

**PALIPERIDONE**



*Group of Confederate High Command, Winchester, Shenandoah Valley, c. 1862, photographic print taken c. 1910 of a now lost original ambrotype glass plate image, that was taken by Captain Fred A. Briscoe, an assistant quartermaster in Jackson's army. (The figure on the left is thought to be Stonewall Jackson - if so, then this is the only extant full length portrait of him in existence).*

*"Always mystify, mislead, and surprise the enemy, if possible. And when you strike and overcome him, never let up in the pursuit so long as your men have strength to follow; for an army routed, if hotly pursued, becomes panic stricken, and then can be destroyed by half their number. The other rule, is never fight against heavy odds, if by any possible maneuvering you can hurl your own force on only a part, and that the weakest part of your*

*enemy and crush it. Such tactics will win every time, and a small army thus destroy a large one in detail, and repeated victory will make it invincible.*  
(Stonewall Jackson)

*.....Outside Richmond, George McClellan continued to call anxiously for more troops, though his 110,000 force already greatly outnumbered Joseph Johnston's army.*

*Meanwhile, west of the Blue Ridge in the Shenandoah Valley, General Thomas J. Jackson was keeping three Federal armies busy.*

*He was a true eccentric. He believed that if he had pepper in his food, it would make his left leg ache. He would never mail a letter that would be in transit on a Sunday. He was a strict observer of the Sabbath. And yet so many of his battles were fought on Sundays that his soldiers began to believe that he fought on Sunday because the Lord would be even more with him*

*(Shelby Foote, Civil War Historian)*

*Jackson was a pious blue-eyed killer, utterly untroubled by the likelihood of death. It was a man's "entire duty" he said, to pray and fight.*

*"He would have shot a man at the drop of a hat, and he'd drop it himself"*  
*Sam Watkins (Confederate Soldier).*

*He had a strange quality of overlooking suffering. It was during one of the battles, he had a young courier and Jackson looked around for him, and he wasn't there and he said "Where is Lieutenant so - and - so?", and they said "He was killed General". Jackson said "Very commendable, very commendable" ....and then put him out of his mind.*

*(Shelby Foote, Civil War Historian)*

*"All old Jackson gave us was a musket, 100 rounds, and a gum blanket, and he drove us like hell". (Confederate Soldier).*

*(At first) his men did not love him. He was too grim, too remote, and he demanded too much. Some even thought him mad.*

*He believed that keeping one hand in the air could stop him from going out of balance, and he sucked constantly on lemons, even in the midst of battle. Others worried that his religious fervor would cloud his judgment. His command, Jackson said, was "an army of the living God as well as of its country". But his men were willing to endure the 36 mile a day marches he demanded because he brought them victories. It was Jackson's duty in the Shenandoah to unsettle the Union and keep Washington from reinforcing McClellan.*

*Operating in the midst of three Federal armies, each with more men than his own force of 17,000, Jackson lashed out at one army and then another. Armed with a detailed map that stretched eight and a half feet, he surprised them every time - at Winchester, Front Royal, Cross keys, Port Republic and a half dozen other places. After routing Nathaniel Banks' army at the Battle of Winchester, Jackson chased it all the way back to the Potomac.*

*"Stop men!", Banks shouted to his retreating troops. "Don't you love your country?"*

*"Yes, by God", said one, "and I'm trying to get back to it just as fast as I can!"*

*Jackson's Valley campaign was a triumph. In just over a month, his men marched almost 400 miles, inflicted 7,000 casualties, seized huge quantities of badly needed supplies and kept almost 40,000 Federal troops off the (Virginia) peninsula.*

*"He who does not see the hand of God in this is blind sir, blind!"*  
(General T.J. Stonewall, Jackson)

*David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.*

*Following on from his heroics at the First Battle of Bull Run, Stonewall Jackson was sent west by Joe Johnston into the Shenandoah valley. There his task would be to distract no fewer than three Union armies each larger than his own force of 17,000 men, as a strategy to keep up to 40,000 Federal troops from joining George B McClellan's already immense newly formed Army of the Potomac with which he was planning to hurl at Richmond in one overwhelming campaign that would quickly end the war. In a brilliant series of lightning hit and run campaigns, that included five pitched battles only one of which he lost (at Kernstown, the only defeat he suffered in the War) Jackson not only managed to "distract" Union forces occupying the Shenandoah, he so thoroughly outmanoeuvred them that General Banks in overall command was obliged to retreat and retreat again and retreat again until it looked like he would have to quit the Valley altogether! Lincoln was shaken by Jackson's audacity and now with the potential to threaten Washington itself, he held back yet more troops for the capital's defence that could have gone to McClellan's growing army. Jackson had given Joe Johnston valuable breathing space. Indeed so firm a grip did the Confederates now have in the Shenandoah, that Johnston recalled Jackson back to Richmond to bolster his own army, against the great "final" assault that was soon to come from McClellan.*

*Until this time, although Jackson had been a hero among his own troops, he was not well known at all by Jefferson Davis, the Southern Government in Richmond, nor to the general public at large. But with his stunning successes in the Shenandoah Valley, however, he had suddenly become the most famous commander South - or North - of the Potomac. People wanted to know who this "Stonewall" Jackson was, but the more they heard about his alarming eccentricities the more enigmatic he became. All this merely added to the mystery of the man, which of course drove his fame to ever greater heights!*

*His eccentricities had been noticed right from his early days as a Professor teaching at the Virginia Military Academy. After meeting Jackson, John Kid Berkenbaugh, a law student from Lexington, considered him such an oddity, that he asked his friend James B. Terrill, a former VMI cadet, what he thought of him. "Old Jack is a character", Terrill said, "he's either a genius or just a little crazy. He lives quietly, and don't meddle. He's as systematic as a multiplication table, and as full of military as an arsenal. Stiff as you see, never laughs, but as kind hearted as a woman; and by Jupiter he also teaches at a nigger Sunday School! But, mind what I say, if this John Brown business leads to war, he'll be heard from!"*

*And he certainly was heard from. After the Valley campaign, the North now had an unpredictable genius to contend with, while the South had their first true hero, before the rise of Robert E. Lee. An image began to emerge of an ice cold killer, who could, as one of his soldiers, remarked, have a man executed at the drop of a hat, if he thought he had shirked his duty. He drove his men almost beyond endurance, achieving marches that Union commanders had not thought possible, and because they did not think these were possible he continually surprised them and caught them off guard. He appeared aloof, and spoke almost monosyllabically. He had the oddest beliefs and mannerisms. Often in battle he would raise an arm into the air, for what reason none really knew, but the gesture certainly marked him out on the field. He was utterly fearless under fire, to the point often of recklessness. His staff were continually alarmed, as he gave calm orders while ignoring soldiers that were being killed within meters of him. He was utterly unconcerned about his appearance, being barely distinguishable from his most barefooted and ragged troops. He was often mistaken for a local farmer who had come in from ploughing the fields.*

*And then there was his religion. Uninterested in fame or ambition, any victory he had was simply the result of the "will of God". He refused to send any communication, should it find its way in transit on the Sabbath. Some wondered if his religious fervor would cloud his judgment, though it never did. He happily fought battles on the Sabbath but only because he thought God would be more with him. He had an inordinate love of fruits, and would often be seen calmly munching on peaches seated on his horse while battle raged all around him amidst the desperate pleas of his commanders to get out of the line of fire. But despite all this, he brought the South great victories, that few other Southern commanders were delivering at this point of the war. And for this his troops loved him dearly. His eccentricities only added to his unsettling charisma. Now whenever he galloped past his troops, he was greeted by a ear an splitting cacophony of cheers and rebel yells that would mark out his progress like a roaring tsunami rushing down the lines. A member of the Danville artillery, in the Shenandoah, wrote, "Yonder in a faded gray coat, on Old Sorrel (his horse), came Stonewall himself, his cap in hand, his eye bright with victory, his hair fluttering in the wind, the very cyclone of battle, followed by his panting staff. Another artillery man commented that, "as he came the men pressed in shoals to the roadside and waved their hats wildly. It was deafening...I never saw a more thrilling scene...General Jackson himself seemed much affected, as he rode uncovered, bowing constantly"*

*At Cedar mountain when a young eighteen year old soldier named William C. Preston noticed Jackson riding toward him he gave out a hyperventilated yell to his comrades, "General Jackson is coming! General Jackson is coming!" Hundreds of soldiers in the area turned his way. Preston later stated, "I thought the heavens would have rent with the cheers!" One soldier from Alabama at Second Bull Run, gave his account of Jackson's popularity with his men, "Around the curve of the old R.R a man on a horse was seen coming in a slow gallop, his head bare and his cap in his hand in acknowledgment of the cheers that were being given, and as he approached someone recognized him and shouted that's Stonewall Jackson and we went wild with enthusiasm, throwing our hats into the air and giving the Rebel Yell at the top of our voices. He came on top of the railroad embankment....followed by one courier. He was dressed in an old dusty, dingy, faded gray uniform with the legs of his pants stuffed in the legs of a course pair of boots. Three stars and a wreath that he wore upon the collar of his coat was the only mark that distinguished his greatness. He did not go far before he halted, and with raised cap in hand, he hollered out at*

*the top of his voice, "Attention". All was ready in a moment, when he in a shrill voice he commanded, "forward" and at the word we dashed over the embankment, and then moved on slowly and cautiously.."*

*Jackson was not unappreciative of his men's hero worship. When moving up to the battlefield of Second Bull Run, absolute quiet was required in order not to alert Federal troops. Suddenly a column of men came across Jackson standing on a large boulder surveying the field ahead. Loud cheers began to rent the air, but Jackson's staff angrily sent the word around "No cheering!" Immediately the troops went quite, but as they marched past Jackson, silent looks, warm smiles, raised caps, uplifted arms as if in imitation of their commander's habit in battle, and lingering salutes gave mute witness to their total devotion. Jackson became affected with a rare show of emotion. A smile broke across his face as he turned to a member of his staff and whispered, "Who would not conquer with such troops as these!" But Jackson never sought personal praise or fame. When asked once what he thought of his accomplishments in the Shenandoah he thundered, "He who does not see the hand of God in this is blind sir, blind!"*

*Extraordinary genius often comes out of unconventional molds. Jackson's genius came from his unpredictability, his ability to think differently to most others. Indeed his oddity was what partly endeared him to his troops - to the point that he would become for them, to use the modern vernacular, a "cult figure". In a secular age many would today also ridicule his strong religious faith, and yet it was precisely his faith that was the source of his unwavering strength, super-human endurance and supreme self-belief; all qualities that made him the greatest commander of the war, bar perhaps only Ulysses S. Grant and Robert E. Lee. There are only two extant photographs, historians tell us, of Stonewall Jackson from the period of the Civil War, these being the famous "Winchester" and "Chancellorsville" portraits. There remains however an enigmatic third possibility - an image taken in the Shenandoah Valley. The portrait appears to be of a high ranking group of Confederate officers. The Briscoe family in whose possession it was long held, had always claimed that the figure on the far left was none other than Stonewall Jackson. He had, according to a number of contemporary reports, a peculiar slouching posture and gait and the figure in the Briscoe image seems to ring true in this sense. Expert historians, however are sharply and hotly divided as to whether the man is Stonewall Jackson. In Ken Burns' magisterial 1990 documentary on the Civil War the image is very strongly implied as one of Jackson, though the commentary does not explicitly confirm this. Unless new documentary evidence comes to light the issue will never be definitively resolved. For the present experts, on either side seemingly base their opinions on their own blind faith - a method of resolution, that the great General himself would have been quite comfortable with.*

*In the 21st century Emergency Physicians in major departments are daily called on to assess the mental health of patients brought to the ED. Stonewall Jackson certainly displayed some alarming oddities, which modern day psychiatry would no doubt have a plethora of ready labels for. Once a label is provided, then Big Pharma is sure to follow with a tailor made medication. Had the legendary Stonewall Jackson been put onto paliperidone depot, however there is no doubt at all he could not have achieved what he did!*

## **PALIPERIDONE**

### **Introduction**

**Paliperidone**, (trade name in Australia “**Invega**”) is a second generation, “atypical” antipsychotic agent.

Paliperidone is actually **9-hydroxyrisperidone** a major *active metabolite* of **risperidone**.

It is as effective as any of the newer antipsychotic agents and has far less (if any) extrapyramidal side effects that are characteristic of the older agents.

It is effective in the treatment of both the “**positive**” and “**negative**” symptoms of schizophrenia.

Formulations available include:

1. Paliperidone **extended release oral** formulation:
  - This acts via the **OROS** extended release system to allow for **once daily** dosing.
2. Paliperidone **palmitate, (Invega Sustenna)**:
  - This is a long acting **injectable IM depot** formulation of paliperidone, that is given once every **28 days** after an initial titration period.
3. Paliperidone **palmitate, (Invega Trinza)**:
  - This is a very long acting **injectable IM depot** formulation of paliperidone, that is given once every **3 months** after an initial stabilization period with the one monthly formulation.

**See also separate documents on:**

- **Risperidone (in Drugs folder)**
- **Paliperidone Overdose (in Toxicology folder).**

### **History**

Chlorpromazine was developed in 1950.

It was the first drug developed with a specific antipsychotic action and served as the prototype of the phenothiazine class of antipsychotic drugs that followed it.

The introduction of chlorpromazine during the 1950s into clinical use for schizophrenia and acute psychoses represented a significant advance in the history of psychiatry.



The “atypical” or second generation antipsychotics were developed and introduced into clinical practice during the 1990s. Olanzapine, **risperidone**, and quetiapine were introduced initially while ziprasidone and aripiprazole came onto the market in the early 2000s.

Paliperidone was introduced into clinical practice in the US in 2006.

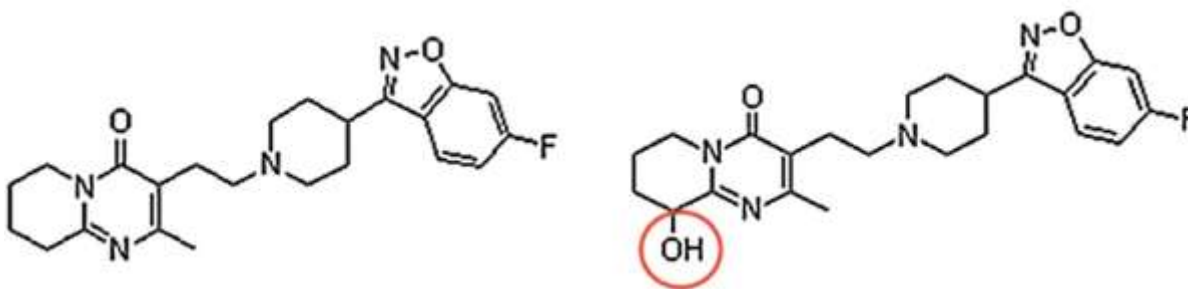
The novel slow release delivery system of paliperidone was developed by the ALZA Corporation, which pioneered the use of osmotic pumps for oral drug delivery.

### Chemistry

Paliperidone is a psychotropic agent belonging to the chemical class of the **benzisoxazoles**.

Paliperidone is actually **9-hydroxyrisperidone** a major *active metabolite* of **risperidone**.

Risperidone → **9-hydroxyrisperidone**



*Left: Risperidone. Right: 9-hydroxyrisperidone (paliperidone).*

Paliperidone **palmitate** is a palmitoyl ester of paliperidone.

### Classification

There is no formal classification of the antipsychotic agents, however by tradition they are loosely divided into two principal groups.

1. The older “**first generation**” or “**typical**” group.
2. The newer “**second generation**” or “**atypical**” group.

**In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the development of neuroleptic malignant syndrome. The risk of these particular adverse effects although small is not completely eliminated with the second generation agents.**

It has also been claimed that the second generation agents are more effective against the “negative” symptoms of schizophrenia, but this has *not* been convincingly proven as a *class* effect.

It should be noted that designating antipsychotics as first generation and second generation may be of limited value as it probably exaggerates the differences between groups and overstates similarities between members within each group. On this basis some prefer not to use this classification; nonetheless the terminology remains widely used.

### First Generation Antipsychotic Agents :

These fall into two major groups:

#### 1. **Phenothiazines:**

- *Lower potency:*
  - Chlorpromazine.
  - Pericyazine.
  - Thioridazine.
- *Higher potency:*
  - Fluphenazine.
  - Flupenthixol
  - Prochlorperazine
  - Trifluoperazine.
  - Zuclopenthixol

#### 2. **Butyrophenones:**

- Droperidol.
- Haloperidol.

### Second Generation Antipsychotic Agents:

These include:

1. Amisulpride
2. Aripiprazole



3. Asenapine
4. Clozapine
5. Olanzapine
6. **Paliperidone**
7. Quetiapine
8. Risperidone
9. Ziprasidone

### Preparations

Paliperidone as:

Extended release tablets (but capsule shaped):

- 3 mg (white, marked PAL 3)
- 6 mg (beige, marked PAL 6)
- 9 mg (pink, marked PAL 9)
- 12 mg (dark yellow, marked PAL 12)

The drug is delivered in a slow controlled fashion, via an **O**smotic Controlled **R**elease **O**ral Delivery **S**ystem (or “OROS”) - **See Appendix 1 below.**

Paliperidone **palmitate** as:

Ampoules for 1 monthly IM depot administration (“Invega Sustenna”):

- 25 mg (syringe)
- 50 mg (syringe)
- 75 mg (syringe)
- 100 mg (syringe)
- 150 mg (syringe)

Ampoules for 3 monthly IM depot administration (“Invega Trinza”):

- 175 mg, 0.875 mL (syringe)
- 263 mg, 1.315 mL (syringe)
- 350 mg, 1.75 mL (syringe)
- 525 mg, 2.625 mL (syringe)

### Mechanism of Action

In general the antipsychotic agents actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system).

Evidence suggests:

- All effective antipsychotics block D2 receptors
- Differential blockade of other dopamine receptors (e.g. D1) may influence therapeutic and adverse effects
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT2 antagonism with some agents.

Paliperidone is a centrally active dopamine D2-antagonist and also has serotonergic 5HT2A antagonistic activity

Paliperidone is also an **antagonist** at:

- $\alpha 1$  and  $\alpha 2$ -adrenergic receptors
- H1-histaminergic receptors.

Paliperidone has **no** affinity for cholinergic muscarinic or  $\beta 1$  and  $\beta 2$ -adrenergic receptors.

### Pharmacodynamics

Paliperidone (like risperidone) is effective in the treatment of both the “**positive**” and “**negative**” symptoms of schizophrenia.

The symptoms of schizophrenia involve:

- 1 Positive symptoms:
  - Delusions:
  - Hallucinations:

- Formal thought disorder
- 2 Negative symptoms:
- Blunted affect (lack of emotional response)
  - Apathy (loss of volition)
  - Social withdrawal
  - Paucity of speech

### Pharmacokinetics

#### Absorption:

- Paliperidone extended release oral tablets:

Following a single dose, the plasma concentration of paliperidone rises steadily to reach peak plasma concentrations in around 24 hours after ingestion.

Levels are dose proportional within the recommended clinical dose range (i.e. 3 - 12 mg).

Steady-state concentrations of paliperidone are attained within four to five days of dosing in most subjects.

The absolute oral bioavailability of paliperidone following a administration of the extended release preparation is around 30 %.

- Paliperidone **palmitate** as IM depot preparation:

Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation.

Paliperidone **palmitate** → paliperidone  
                                  ↑  
                                  Hydrolysis

Following a single IM (**1 monthly formulation**) dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of **13 days**. The release of the drug starts as early as day 1 (and may last for as long as 126 days).

Following a single IM (**3 monthly formulation**) dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of **30-33 days**.

### Distribution

- The apparent volume of distribution of the oral extended release preparation of paliperidone is 487 L.
- The plasma protein binding of paliperidone is around 75%.  
It binds primarily to  $\alpha$ 1-acid glycoprotein and albumin
- It is unknown if paliperidone crosses the human placenta.
- Paliperidone is excreted into human breast milk but only in very small amounts.

### Metabolism and excretion:

- Around 30 % is metabolized in the liver, primarily by cytochrome P450 - CYP2D6 and CYP3A4 enzymes.

Despite the large variation in the general population with regard to the ability to metabolize CYP2D6 substrates, population pharmacokinetic analyses indicated no discernable difference on the exposure and apparent clearance of paliperidone after administration of Invega between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

Up to 70 % is excreted unchanged in the urine.

- The terminal elimination half-life of oral paliperidone is prolonged at approximately 23 hours.

The terminal elimination half-life of IM (1 monthly) depot paliperidone is around 25 to 49 days.

### Indications

Indications include:

1. Acute and chronic psychoses (e.g. schizophrenia)
2. Acute exacerbations of schizoaffective disorder
3. Bipolar disorder

### Contra-indications/precautions

These include:

1. Known hypersensitivity to paliperidone (or risperidone)

2. Caution with other CNS depressants, including alcohol, (synergistic sedation)
3. Caution with other agents of conditions that prolong the QT interval
4. Hypotension
5. Renal impairment
  - Dose should be reduced.
6. Parkinson's disease:
  - Antipsychotics used in Parkinson's disease may aggravate the condition and may oppose the action of the dopamine agonists used to treat it.  
  
Quetiapine or clozapine may be more suitable.
7. Hepatic
  - Use with caution in severe hepatic impairment; consider dose reduction.

### Pregnancy

Paliperidone is a class C drug with respect to pregnancy.

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

A case report described a woman with schizophrenia who had been using paliperidone before and during pregnancy until week 28 of gestation and resulted in a normal pregnancy outcome. Consultation with a perinatal psychiatrist is recommended if the initiation or continuation of paliperidone therapy is required during pregnancy.

Paliperidone is the major active metabolite of risperidone. Based on the limited information available, maternal use of risperidone has not been associated with an increased risk of birth defects or spontaneous abortions.

However, a recent study has suggested that the use of risperidone may increase the risk of developing gestational diabetes and other glucose related adverse events.

Newborns exposed to risperidone during pregnancy have in been reported to have experienced self-limiting withdrawal symptoms. These symptoms include jitteriness, poor sucking reflex, tremors and restlessness.

Pregnant women treated with paliperidone should be closely monitored for gestational diabetes and fetal growth.

Inform neonatal care providers about maternal use of paliperidone, as adverse effects or withdrawal signs may present in newborns and supportive treatments may be required.

### Breast feeding

While there have been no reports describing paliperidone use during breastfeeding, there is limited safety information available on the use of risperidone; the parent compound of paliperidone.

Very small amounts of risperidone and the active metabolite, paliperidone, have been shown to be transferred into breast milk. Paliperidone is known to increase prolactin levels, but no serious adverse effects have been noted in the breastfed infants.

However, consider an alternative medicine with better clinical safety information for breastfeeding mothers where possible.

If paliperidone is the treatment of choice during breastfeeding, use the lowest effective dose.

The breastfed infant should be closely observed for adverse effects such as excessive drowsiness, irritability, poor feeding and restlessness.

Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

### Adverse Effects

These include:

1. Sedation
2. Orthostatic hypotension
3. Mild prolongation of QT<sub>c</sub> interval
4. Extrapyramidal side effects:
  - As paliperidone is a second generation antipsychotic, extrapyramidal effects are minimal compared to the older generation agents when used in usual therapeutic doses.

**See Chlorpromazine for a description of these effects.**

5. Neuroleptic malignant syndrome (NMS)
  - Again this is much less seen compared to the older generation of antipsychotic agents.

## Dosing

### Oral:

To preserve the integrity of the OROS delivery system, the tablet should be **swallowed whole** and **not** chewed, split or crushed.

Since the shell of the tablet is non-absorbable, patients should be informed that the undissolved shell may be passed in the stool.

Usual adult extended release oral dosing is:

- Start at **6 mg** once daily.
- If required, increase or decrease dose by **3 mg** at **4 - 5-day** intervals.
- The usual dose range is **3 - 12 mg** once daily.

### *In Renal impairment:*

- CrCl 50 - 80 mL/minute, start at 3 mg once daily, increasing to 6 mg once daily if appropriate.
- CrCl 30 - 50 mL/minute, 3 mg once daily.
- CrCl 10 - 30 mL/minute, start at 3 mg once every second day, increasing to 3 mg once daily if appropriate.

### IM Depot (one monthly):

Usual adult 1 monthly dosing is:

- Long-acting IM **150 mg** on day 1  
Then 100 mg on day 8  
Then 75 mg 1 month later (maintenance dose).

Give the maintenance dose **once a month** and then adjust dosing as required (usual range 25 - 150 mg once a month).

Give slowly deep into the deltoid or gluteal muscle (use the deltoid muscle for the first 2 injections).

### *In Renal impairment:*

- CrCl 50 - 80 mL/minute, adult, long-acting IM 100 mg on day 1, then 75 mg on day 8, then 50 mg 1 month later (maintenance dose).



Give the maintenance dose once a month (range 25 - 100 mg once a month).

*IM Depot (three monthly):*

Usual adult 3 monthly dosing is:

The patient must be stabilised on the paliperidone once-monthly long-acting injection for at least 4 months, with the last 2 doses the same. Start when the next dose is due.

Adult, long-acting IM, is given once every 3 months and then adjust the dose according to response.

If the previous paliperidone **once**-monthly long-acting injection dose is:

- 50 mg, then use **175 mg** IM 3 monthly dose.
- 75 mg, then use **263 mg** IM 3 monthly dose.
- 100 mg, then use **350 mg** IM 3 monthly dose.
- 150 mg, then use **525 mg** IM 3 monthly dose.

To switch from 3-monthly long-acting injection to the once-monthly long-acting injection, divide dose by 3.5 and give this dose when the next dose is due.

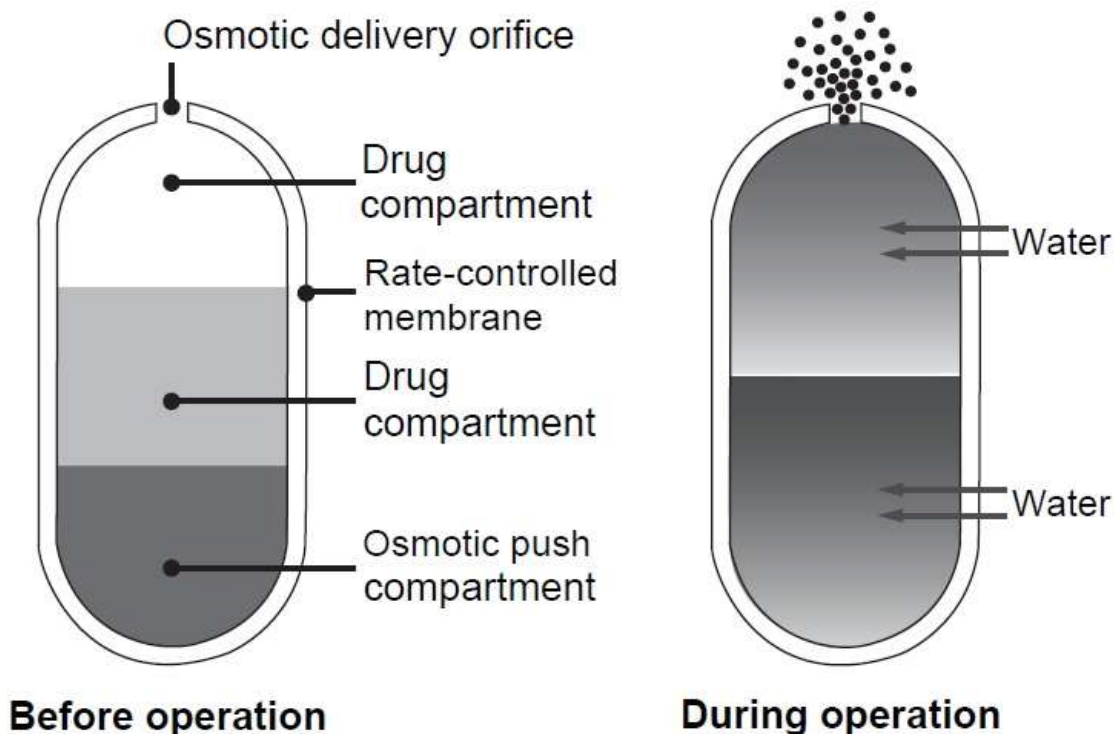
See product information if switching from 3-monthly long-acting injection to oral paliperidone.

Renal impairment:

- CrCl 50 - 80 mL/minute, maximum dose should be 350 mg once every 3 months.

## Appendix 1

### Osmotic Controlled Release Oral Delivery System (OROS):



*Paliperidone is delivered slowly via a novel osmotic delivery system.*

*The “OROS” (Osmotic Controlled Release Oral Delivery System) is a controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it.*

*As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, into an osmotic push compartment, and the resulting osmotic pressure swells this compartment and so pushes the active drug through the opening(s) in the tablet.*

*Multiple drug layers provide increased flexibility and control over the pattern of release of medication from the system, as opposed to the single layer, which can deliver a drug only in a zero order fashion. For example, two drug layers can be formulated with different drug concentration to provide modulation in the release rate profile.*

*Osmotic release systems have a number of major advantages over other controlled-release mechanisms.*

*They are significantly less affected by factors such as pH, food intake, GI motility, and differing intestinal environments. Using an osmotic pump to deliver drugs has additional inherent advantages regarding control over drug delivery rates.*

*This allows for much more precise drug delivery over an extended period of time, which results in much more predictable pharmacokinetics.*

*However, osmotic release systems are relatively complicated, somewhat difficult to manufacture, and may cause irritation or even blockage of the GI tract due to prolonged release of irritating drugs from the non-deformable tablet.*



*High resolution image of the Briscoe photograph (left), compared with the only two known extant photographs of Stonewall Jackson from the Civil War Period - the “Chancellorsville” portrait (middle) and the “Winchester” portrait (right)*

## References

1. eTG - July 2017.
2. Paliperidone in Australian Medicines Handbook Website Accessed October 2017.
3. Paliperidone in MIMs Website:
  - Paliperidone extended release tablets; 1 August 2017.
  - Paliperidone palmitate Depot IM Injection; 1 July 2016.
4. Paliperidone in RWH Pregnancy & Breastfeeding Guidelines; 21 August 2017.

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Reviewed 5 June 2018.