countries. Please refer to local Product Information guides.

Mechanism of Action[1, 2]

The therapeutic activity of olanzapine is mediated through a combination of $5HT_{2A}$, $5HT_{2C}$, $5HT_6$ serotonin, H_1, H_2 histamine, D_1, D_2, D_3, D_4, D_5 dopamine, M_5 muscarinic, α_1, and α_2-adrenergic receptor antagonism. It also has moderate M_1, M_2, and M_3 blocking properties.

Dosing and Administration[1]

Indication	Initial dose	Effective dose	Maximum dose
Schizophrenia	10 mg once daily	5–20 mg/day	20 mg/day
Manic episode	15 mg once daily in monotherapy 10 mg once daily in combination therapy	5–20 mg/day	20 mg/day

During treatment for schizophrenia, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range of 5–20 mg/day.

Increase to a dose greater than recommended starting dose is advised only after clinical reassessment and should occur at intervals of not less than 24 hours.

Gradual tapering should be considered when discontinuing.

Special Considerations[1]

Olanzapine is not approved for treatment of dementia-related psychosis, and is not recommended for the treatment of Parkinson's disease symptoms.

Caution is advised when prescribing for patients with prostatic hypertrophy, paralytic ileus and related conditions, and low leukocyte and/or neutrophil counts.

Olanzapine is contraindicated for patients with known risk of narrow-angle glaucoma.

A lower starting dose should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors such as ciprofloxacin.

Pharmacokinetics[1]

Dose	Time to Peak Plasma Concentration	Mean Elimination Half-Life (hrs)	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	Creatinine Clearance (L/hr)	CYP450 Enzymes Responsible for Biotransformation
10 mg	6 hrs	30	1 week (pooled data)	7%	18.2	**CYP1A2**, CYP2D6
Elderly (65 and over)	6 hrs	52	—*	7%	17.5	**CYP1A2**, CYP2D6
Smokers	6 hrs	39	—*	7%	Reduced 67%	**CYP1A2**, CYP2D6
Smokers with mild hepatic impairment	6 hrs	49	—*	7%	14	**CYP1A2**, CYP2D6

CYP450 = Cytochrome P450

*Time to steady-state concentration varies between populations.

Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Recommended Initial Dose
Mild	Highly metabolized, dosing adjustment not required; 5 mg/day starting dose should be considered				5 mg/day
Moderate					
Severe					

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Hepatic Impairment

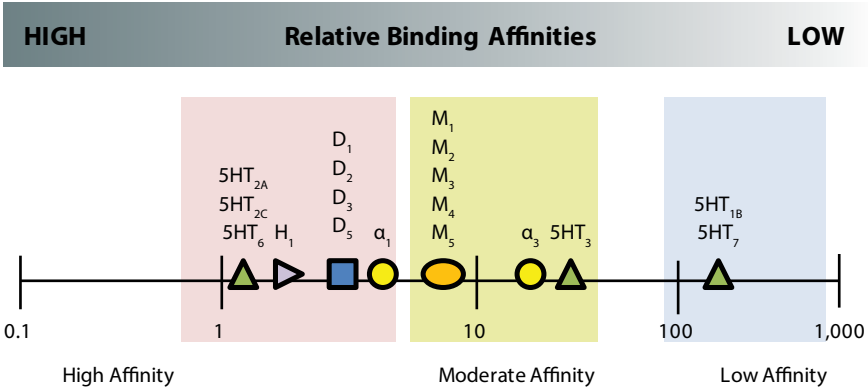
Transient, asymptomatic elevations of hepatic aminotransferases, ALT and AST, have been seen commonly, especially in early treatment. Starting dose should be 5 mg/day for patients with hepatic impairment, and only increased with caution.

Caution should be exercised and follow-up organized in patients with elevated ALT and/or AST, in patients:

- with signs and symptoms of hepatic impairment
- with pre-existing conditions associated with limited hepatic functional reserve
- who are being treated with potentially hepatotoxic medicines

In cases where hepatitis (including hepatocellular, cholestatic, or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Pharmacodynamics[2]



Efficacy[3]

Summary of Results for Efficacy in the Treatment of Schizophrenia

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R criteria for schizophrenia	10 mg/day	6 wks	BRPS, PANSS, CGI-S	✓ 10, 15 mg vs. placebo No advantage in medium vs. high dose
	5 ± 2.5 mg/day 10 ± 2.5 mg/day 15 ± 2.5 mg/day			
Adult DSM-IV criteria for schizophrenia	10–20 mg/day	8 wks, observed for 8 months[1]	BPRS	✓ superior to placebo in time to relapse

[1]Patients remained stable on olanzapine for 8 weeks and then were observed for relapse over an 8-month period. An excess of placebo relapses compared to olanzapine relapses resulted in early termination of the long-term study.

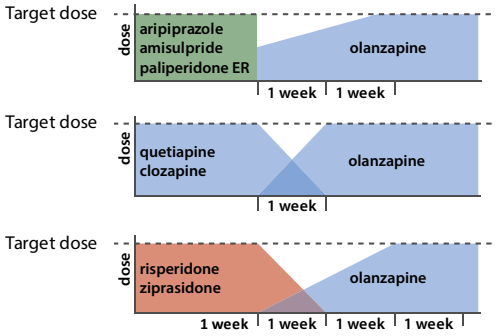
Safety and Tolerability[3]

	Percent of Patients Reporting	
	Placebo (n=294)	Olanzapine (n=160)
Somnolence	13	29
Accidental injury	8	12
Insomnia	11	12
Dizziness	4	11
Asthenia	9	10
Dry mouth	5	9
Constipation	4	9
Dyspepsia	5	7
Rhinitis	6	7
Fever	2	6
Abnormal gait	1	6
Cough increased	3	6
Back pain	2	5
Ecchymosis	3	5
Weight gain	3	5
Extremity pain	3	5
Joint pain	3	5

Adverse reactions reported by ≥ 5% among patients treated with oral olanzapine (doses ≥ 2.5 mg/day) in short-term, placebo-controlled trials.

Switching[2]

Switching from Oral Antipsychotics to Olanzapine



Immediate stop possible, begin olanzapine at middle dose

Begin olanzapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect.

References

1. Olanzapine 15 mg Film-coated Tablets, Summary of Product Characteristics, Accord Healthcare Ltd, electronic Medicines Compendium, November 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408-422, 431-436.
3. ZYPREXA Prescribing Information, Lilly USA, LLC, June 2011.

Indications and Usage[1]

Olanzapine pamoate monohydrate is a long-acting injectable (LAI) atypical antipsychotic agent indicated for the maintenance treatment of adult patients with schizophrenia sufficiently stabilized during acute treatment with oral olanzapine*.

Mechanism of Action[1, 2]

The therapeutic activity of olanzapine is mediated through a combination of $5HT_{2A}$, $5HT_{2C}$, $5HT_6$ serotonin, H_1, H_2 histamine, D_1, D_2, D_3, D_4, D_5 dopamine, M_5 muscarinic, α_1, and α_2-adrenergic receptor antagonism. It also has moderate M_1, M_2, and M_3 blocking properties.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

Patients should be treated initially with oral olanzapine before administering olanzapine LAI to establish tolerability and response.

Recommended dose scheme between oral olanzapine and olanzapine LAI

Target oral olanzapine dose	Recommended starting dose of olanzapine LAI	Maintenance dose after 2 months of olanzapine LAI treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

After each injection, observe patient in a healthcare facility for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

Patients should be monitored carefully for signs of relapse during the first one to two months of treatment.

During treatment, dose may subsequently be adjusted on the basis of individual clinical status within the range of 150 mg-300 mg every 2 weeks or 300–405 mg every 4 weeks.

Dosing and Administration[1]

olanzapine LAI vial strength (mg)	Volume of solvent to add, mL
210	1.3
300	1.8
405	2.3

Final olanzapine LAI Suspension Volume to Inject

Dose (mg)	Final volume to inject (mL)
150	1.0
210	1.4
300	2.0
405	2.7

Olanzapine LAI should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique and in locations where post-injection observation and access to appropriate medical care in the case of overdose can be assured.

If oral olanzapine supplementation is clinically indicated, then the combined total dose of olanzapine from both formulations should not exceed the corresponding maximum oral olanzapine dose of 20 mg/day.

Special Considerations[1]

Olanzapine LAI should not be used to treat patients with schizophrenia who are in acutely agitated or severely psychotic state such that immediate symptom control is warranted.

Olanzapine LAI is contraindicated for patients with known risk of narrow-angle glaucoma.

Olanzapine is not approved for treatment of dementia-related psychosis, and is not recommended for the treatment of Parkinson's disease symptoms.

Caution is advised when prescribing for patients with prostatic hypertrophy, paralytic ileus and related conditions, and low leukocyte and/or neutrophil counts.

A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin.

A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

In cases where hepatitis (including hepatocellular, cholestatic, or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Pharmacokinetics[1]

Time to Peak Plasma Concentration	Mean Elimination Half-Life	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
15–45 min	30 days	After 5 months*	7%	CYP1A2, CYP2D6

CYP450 = Cytochrome P450

*Steady-state is reached after 5 months, although steady-state like concentrations are reached much faster.

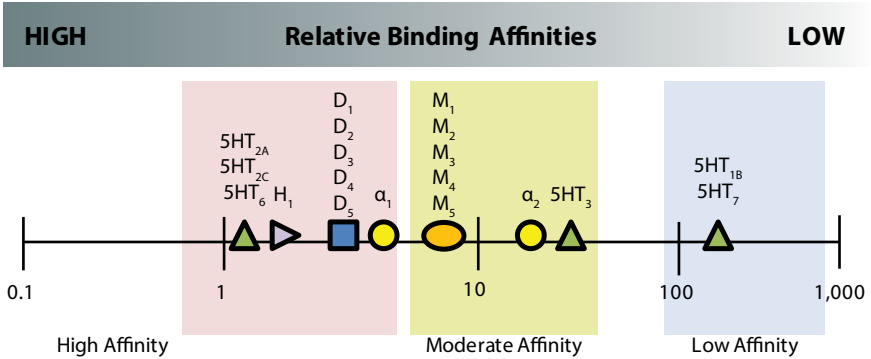
Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Dosing
Mild	< 10 mL/min	No significant difference in renally impaired versus healthy subjects.			A well-tolerated and effective dosage regimen using oral olanzapine should be established in patients before treatment with olanzapine LAI. A lower starting dose (150 mg every 4 weeks) should be considered.
Moderate					
Severe					

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Hepatic Impairment
Transient, asymptomatic elevations of hepatic aminotransferases, ALT, and AST have been seen commonly, especially in early treatment. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 150 mg every 4 weeks and only increased with caution. Caution should be exercised and follow-up organized in patients with elevated ALT and/or AST, in patients: • with signs and symptoms of hepatic impairment • with pre-existing conditions associated with limited hepatic functional reserve • who are being treated with potentially hepatotoxic medicines

Pharmacodynamics[1, 2, 3]



Efficacy[1]

Summary of Results for Efficacy in the Treatment of Schizophrenia

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult schizophrenia	405 mg/4 weeks 300 mg/2 weeks 210 mg/2 weeks	8 wks	PANSS	✓ 405 mg, 300 mg, 210 mg vs. placebo
Adult schizophrenia stabilized on oral olanzapine for 4-8 weeks	150 mg/2 weeks 300 mg/2 weeks 405 mg/4 weeks	24 wks	Exacerbation of schizophrenia symptoms*, BPRS Positive Scale	✓ 150, 300, 405 mg non-inferior to oral olanzapine 10, 15, and 20 mg pooled doses

*Exacerbation was measured by worsening of items on PANSS and BPRS Positive Scale, and hospitalization due to worsening of positive psychotic symptoms.

Safety and Tolerability[1]

Post-injection syndrome reactions have occurred with olanzapine LAI leading to symptoms consistent with olanzapine overdose:

- Sedation (mild to coma)
- Delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment)
- Extrapyramidal symptoms
- Dysarthria
- Ataxia
- Aggression dizziness
- Weakness
- Hypertension
- Convulsion

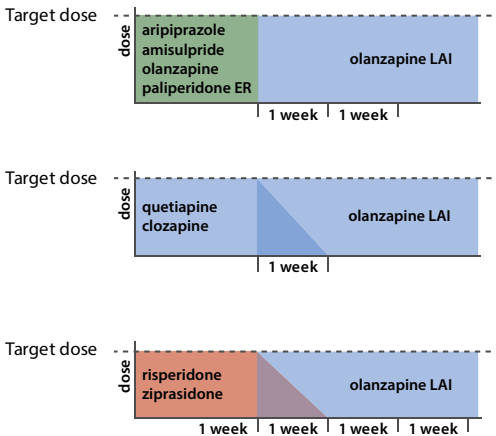
In clinical trials, the incidence of injection site-related adverse reactions was approximately 8%.

The most commonly reported injection site-related adverse reaction was pain (5%).

Other adverse reactions observed in patients treated with olanzapine LAI were similar to those seen with oral olanzapine.

Switching[2]

Switching from Oral Antipsychotics to Olanzapine LAI



Immediate stop possible for aripiprazole, amisulpride, oral olanzapine, and paliperidone ER. Begin olanzapine LAI at equivalent oral olanzapine dose.

Patients should be treated initially with oral olanzapine before administering olanzapine LAI to establish tolerability and response.

References

1. ZYPADHERA 210 mg, 300 mg, and 405 mg, powder and solvent for prolonged release suspension for injection, Summary of Product Characteristics, Eli Lilly and Company Ltd., July 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422, 431–436.

Indications and Usage[1]

Paliperidone ER is an oral atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in adults.

2. The treatment of psychotic or manic symptoms of schizoaffective disorder in adults. (The effect on depressive symptoms has not been demonstrated.)

Mechanism of Action[1, 2]

The therapeutic activity of paliperidone ER is mediated through a combination of serotonin $5HT_{2A}$, $5HT_7$, dopamine D_2, and α_1-adrenergic receptor antagonism. Paliperidone ER also blocks, to a lesser extent, histamine H_1 and α_2-adrenergic receptors.

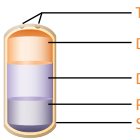
*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

	Initial Dose	Recommended Dose Range
Schizophrenia (Adults)	6 mg/day	3–12 mg/day
Acute Schizophrenia (Adults)*	9 mg/day	9–12 mg/day
Schizoaffective Disorder (Adults)	6 mg/day	6–12 mg/day

* Based on clinical experience/trials.

Dosing and Titration[3]



In the gastrointestinal tract, osmotic pressure pulls water into the tablet core.

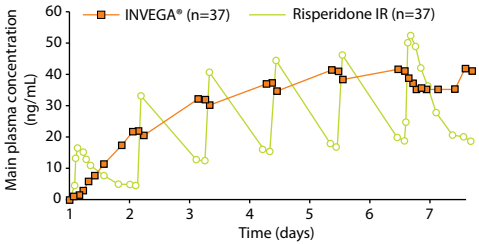
As water enters the core, it is absorbed by the push layer. The push layer expands, forcing INVEGA® from drug compartment 1 through the holes in the dome.

Over time, the push layer continues to expand. This expansion forces INVEGA® from drug compartment 2, providing continued release for up to 24 hours.

(1) In the gastrointestinal tract, the water-dispersible colour overcoat erodes quickly. (2) Water is then absorbed through the semipermeable membrane at a controlled rate, which then controls the rate of drug delivery. (3) The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone ER that is then pushed out through the tablet orifices.

Invega uses OROS® technology to deliver paliperidone ER at a controlled rate via osmotic pressure.

Dosing and Titration[4]



IR=immediate-release

Reprinted from: Birnbaum M, Sharif Z. Medication adherence in schizophrenia: patient perspectives and the clinical utility of paliperidone ER. *Patient Preference and Adherence* 2008 2: 233–240. With permission from Dove Medical Press Ltd

The constant rate of release minimizes the fluctuations associated with immediate-release second-generation antipsychotic agents.

Special Considerations[1]

Because the paliperidone ER tablet is non-deformable and does not change shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets.

Antipsychotic medicinal products (including risperidone) with α-adrenergic blocking effects have been reported to induce priapism. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3-4 hours.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Caution is advised when prescribing with medicines known to prolong the QT interval, e.g., class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine).

Paliperidone ER may induce orthostatic hypotension in some patients based on its alpha-blocking activity, and should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g. dehydration and hypovolemia).

Pharmacokinetics[1]

Time to Peak Plasma Concentration (Hours)	Time to Steady-State Concentration (Days)	Mean Elimination Half-Life (Hours)
24	4–5	24

Oral Bioavailability	Bioavailability with Food	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
28%	42%	59%	N/A

CYP450 = Cytochrome P450

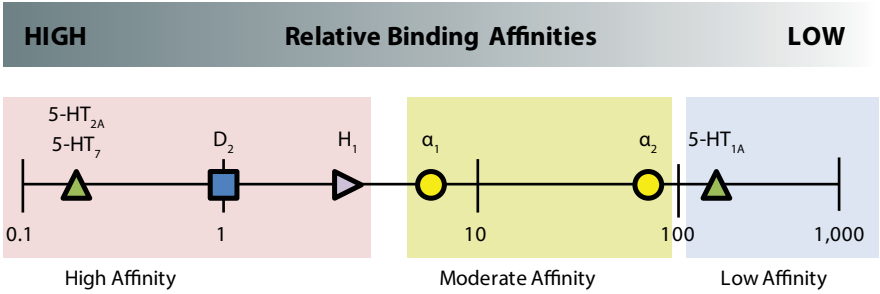
Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Recommended Initial Dose (mg/day)	Maximum Recommended Dose (mg)
Mild	≥50 - <80	32	24	1.5 Fold	3	6
Moderate	≥30 - <50	64	40	2.6 Fold	1.5	3
Severe	≥10 - <30	71	51	4.8 Fold	1.5	3
Paliperidone ER is not recommended for patients with CLcr < 10ml/min						

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment.

Pharmacodynamics[1, 2, 5, 6, 7]



The clinical significance of receptor binding is unknown.

Efficacy[8, 9, 10]

The efficacy of Paliperidone ER (3 mg to 12 mg once daily**) was established in three placebo- and active-controlled (olanzapine), 6-week, fixed-dose trials in non-elderly adult subjects who met the DSM-IV criteria for schizophrenia. Trials were conducted in North America, Eastern and Western Europe, and Asia. Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS).

	Placebo	3 mg/day Paliperidone ER	6 mg/day Paliperidone ER	9 mg/day Paliperidone ER	12 mg/day Paliperidone ER
Davidson et al. (2007) Total PANSS Score[a] Change from Baseline[a] *p*-value vs. Placebo	(n=123) 93.9 (12.7) -2.8 (20.9)	(n=127) 91.6 (12.2) -15 (19.6) < 0.001		(n=125) 93.9 (13.2) -16.3 (21.8) < 0.001	
Kane et al. (2007) Total PANSS Score[a] Change from Baseline[a] *p*-value vs. Placebo	(n=126) 94.1 (10.7) -4.1 (23.2)		(n=123) 94.3 (10.5) -17.9 (22.2) < 0.001	(n=122) 93.2 (11.9) -17.2 (20.2) < 0.001	(n=129) 94.6 (11.0) -23.3 (20.1) < 0.001
Marder et al. (2007) Total PANSS Score[a] Change from Baseline[a] *p*-value vs. Placebo	(n=105) 93.6 (11.7) -8.0 (21.5)		(n=111) 92.3 (12.0) -15.7 (18.9) < 0.01		(n=111) 94.1 (11.4) -17.5 (19.8) < 0.001

[a]Mean (Standard Deviation), **The highest approved dose of paliperidone ER is 12 mg/day.

Patient Functioning[11]

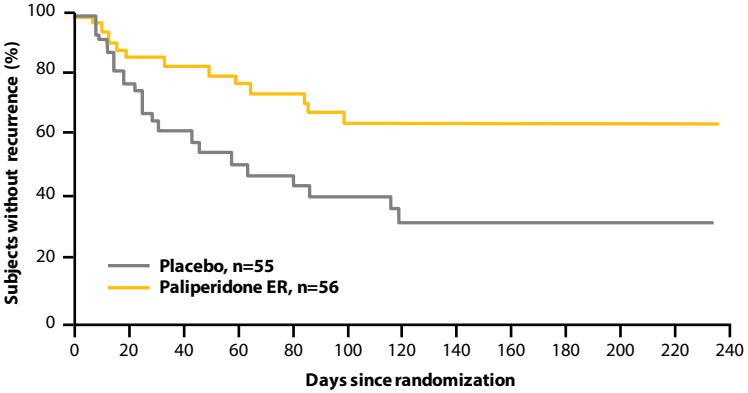
Efficacy was further demonstrated in a pooled analysis of three placebo- and active-controlled (olanzapine), 6-week, fixed-dose trials in non-elderly adult subjects who met the DSM-IV criteria for schizophrenia. Efficacy on patient functioning was evaluated using the Personal and Social Performance scale (PSP).

	Placebo (n=317)	3 mg/day Paliperidone ER (n=113)	6 mg/day Paliperidone ER (n=212)	9 mg/day Paliperidone ER (n=234)	12 mg/day Paliperidone ER (n=220)
Baseline PSP Score*	48.1 (13.8)	48.4 (13.7)	46.8 (13.6)	49.0 (15.2)	46.0 (13.7)
Change from Baseline*	0.5 (15.0)	8.3 (17.1)	9.0 (14.8)	7.8 (14.3)	9.5 (15.0)
p-value vs. Placebo†,‡		< 0.001	< 0.001	< 0.001	< 0.001

*Mean (Standard Deviation), †Based on analysis of covariance model with protocol, treatment (placebo and Paliperidone ER 3 mg, 6 mg, 9 mg, and 12 mg), and analysis center within protocol as factors and baseline value as a covariate., ‡Comparisons with placebo without multiplicity adjustment.

Efficacy[12, 13]

Paliperidone ER demonstrated positive efficacy, and the time to relapse of symptoms was significantly longer in patients treated with paliperidone ER compared with those treated with placebo (p = 0.005). Relapse events were experienced by 53% (n=29) of patients in the placebo group compared with 25% of patients treated with paliperidone ER. Using Kaplan Meier analysis, the time points at which 25% of patients experienced a relapse in the placebo and paliperidone ER groups were 23 and 83 days, respectively.



Safety and Tolerability[1, 11]

The following table summarizes treatment-emergent adverse events (AEs) reported by ≥5% of adult patients with schizophrenia who received at least 1 dose of double-blind study medication during the phase 3 double-blind studies. The AEs that appeared to be dose-related in the three 6-week trials included: akathisia, extrapyramidal disorder, and tachycardia. With the exception of tachycardia (6 mg dose), the increased response was seen at the 9 mg dose.

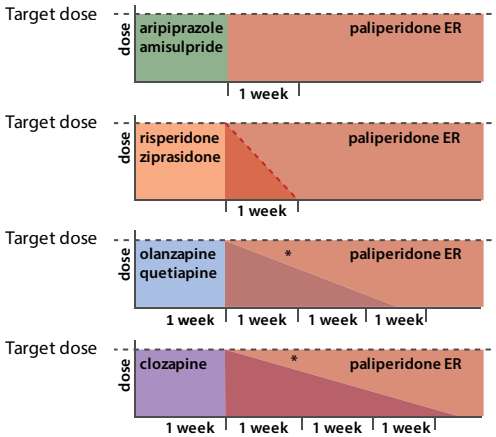
	Placebo (n=127)	3 mg/day Paliperidone ER (n=127)	6 mg/day Paliperidone ER (n=235)	9 mg/day Paliperidone ER (n=246)	12 mg/day Paliperidone ER (n=242)
Headache	12	12	12	14	14
Akathisia	4	4	3	8	10
Extrapyramidal symptoms	2	2	2	7	7
Somnolence	3	3	3	7	5
Dizziness	4	4	5	4	5
Sedation	4	4	5	3	6
Insomnia	14	11	12	14	11
Anxiety	8	9	7	6	5
Agitation	8	6	7	5	5

Safety and Tolerability[1, 11] continued

	Placebo (n=127)	3 mg/day Paliperidone ER (n=127)	6 mg/day Paliperidone ER (n=235)	9 mg/day Paliperidone ER (n=246)	12 mg/day Paliperidone ER (n=242)
Psychotic disorder	5	4	3	3	2
Nausea	5	6	4	4	4
Vomiting	5	2	3	4	5
Constipation	6	6	3	3	3
Dyspepsia	4	2	3	2	5
Tachycardia	3	2	7	7	7
Sinus tachycardia	4	9	4	4	7
QTc prolonged	3	3	4	3	5

Switching[2]

Switching from Oral Antipsychotics to Paliperidone ER



Immediate stop possible; initiate paliperidone ER at an intermediate, or if needed, effective dose.

Due to OROS technology, paliperidone ER can be initiated at full desired dose, however, titration over 1-2 weeks may be appropriate for some patients.

Clinical experience has shown that olanzapine and quetiapine should be tapered off gradually over a period of 3-4 weeks due to the risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha-1 receptor blocking.

Clozapine should always be tapered off gradually, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication administered during reduction of olanzapine, quetiapine, and clozapine can alleviate side effects such as insomnia, anxiety, agitation, and/or psychosis.

References

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8. Davidson M et al. Efficacy, Safety and Early Response of Paliperidone Extended Release Tablets (Paliperidone ER): Results of a 6-week, Randomized, Placebo-controlled Study, 2007, *Schizophrenia Research*, 93, 117–30.

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9. Kane J et al. Treatment of Schizophrenia with Paliperidone Extended-Release Tablets: A 6-week Placebo-Controlled Trial, 2007, *Schizophrenia Research*, 90, 147–61.
10. Marder SR et al. Efficacy and Safety of Paliperidone Extended-Release Tablets: Results of a 6-Week, Randomized, Placebo-Controlled Study, 2007, *Biological Psychiatry*, 62, 1363–70.
11. Meltzer H et al. Efficacy and Tolerability of Oral Paliperidone Extended-Release Tablets in the Treatment of Schizophrenia: Pooled Data from Three 6-Week, Placebo-Controlled Studies, 2008, *Journal of Clinical Psychiatry*, 69 (5), 817–29.
12. INVEGA Prescribing Information, Janssen Pharmaceuticals, Inc., June 2011.
13. Kramer M et al. Paliperidone Extended-Release Tablets for Prevention of Symptom Recurrence in Patients with Schizophrenia, *J Clin Psychopharmacol*, 2007, 27, 6-14.

Indications and Usage[1]

Paliperidone palmitate is a long-acting (once monthly) atypical antipsychotic agent indicated for the maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone*.

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone palmitate may be used without prior stabilization with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

Mechanism of Action[1, 2, 3]

The therapeutic activity of paliperidone is mediated through a combination of serotonin $5HT_{2A}$, $5HT_7$, dopamine D_2, and α_1-adrenergic receptor antagonism. Paliperidone ER also blocks, to a lesser extent, histamine H_1 and α_2-adrenergic receptors.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

	Initial Dose Day 1	Second Dose Day 8 (+/- 2 Days)	Monthly Dose
Schizophrenia (Adults)	150 mg eq. Deltoid	100 mg eq. Deltoid	25–150 mg eq.* Deltoid/gluteal

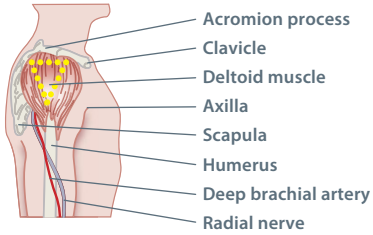
Dose of paliperidone palmitate (mg)	Dose of paliperidone palmitate (mg eq. of paliperidone)
39 mg	25 mg eq.
78 mg	50 mg eq.
117 mg	75 mg eq.
156 mg	100 mg eq.
234 mg	150 mg eq.

***Higher dosing within this range may be appropriate in patients who have had:**

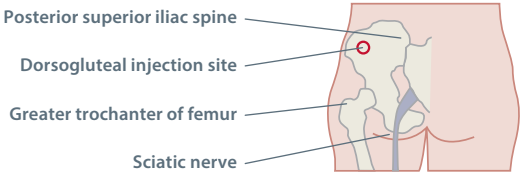
- high dosages of the previous antipsychotic
- prior antipsychotic combination therapy
- persistent or (post) acute psychotic symptoms

Dosing and Administration[4]

Location of the deltoid muscle (upper arm) site for IM injection



Location of the dorsogluteal muscle (buttock) site for IM injection



Special Considerations[1]

Paliperidone palmitate should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

Antipsychotic medicinal products (including risperidone) with α-adrenergic blocking effects have been reported to induce priapism. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3–4 hours.

Paliperidone palmitate should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Caution should be exercised when paliperidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity.

Paliperidone should be used with caution in patients with possible prolactin-dependent tumors.

Pharmacokinetics[1, 3, 4]

Time to Peak Plasma Concentration (Days)	Mean Elimination Half-life (Days)	Time to Steady-state Concentration (Days)	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
13	25–49*	120–250 days**	59%	N/A

*Dose-dependent

**After approximately 4-5 half-lives, depending on selected maintenance dose

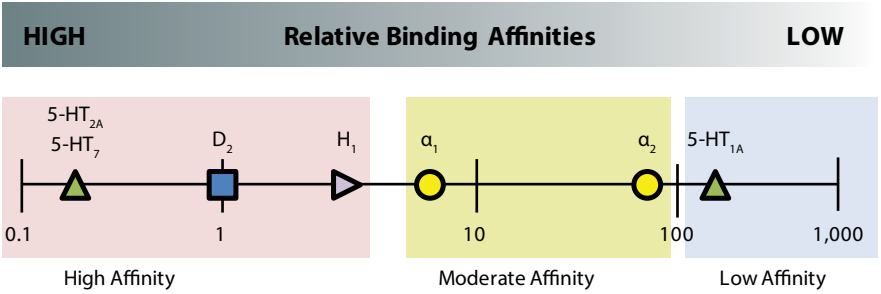
Pharmacokinetics in Special Populations[1, 3]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Recommended Initial Dose (Day 1)	Second Dose (Day 8)	Monthly Dose
Mild	$50 \leq CL_{cr} < 80$	32	24	1.5	100 mg eq. Deltoid	75 mg eq. Deltoid	50 mg eq. Deltoid/gluteal (25–100mg eq.)
Moderate	Not recommended						
Severe	Not recommended						

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment.

Pharmacodynamics[1, 2, 3, 5, 6]



The clinical significance of receptor binding is unknown.

Efficacy[3, 7]

The efficacy of intramuscular paliperidone palmitate (PP) in the acute therapy of adult patients with schizophrenia was analyzed in three randomized, double-blind, placebo-controlled, multi-center, fixed-dose studies of 9 or 13 weeks in duration. Analyses were conducted on randomized patients who received at least one dose of double-blind study medication and had at least one valid post-baseline efficacy measurement.

	Placebo	25 mg eq./ month PP	50 mg eq./ month PP	100 mg eq./ month PP	150 mg eq./ month PP
Pandina et al. 2010[†, ‡]	n=160	n=155		n=161	n=160
Total PANSS Score[5]	83.9 (21.44)	78.8 (19.88)		74.6 (18.06)	75.2 (18.59)
Change from Baseline	- 2.9	- 8.0		- 11.6	- 13.2
p-value vs. Placebo		< 0.05		< 0.05	< 0.05

*Patients received gluteal injections of PP or PL on days 1 and 8, and monthly thereafter, †Patients received deltoid injections of PP 150 mg eq. on day 1, deltoid or gluteal injections of PP 25, 100, 150 mg eq. on day 8, and monthly thereafter, ‡Mean (Standard Deviation)

Patient Functioning[1]

Efficacy was further demonstrated in a randomized placebo-controlled study to asses the efficacy of three doses of paliperidone palmitate, 13-week, fixed-dose trials in non-elderly adult subjects who met the DSM-IV criteria for schizophrenia. Efficacy was evaluated using the Personal and Social Performance scale (PSP).

	Placebo (n=160)	25 mg eq./month PP (n=155)	100 mg eq./month PP (n=161)	150 mg eq./month PP (n=160)
Baseline PSP Score[a, b]	49.7 (12.3)	49.6 (12.5)	50.2 (12.8)	48.8 (13.0)
Change from Baseline[a]	1.7 (15.6)	2.9 (15.3)	6.1 (13.6)	8.3 (14.7)
***p*-value vs. Placebo[c, d]**	—	0.51	0.007	< 0.001

[a]Mean (Standard Deviation)

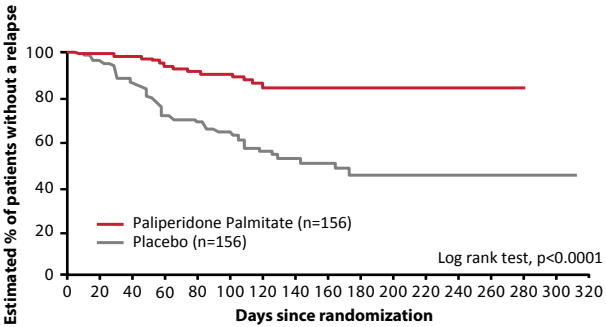
[b]Range of patient functioning is evaluated and rated with a score between 1-100, with higher values reflecting better personal and social functional levels.

[c]Based on analysis of covariance model with protocol, treatment (placebo and paliperidone palmitate 25, 100, and 150 mg eq.), and country as factors and baseline value as a covariate.

[d]Comparisons with placebo without multiplicity adjustment.

Efficacy[8]

A randomized, double-blind, placebo-controlled study assessing the efficacy and safety of paliperidone palmitate (PP) in delaying time to relapse in patients with schizophrenia demonstrated that relapse event rates were significantly lower in the paliperidone palmitate group (10% of patients [n=15/156]), vs. placebo (34% of patients [n=53/156]).



Relapse was defined as one or more of the following:

- hospitalization for symptoms of schizophrenia (involuntary or voluntary)
- 25% increase in PANSS total score for patients scores >40 at randomization, or a 10-point increase for patients scores ≤40 at randomization
- deliberate self-injury or aggressive behavior or suicidal or homicidal ideation
- increase in pre-specified individual PANSS items scores ≥5 for patients scores ≤3, or to ≥6 for patients scores = 4 at randomization

Safety and Tolerability[4]

	Placebo (n=164)	25 mg eq./ month PP (n=160)	100 mg eq./ month PP (n=165)	150 mg eq./ month PP (n=163)
Insomnia	16.5	12	10	13
Schizophrenia	11.5	8	8	8
Headache	7.5	10.5	6.5	6
Injection site pain	3.5	8.5	6	8
Anxiety	6.5	5	6	7.5
Agitation	6.5	7.5	5	4
Psychotic disorder	5	4.5	4	3.5
Akathisia	5	1.5	5	5.5

Adverse reactions reported by greater than or equal to 5% of paliperidone palmitate-treated adult subjects with schizophrenia in pivotal clinical trials.

Switching[1, 9]

Switching to Paliperidone Palmitate (from oral paliperidone ER or oral risperidone)
Patients who are taking oral paliperidone ER or oral risperidone can switch to paliperidone palmitate (PP) beginning with the optimized dosing initiation regimen below.

Initial Dose, Day 1	Second Dose, Day 8 (+/- 2 days)	Maintenance Dose*
150 mg eq. Deltoid	100 mg eq. Deltoid	25–150 mg eq. Deltoid/gluteal

*** Higher maintenance dose (within the range of 25-150 mg eq.) may be appropriate in patients who:**

- **are at imminent risk of relapse**
- **have needed high dosages of previous antipsychotics**
- **have persistent or (post) acute psychotic symptoms**
- **are overweight**

***Lower maintenance dose (within the range of 25-150 mg eq.) may be considered if the patient has previously been stabilized at a lower dose of antipsychotic medication or is known to be sensitive to side effects**

Switching to Paliperidone Palmitate (from previous long-acting antipsychotics)
When switching from RLAI, the Xeplion EU Summary of Product Characteristics provides pharmacokinetic data which may help identify the most appropriate dose for the individual patient. However, as with any switching, the dose of paliperidone palmitate must be individualized by taking into account patient-specific variables, such as:

- Type and dose of previous antipsychotic
- Response to previous medication
- Acuity and severity of psychotic symptoms
- Relevant psychotropic concomitant medication
- Body weight
- Age
- Renal impairment, etc.

When switching from previous LAI antipsychotics, PP can be administered in place of the next scheduled injection and then monthly thereafter, with no need for the 1-week initiation dose.

Switching[1, 9]

Use the dosing charts below to guide the selection of the most appropriate maintenance dose of PP. The doses listed will achieve similar plasma levels, however, this is not equivalence.

Conversion from Paliperidone ER to Paliperidone Palmitate

Formulation	Paliperidone ER Tablets	Paliperidone palmitate
Dosing Frequency	Once daily (mg)	Monthly Maintenance Dose (mg eq.)
Dose	3	25–50
	6	75
	9	100
	12	150

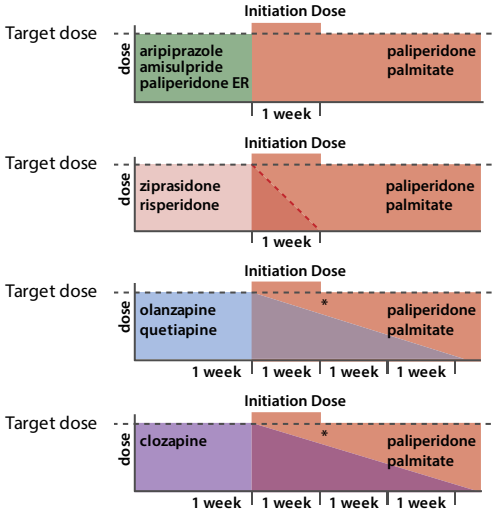
Conversion from Risperidone LAI to Paliperidone Palmitate

Formulation	Risperidone LAI	Paliperidone palmitate
Dosing Frequency	Every 2 Weeks (mg)	Monthly Maintenance Dose (mg eq.)
Dose	25	25–50
	37.5	75
	50	100
	—	150

Please see the next page for guidance on tapering off previous oral antipsychotics.

Switching[2]

Switching from Oral Antipsychotics to Paliperidone Palmitate



Risperidone and ziprasidone can be tapered off over a period of 1 week due to the risk of withdrawal symptoms such as insomnia.

Clinical experience has shown that olanzapine and quetiapine should be tapered off over a period of 3–4 weeks due to the risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha-1 receptor blocking.

Clozapine should always be stopped gradually, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication administered during reduction of olanzapine, quetiapine, and clozapine can alleviate side effects.

References

1. Xeplion 50 mg, 75 mg, 100 mg, and 150 mg prolonged release suspension for injection, Summary of Product Characteristics, Janssen Pharmaceuticals Inc., electronic Medicines Compendium, August 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422,431–436.
3. Hoy et al. Intramuscular paliperidone palmitate. *CNS Drugs* 2010;24:227–244.
4. Xeplion for the treatment of schizophrenia Product Monograph, Janssen Pharmaceuticals, Inc. 2011
5. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics, 2010, *European Psychiatry*, 25, S12-S21.
6. National Institutes of Mental Health Psychoactive Drug Screening Program. Cited March 2013. Available http://pdsp.med.unc.edu/indexR.html.
7. Pandina et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacology* 2010;30:235–244.
8. Hough et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 2010;116:107–117.
9. Samtani et al. Dosing and switching strategies for paliperidone palmitate. *CNS Drugs* 2011;25:1–17.

Indications and Usage[1, 2]

Quetiapine fumarate is an atypical antipsychotic agent indicated for:

1. The treatment of schizophrenia in adults, including preventing relapse in stable schizophrenic patients who have been maintained on quetiapine.

2. The treatment of symptoms of bipolar I disorder, including:
   - moderate to severe manic episodes
   - major depressive episodes
   - the prevention of recurrence in patients whose manic or depressive episodes have responded to quetiapine treatment

3. Add-on treatment of major depressive disorder (MDD)*.

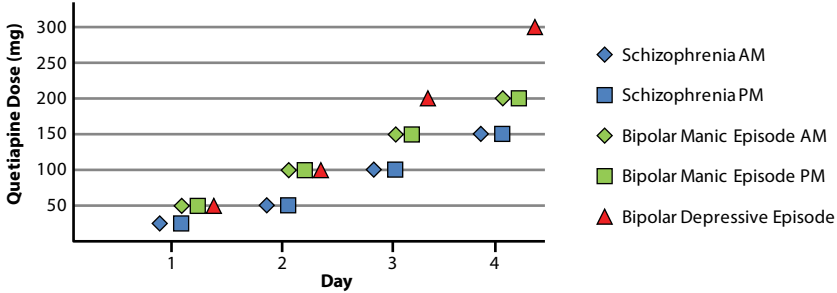
*Licenses differ between countries. Please refer to local Product Information guides.

Mechanism of Action[1, 2, 3]

The therapeutic activity of quetiapine is mediated through a combination of $5HT_{1A}$ and $5HT_2$ serotonin, H_1 histamine, D_1 and D_2 dopamine, α_1 and α_2-adrenergic receptor antagonism. Norquetiapine also has high affinity for the NET, norepinephrine transporter, and M_1 muscarinic receptors.

Dosing and Administration Quetiapine IR[1]

Titration Schedule for quetiapine fumarate (immediate–release tablets)



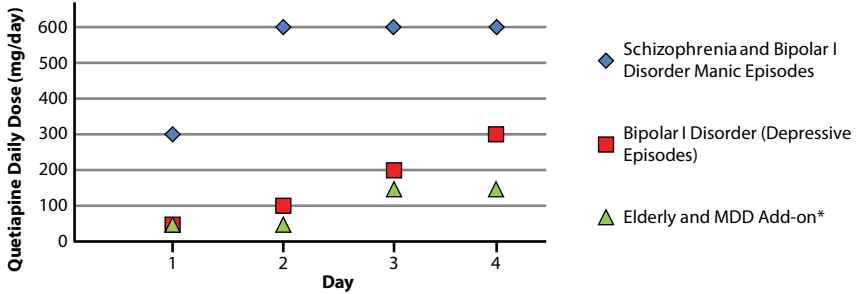
From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300–450 mg/day. The dose range may be adjusted within range of 150–750 mg/day.

Can be administered as monotherapy or as adjunct therapy to mood stabilizers. Effective dose range is 400–800 mg/day. Dosage up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

Should be administered once daily at bedtime. Recommended daily dose is 300 mg/day. No additional benefit was seen in 600 mg group compared to 300 mg group in clinical trials. Dose can be reduced to a minimum of 200 mg/day in the event of tolerance concerns.

Dosing and Administration Quetiapine ER[2]

Titration Schedule for quetiapine fumarate (extended-release)



Medication should be taken 1 hour before a meal. Effective dose range is 400–800 mg/day. Maximum dose is 800 mg/day.

Medication should be taken at bedtime. Doses > 300 mg should be initiated with caution.

Antidepressent effect was seen at 150 and 300 mg/day in MDD add-on therapy trials, and at 50 mg/day in short-term monotherapy trials.

*Licenses differ between countries. Please refer to local Product Information guides.

Special Considerations[1, 2]

Use with caution in elderly patients, starting with 25 mg/day increasing in increments of 25 to 50 mg/day, to an effective dose.

Quetiapine may indude orthostatic hypotension, especially during the initial dose-titration period, more common in elderly patients. Dose reduction or more gradual titration should be considered if this occurs.

Slower titration regime could be considered in patients with underlying cardiovascular disease.

Quetiapine fumarate (extended release) should be used with caution in patients with: hepatic impairment, cardiovascular disease, cerebrovascular disease, or risk for aspiration pneumonia.

In these patients, a lower starting dose and slower titration regimen is recommended as: 50 mg/day initial dose, increased in increments of 50 mg/day.

Pharmacokinetics[1, 2]

Time to Peak Plasma Concentration	Mean Elimination Half-Life	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	CYP450 Enzymes Responsible for Biotransformation
1–2 hrs	6–7 hrs	2 days	< 5%	CYP3A4

CYP450 = Cytochrome P450

The area under the plasma concentration-time curve (AUC) is equivalent for quetiapine IR administered twice daily compared to quetiapine ER administered once daily, however, the maximum plasma concentration (C_{max}) of quetiapine ER is 13% lower at steady state.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin, and nefazodone, is contraindicated.

The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients.

Pharmacokinetics in Special Populations[1, 2]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Elimination $T_{1/2}$ (Hours)	Increase in AUC	Recommended Initial Dose
Mild	CL_{cr} < 30/1.73m^2	25%	No change	No change	Dosing adjustment not required
Moderate					
Severe					

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve, $T_{1/2}$ = Mean Elimination Half-Life

Hepatic Impairment

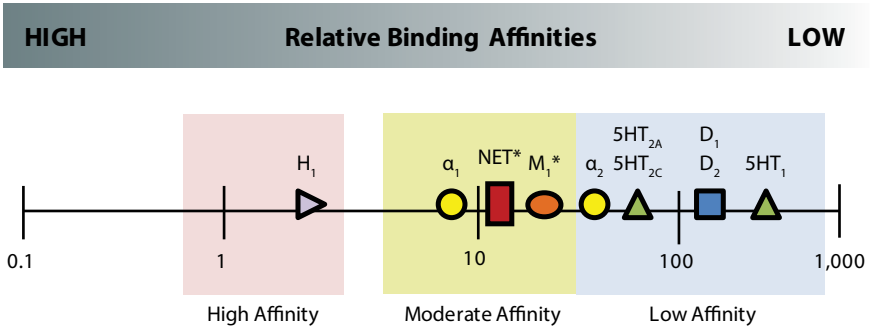
Quetiapine is extensively metabolised by the liver and should be used with caution in patients with known hepatic impairment, especially during the initial dosing period.

The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis).

Patients with known hepatic impairment should be started on quetiapine immediate-release tablets at 25 mg/day. The dosage should be increased daily with increments of 25–50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

It is recommended to adjust the initial dose of quetiapine fumarate (extended-release) to 50 mg/day, increased in increments of 50 mg/day.

Pharmacodynamics[1, 2, 3]



* Binding primarily due to norquetiapine (a metabolite of quetiapine).

Efficacy[4]

Summary of Results for Efficacy in the Treatment of Schizophrenia

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM III-R criteria for schizophrenia	75 mg/day 150 mg/day 300 mg/day 600 mg/day 750 mg/day	6 wks	BPRS, CGI	✓ 150, 300, 600, 750 mg vs. placebo Maximum effect at 300 mg/day
	High: Titrated doses up to 750 mg/day* Low: Titrated doses up to 250 mg/day*	6 wks	BPRS, CGI	✓ High dose superior to placebo (mean 500 mg/day)

*Doses were given as divided doses three times per day

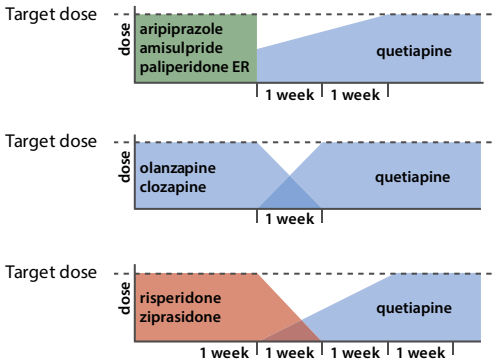
Safety and Tolerability[4]

	Percent of Patients Reporting	
	Placebo (n=404)	Quetiapine (n=719)
Headache	13	29
Agitation	8	12
Somnolence	11	12
Dizziness	4	11
Dry mouth	9	10
Constipation	5	9
Pain	4	9
Tachycardia	5	7
Vomiting	6	7
Asthenia	2	6
Dyspepsia	1	6
Weight gain	3	6
ALT increased	2	5

Adverse reactions reported by ≥ 5% among patients treated with quetiapine (doses ranging from 7 to 800 mg/day) in 3-12 week, placebo-controlled trials.

Switching[3]

Switching from Oral Antipsychotics to Quetiapine



Immediate stop possible; begin quetiapine at middle dose.

It is generally advisable to begin quetiapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect.

For more convenient dosing, patients who are currently being treated with divided doses of immediate-release tablets may be switched to extended-release quetiapine at the equivalent total daily dose taken once daily.

References

1. SEROQUEL Summary of Product Characteristics, AstraZeneca Pharmaceuticals, electronic Medicines Compendium, May 2012.
2. SEROQUEL prescribing information, AstraZeneca Pharmaceuticals, EU, November 2010.
3. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422, 431–436.
4. SEROQUEL prescribing information, AstraZeneca Pharmaceuticals LP, December 2011.

Indications and Usage[1]

Risperidone is an oral atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia in adults.

2. The treatment of moderate to severe manic episodes associated with bipolar disorders.

3. The short-term (up to 6 weeks) treatment of persistent aggression associated with Alzheimer's dementia unresponsive to non-pharmaceutical approaches and when at risk of harm to self or others.

4. The short-term (up to 6 weeks) treatment of persistent aggression in conduct disorder children from the age of 5 years to adolescent.

*Licenses differ between countries. Please refer to local Product Information guides.

Mechanism of Action[1, 2]

The therapeutic activity of risperidone is mediated through a combination of $5HT_2$, $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ serotonin, D_2 dopamine, and α_1-adrenergic receptor antagonism. Risperidone also blocks, to a lesser extent, histamine H_1 and α_2-adrenergic receptors.

Dosing and Administration[3]

Indication	Initial Dose Day 1	Titration	Second Dose Day 2	Target Dose	Maximum Dose
Schizophrenia	2 mg	1–2 mg/day	Up to 4 mg	4–6 mg	16 mg**
Bipolar disorder	2 mg	1 mg/day	Up to 3 mg	3 mg	6 mg**
Schizophrenia/Bipolar disorder (Elderly)*	0.5 mg twice daily	0.5 mg twice daily	Up to 1 mg twice daily	1–2 mg twice daily	2 mg twice daily
Persistent Aggression in Patients with Moderate to Severe Alzheimer's Dementia (short-term treatment)	0.25 mg once daily	0.25 mg twice daily *Every other day*	—	0.5–1 mg twice daily	1 mg twice daily
Conduct disorder*** 5–18 years, ≥ 50 kg	0.5 mg once daily	0.5 mg twice daily *Every other day*	—	0.5–1.5 mg/ day	1.5 mg/day
Conduct disorder*** 5–18 years, < 50 kg	0.25 mg once daily	0.25 mg twice daily *Every other day*	—	0.25–0.75 mg/day	0.75 mg/day

*Clinical experience in elderly is limited, caution should be exercised.

**Doses above 10 mg/day for schizophrenia have not demonstrated superior efficacy to lower doses and may cause extrapyramidal symptoms. Safety of doses above 16 mg/day for schizophrenia, and above 6 mg/day for bipolar disorder have not been evaluated, and are therefore not recommended.

***Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behavior such as pain or inappropriate environmental demands.

Special Considerations[1]

Risperidone should not be used for more than 6 weeks in patients with persistent aggression in Alzheimer's dementia.

Patients with other types of dementias than Alzheimer's should not be treated with risperidone.

Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism may occur with treatment due to its alpha-adrenergic blocking effects.

Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumors.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

The sedative effect of risperidone should be closely monitored in the pediatric population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Pharmacokinetics[1]

Time to Peak Plasma Concentration	Oral Bioavailability	Mean Elimination Half-Life of Active Moiety	Time to Steady-State Concentration	CYP450 Enzymes Responsible for Biotransformation
1–2 hrs	70%	24 hrs	1 day (4-5 days for active moiety)	CYP2D6

CYP450 = Cytochrome P450

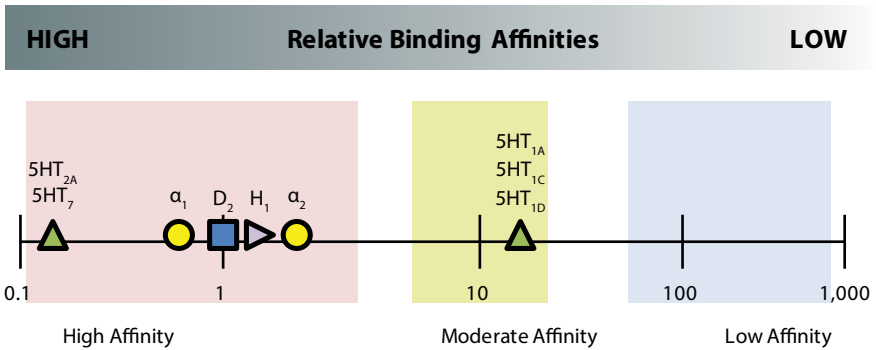
Pharmacokinetics in Special Populations[1]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Recommended Initial Dose	Titration
Moderate	< 30 mL/min	60	Half of Recommended Starting Dose	Increases in increments of ≤ 0.5 mg gradually
Severe				

CL_{cr} = Creatinine Clearance

Hepatic Impairment
The pharmacokinetics of risperidone in subjects with liver disease were comparable to those in healthy subjects. **However, the mean free fraction of risperidone in plasma was increased in patients with liver disease by about 35% because of the diminished concentration of both albumin and α1-acid glycoprotein.** **Risperidone doses should be adjusted as follows:** • A lower starting dose of 0.5 mg twice daily • Dosage increases in these patients should be in increments of no more than 0.5 mg every other day

Pharmacodynamics[1, 2, 3, 4, 5]



Efficacy[3]

The efficacy of risperidone in the treatment of schizophrenia was established in four short-term controlled trials of inpatients who met DSM-III-R criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression (CGI).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R criteria for schizophrenia	10 mg/day	6 wks	BPRS	✓ 10 mg vs. placebo
	2 mg/day 6 mg/day 10 mg/day 16 mg/day	8 wks	PANSS, BPRS, CGI	✓ 6 mg/day vs. placebo; no increased benefit from larger doses
	1 mg/day 4 mg/day 8 mg/day 12 mg/day 16 mg/day	8 wks	PANSS, BPRS, CGI	✓ 4 mg/day vs. placebo
	4 mg/day 8 mg/day	4 wks	PANSS, BPRS	✓ 8 mg/day vs. placebo; (>20% reduction in PANSS total score)

Efficacy[3]

Results from one of the longer-term trial studies establishing efficacy of risperidone in the treatment of inpatients who met DSM-IV criteria for schizophrenia is summarized below. These patients had been clinically stable for at least 4 weeks on an antipsychotic medication, and then monitored for time to relapse of symptoms.

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
DSM-IV	2–8 mg/day	Stabilized for 4 wks, observed for 1 to 2 years	Time to relapse	✓

Efficacy in Adolescents[3]

The efficacy of risperidone in the treatment of schizophrenia in adolescents aged 13–17 years was demonstrated in two short-term double-blind controlled trials. All patients met DSM-IV criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adolescent DSM-IV criteria for schizophrenia	1–3 mg/day 4–6 mg/day	6 wks	PANSS	✓ All dose groups vs. placebo
	0.15–0.6 mg/day 1.5–6 mg/day	8 wks	PANSS	✓ All dose groups vs. placebo; 1.5–6 mg/day vs. placebo was significantly greater than 0.15–0.6 mg/day; no increased benefit from doses > 3 mg/day

Safety and Tolerability[3]

	Percent of Patients Reporting		
	Placebo (n=225)	Risperidone 2–8 mg/day (n=366)	Risperidone > 8–16 mg/day (n=198)
Insomnia	27	32	25
Anxiety	11	16	11
Parkinsonism*	8	14	17
Akathisia*	3	10	10
Nausea	4	9	4
Constipation	6	8	9
Dyspepsia	5	8	6
Vomiting	7	7	5
Somnolence	1	7	2
Nasal congestion	2	4	6

Adverse reactions reported by ≥ 5% among patients treated with risperidone in three separate, 4- to 8-week, double-blind, placebo-controlled trials.

*Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness.

Safety and Tolerability in Adolescents[3]

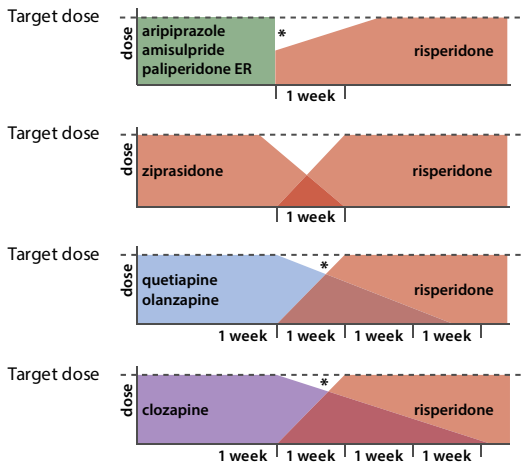
	Percent of Patients Reporting		
	Placebo (n=54)	Risperidone 1–3 mg/day (n=51)	Risperidone 4–6 mg/day (n=55)
Parkinsonism*	11	16	28
Dizziness	2	7	14
Sedation	2	13	8
Somnolence	2	11	4
Tremor	6	11	10
Akathisia*	4	9	10
Salivary hypersecretion	2	0	10
Anxiety	0	7	6
Dystonia*	0	2	6

Adverse reaction reported in 5% or more of risperidone-treated pediatric patients with schizophrenia in a 6-week, double-blind, placebo-controlled trial.

*Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, hypokinesia, and muscle rigidity. Akathisia includes akathisia and restlessness. Dystonia includes dystonia and oculogyration.

Switching[2]

Switching from Oral Antipsychotics to Risperidone



Immediate stop possible; begin risperidone at an intermediate dose.

Concomitant use with paliperidone ER is not recommended. Paliperidone ER is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

Clinical experience has shown that olanzapine and quetiapine should be tapered off over a period of 3-4 weeks due to risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha-1 receptor blocking.

Clozapine should always be tapered off gradually, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication administered during cross tapering and/or reduction of olanzapine, quetiapine, and clozapine can alleviate side effects such as insomnia, anxiety, agitation, and/or psychosis.

References

1. RISPERDAL Tablets, Liquid, and Quicklet, Summary of Product Characterstics, Janssen Pharmaceuticals Inc., electronic Medicines Compendium, June 7, 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 431–436.
3. RISPERDAL prescribing information, Janssen Pharmaceuticals Inc., September 2011.
4. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics, 2010, *European Psychiatry*, 25, S12-S21.
5. National Institutes of Mental Health Psychoactive Drug Screening Program. Cited March 2013. Available http://pdsp.med.unc.edu/indexR.html.

Indications and Usage[1]

Risperidone as a long-acting injectable atypical antipsychotic agent is indicated for the maintenance treatment of schizophrenia in patients currently stabilized with oral antipsychotics*.

Mechanism of Action[1, 2]

The therapeutic activity of risperidone is mediated through a combination of $5HT_2$, $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ serotonin, D_2 dopamine, and α_1-adrenergic receptor antagonism. Risperidone also blocks, to a lesser extent, histamine H_1 and α_2-adrenergic receptors.

*Licenses differ between countries. Please refer to local Product Information guides.

Dosing and Administration[1]

For most patients, the recommended dose is 25 mg intramuscular every two weeks.

For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered:

Recommended dose scheme between oral risperidone and risperidone LAI

Oral risperidone dose	Recommended dose of risperidone LAI	Maintenance dose	Maximum dose
≤ 4mg/day	25 mg/2 weeks	25 mg/2 weeks*	50 mg/2 weeks*
> 4 mg/day	37.5 mg/2 weeks	37.5 mg/2 weeks*	50 mg/2 weeks*

* Some patients may benefit from the higher doses of 37.5 or 50 mg/2 weeks. Upward dosage adjustment should not be made more frequently than every 4 weeks. No additional benefit was observed with 75 mg in clinical trials.

The effect of dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

The main release of risperidone starts from Week 3 onwards, is maintained from 4-6 weeks, and subsides by Week 7. Therefore, sufficient antipsychotic coverage should be provided for the first 3-weeks.

Special Considerations[1]

Sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic should be ensured during the three-week lag period following the first risperidone LAI injection.

Risperidone LAI is not indicated for use in elderly patients with dementia.

Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism and orthostatic hypertension may occur with risperidone treatment due to its alpha-adrenergic blocking effects.

Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumors.

Carbamazepine, rifampicin, phenytoin, phenobarbital, and other medications that induce CYP3A4 hepatic enzyme have been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. When carbamazepine or other CYP3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of risperidone LAI.

Fluoxetine and paroxetine, CYP2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. When concomitant fluoxetine, paroxetine, or other CYP2D6 inhibitors are initiated or discontinued, the physician should reevaluate the dosing of risperidone LAI.

Pharmacokinetics[1]

Time to Peak Plasma Concentration	Bioavailability	Mean Elimination Half-Life	Time to Steady-State Concentration	CYP450 Enzymes Responsible for Biotransformation
*	100%	3–6 days	8 weeks (after 4 injections)	CYP2D6

CYP450 = Cytochrome P450

*After a single intramuscular injection with risperidone LAI, the release profile consists of a small initial release of risperidone (<1% of the dose), followed by a lag time of 3 weeks.

*The main release of risperidone starts from Week 3 onwards, is maintained from 4-6 weeks, and subsides by week 7.

Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

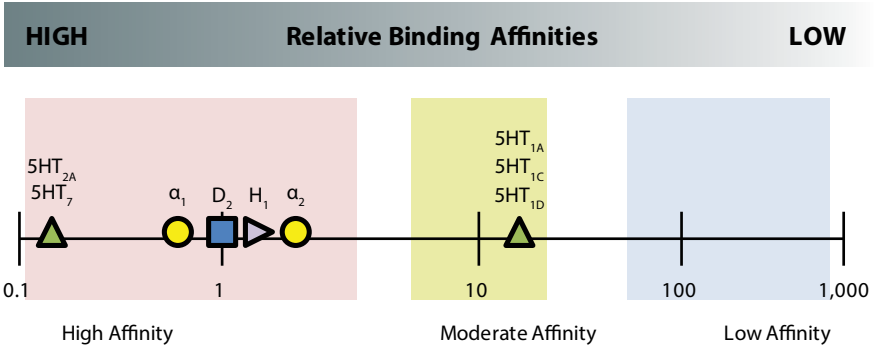
Pharmacokinetics in Special Populations[1]

Renal Impairment	Recommended Initial Dose	Titration	Maintenance dose
Risperidone LAI has not been studied in renally impaired patients.	A starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week.	Second week 1 mg twice daily or 2 mg once daily.	If an oral total daily dose of at least 2 mg is well tolerated, an injection of 25 mg risperidone LAI can be administered every 2 weeks.

CL_{cr} = Creatinine Clearance

Hepatic Impairment
Risperidone LAI has not been studied in hepatically-impaired patients. The pharmacokinetics of oral risperidone in subjects with liver disease were comparable to those in healthy subjects. However, the mean free fraction of risperidone in plasma was increased in patients with liver disease by about 35% because of the diminished concentration of both albumin and α1-acid glycoprotein. If hepatically-impaired patients require treatment with risperidone LAI, a starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week. During the second week, 1 mg twice daily or 2 mg once daily can be given. If an oral dose of at least 2 mg is well tolerated, an injection of 25 mg risperidone LAI can be administered every 2 weeks.

Pharmacodynamics[1, 2, 3, 4]



Efficacy[1, 5]

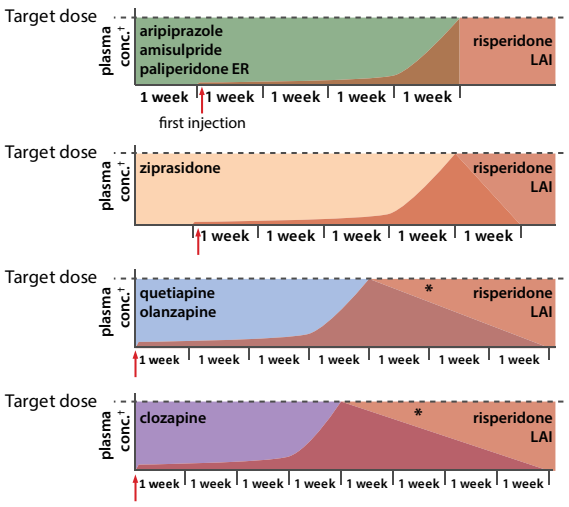
The efficacy of risperidone LAI in the treatment of schizophrenia was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral risperidone over 1 week. Patients who received risperidone LAI were given doses of oral risperidone for the 3 weeks after the first injection to provide therapeutic plasma concentrations until the main release phase of risperidone from the injection site had begun.

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-IV Criteria for Schizophrenia	25 mg/2 weeks 50 mg/2 weeks 75 mg/2 weeks	12 wks	PANSS	✓ 25, 50, and 75* mg vs. placebo

*75 mg is not a licensed dose.

Switching[1, 2]

Switching from Oral Antipsychotics to Risperidone LAI



†plasma concentration of active moiety

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first risperidone injection.

* Benzodiazepine administered during cross tapering and/or reduction of olanzapine, quetiapine, and clozapine can alleviate side effects such as insomnia, anxiety, agitation, and/or psychosis.

Olanzapine and quetiapine should be tapered off over a period of 3-4 weeks due to risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha-1 receptor blocking.

Clozapine should always be tapered off gradually, over a period of 4 weeks or more.

References

1. RISPERDAL CONSTA 25, 37.5, and 50 mg powder and solvent for prolonged-release suspension for intramuscular injection, Summary of Product Characteristics, electronic Medicines Compendium, Janssen Pharmaceuticals Inc., November 2012.
2. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422, 431–436.
3. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics, 2010, *European Psychiatry*, 25, S12-S21.
4. National Institutes of Mental Health Psychoactive Drug Screening Program. Cited March 2013. Available http://pdsp.med.unc.edu/indexR.html.
5. RISPERDAL CONSTA Prescribing Information, Janssen Pharmaceuticals Inc., June 2012.

Indications and Usage[1, 2]

Ziprasidone is an atypical antipsychotic agent indicated for*:

1. The treatment of schizophrenia and agitation associated with schizophrenia in adults.

2. The treatment of symptoms of bipolar I disorder in adults, including manic or mixed episodes.

3. Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate.

4. Treatment with ziprasidone powder and solvent for injection for the control of agitation in patients with schizophrenia, when oral therapy is not appropriate, for a maximum of 3 days.

*Licenses differ between countries. Please refer to local Product Information guides.

Mechanism of Action[1, 2, 3]

The therapeutic activity of ziprasidone is mediated through a combination of $5HT_{2A}$, $5HT_{2C}$, $5HT_{7}$, and $5HT_{1D}$, serotonin, H1 histamine, D_2 and D_3 dopamine, α_1 and α_2-adrenergic receptor antagonism. Ziprasidone acts as an agonist at the $5HT_{1A}$ receptor, and is a moderate NE, norepinehphrine and serotonin reuptake inhibitor.

Dosing and Administration[1, 2]

Indication	Initial Dose	Titration	Maximum Dose
Schizophrenia	Oral: 20 mg twice daily	Any dose adjustment at intervals > 2 days	80 mg twice daily*
Agitation Associated with Schizophrenia	IM: 10–20 mg	20 mg followed by 10 mg after 4 hrs	40 mg/day**

*Medication should be taken with food.

**IM administration of ziprasidone for more than three consecutive days has not been studied.

Clinical experience with IM treatment in elderly patients (> 65 years) is limited. IM injection is not recommended in these patients.

Special Considerations[2]

Ziprasidone should not be given together with medicinal products that are known to prolong the QT interval.

Ziprasidone should be used with caution and with an ECG review in patients with:

- congenital long QT syndrome
- a history of cardiac arrhythmias
- recent acute myocardial infarction

If the QTc-interval is > 500 msec, then it is recommended that the treatment should be stopped.

Caution is advised when treating patients with a history of seizures.

Intramuscular ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.

Pharmacokinetics[2]

Administration	Time to Peak Plasma Concentration	Mean Elimination Half-Life	Time to Steady-State Concentration	% of Administered Dose Excreted as Unchanged Drug	Bioavailability	CYP450 Enzymes Responsible for Biotransformation
Oral	6–8 hrs	7 hrs	1–3 days	< 1%	60% with food	CYP3A4
IM	1 hr	6 hrs	3 days	< 1%	100%	CYP3A4

CYP450 = Cytochrome P450

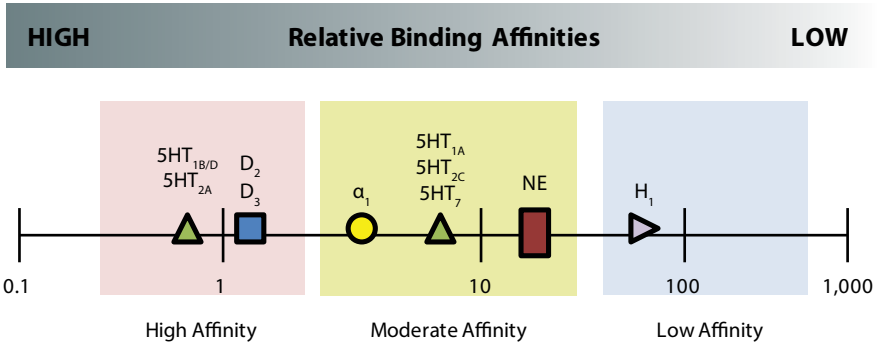
Pharmacokinetics in Special Populations[2]

Renal Impairment	CL_{cr} (mL/min)	% Decrease in CL_{cr}	Increase in AUC	Recommended Initial Dose	Titration	Max Dosage
Mild	Dosage adjustment based upon the degree of renal impairment is not required.					
Moderate						
Severe						

Hepatic Impairment			
As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment is expected to increase the AUC of ziprasidone.			
Cirrhosis	**Mean Elimination Half-Life**	**Increase in AUC_{0-12}**	**Dose Adjustment**
Childs – Pugh A **Childs – Pugh B**	Increased by 2 hrs	30%	Use lowest effective dose

CL_{cr} = Creatinine Clearance, AUC = Area Under the Curve

Pharmacodynamics[2, 3]



Efficacy[1]

The efficacy of ziprasidone in the treatment of schizophrenia was established in four short-term controlled trials of inpatients who met DSM-III-R criteria for schizophrenia. Psychiatric signs and symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression (CGI).

Study	Doses Tested	Duration	Main Endpoints	Dose-related improvement
Adult DSM-III-R criteria for schizophrenia	20 mg twice daily 60 mg twice daily	4 wks	BPRS, CGI	✓ 60 mg vs. placebo
	40 mg twice daily 80 mg twice daily	6 wks	PANSS, BPRS, CGI	✓ 40 and 80 mg vs. placebo; no statistically significant benefit from higher dose
	20 mg twice daily 60 mg twice daily 100 mg twice daily	6 wks	PANSS, BPRS, CGI	✓ 20, 60, and 100 mg vs. placebo
	5 mg twice daily 20 mg twice daily 40 mg twice daily	4 wks	PANSS, BPRS	None were statistically superior to placebo

Safety and Tolerability[2]

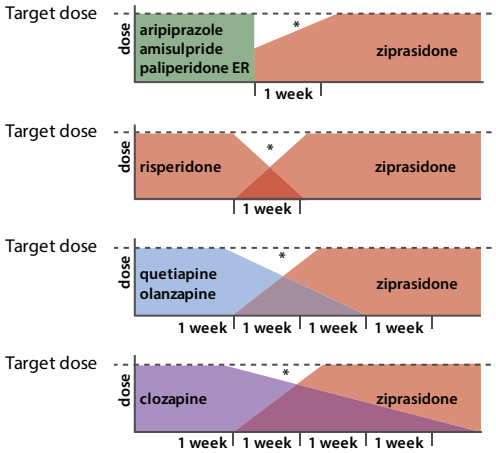
The table below summarizes common adverse events which occur at an incidence greater than placebo reported by patients who received IM treatment in phase 2/3 trials, and patients who received a short-term (4-6 week), fixed oral dose, for schizophrenia, or a short-term (3 week), flexible oral dose, for bipolar mania.

Common Adverse drug reactions IM ziprasidone	Common Adverse drug reactions Oral ziprasidone
General Asthenia, fatigue, injection-site burning, injection-site pain	**General** Asthenia, fatigue, blurred vision
Musculoskeletal Muscle rigidity	**Musculoskeletal** Muscle rigidity
Nervous system Akathisia, dizziness, dystonia, headache, sedation, somnolence, extrapyramidal disorder	**Nervous system** Dystonia, akathisia, extrapyramidal disorder, parkinsonism, tremor, dizziness, sedation, somnolence, headache
Gastrointestinal disorders Nausea, vomiting	**Gastrointestinal disorders** Nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion
Vascular disorders Hypertension, hypotension	**Psychiatric disorders** Restlessness

Common adverse reactions occurred in patients at a frequency ≥ 1% to < 10%.

Switching[3]

Switching from Oral Antipsychotics to Ziprasidone



Clinical experience has shown that olanzapine and quetiapine should be tapered off over a period of 3–4 weeks due to the risk of withdrawal symptoms associated with cholinergic, histaminergic, and alpha–1 receptor blocking.

Clozapine should always be tapered off gradually, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication administered during reduction of olanzapine, quetiapine, and clozapine can alleviate side effects such as insomnia, anxiety, agitation, and/or psychosis.

References

1. GEODON prescribing information, Pfizer Pharmaceuticals, December 2010.
2. ZELDOX Summary of Product Characteristics, Pfizer Pharmaceuticals, March 3, 2012.
3. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 408–422,431–436.

Class Warnings[1,2,3,4]

Atypical antipsychotics are associated with significant cardiometabolic risk, and with pharmacological actions that may mediate that risk. Weight gain, obesity, increased risk for dyslipidemia, diabetes, accelerated cardiovascular disease, and premature death have been linked to drugs in this class as well. Specific risks and other additional special considerations include:

Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with many atypical antipsychotics. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotics should be discontinued.

Tardive dyskinesia/extrapyramidal symptoms: Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Leukopenia, neutropenia, and agranulocytosis: Events of leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance. Patients with a history of a clinically significant low white

Class Warnings, continued[2,3]

blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of antipsychotic medication should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 109/L) should discontinue antipsychotic use and have their WBC followed until recovery.

Hyperglycaemia and diabetes mellitus: Patients treated with any atypical antipsychotic should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain: Significant weight gain has been reported with antipsychotic use. Weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight should be monitored regularly.

Suicidal behavior: The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany antipsychotic therapy.

Elderly and elderly with dementia: In a meta-analysis of 17 controlled clinical trials, elderly patients with

Class Warnings, continued[2]

dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo. In elderly patients (over 65 years), antipsychotics should be used with particular caution because of a possible risk of hypotension or sedation.

Cerebrovascular adverse reactions: An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known.

Priapism: Antipsychotic medicinal products with alpha-adrenergic blocking effects have been reported to induce priapism. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3-4 hours.

Body temperature regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing antipsychotics to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity, or being subject to dehydration.

Venous thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired

Class Warnings, continued[1,2,3,4]

risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with antipyschotics and preventative measures undertaken.

Withdrawal: Acute withdrawal symptoms including nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotics. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia, and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Seizures: Caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

Parkinson's disease and dementia with Lewy bodies: Physicians should weigh the risks versus the benefits when prescribing antipsychotics to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Cardiac effects: QT prolongation has been reported with many antipsychotics. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest, and Torsades de Pointes.

References

1. Stahl SM. *Stahl's Essential Psychopharmacology* 3rd ed. 2008, Cambridge University Press, New York, pgs. 327-452.
2. Xeplion 50 mg, 75 mg, 100 mg, and 150 mg prolonged release suspension for injection, Summary of Product Characteristics, Janssen Pharmaceuticals Inc., electronic Medicines Compendium, August 2012.
3. Amisulpride prescribing information, electronic Medicines Compendium, July 31, 2012.
4. RISPERDAL Tablets, Liquid, and Quicklet, Summary of Product Characterstics, Janssen Pharmaceuticals Inc., electronic Medicines Compendium, June 7, 2012.