

VI.2.1 Overview of disease epidemiology

Schizophrenia is a mental condition with symptoms such as hearing voices, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech, and behavioural and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense.

Schizoaffective disorder is a mental condition in which a person experiences a combination of schizophrenia symptoms and mood disorder symptoms (for example, feeling very "high", feeling sad, feeling agitated, feeling distracted, sleeplessness, talkativeness, loss of interest in everyday activities, sleeping too much or too little, eating too much or too little, and recurrent thoughts of suicide).

The World Health Organization estimates that 24 million people have schizophrenia worldwide. Schizophrenia is a chronic disease and one of the leading causes of disability in adults. People with schizophrenia and schizoaffective disorder tend to have additional health risk factors, including substance abuse, alcohol abuse, and smoking.

VI.2.2 Efficacy of treatment benefits

Patients with schizophrenia or schizoaffective disorder are usually treated with "atypical antipsychotics." For schizoaffective disorder, mood stabilisers and antidepressants also have a role in treatment.

Paliperidone is an atypical antipsychotic used to treat schizophrenia in adults and in adolescents 15 years and older, and to treat schizoaffective disorder in adults. Paliperidone tablets release the medicine slowly over a day.

Paliperidone was approved in the European Union based on 7 clinical trials in schizophrenia (4 in adults, 3 in adolescents), and 2 trials in adults with schizoaffective disorder.

- In 3 short-term trials, paliperidone was compared with placebo (a dummy treatment) and with olanzapine (another antipsychotic) in 1,692 adults with schizophrenia. Paliperidone improved the symptoms of schizophrenia after 6 weeks and showed benefits similar to olanzapine.
- In a long-term trial in 207 adults with schizophrenia stabilised with paliperidone, the treatment prevented the return of symptoms for up to 35 weeks in most patients.
- In 1 short-term trial involving 201 adolescents with schizophrenia, paliperidone was better than placebo in improving symptoms after 6 weeks of treatment.
- In a 26-week trial involving 227 adolescents with schizophrenia, paliperidone showed similar benefits to aripiprazole (another antipsychotic) in the improvement of symptoms and severity of schizophrenia.
- In a long-term trial in 400 adolescents with schizophrenia, treatment with paliperidone showed symptom improvement and continued stabilisation over the 2-year treatment period.
- In 2 trials in 614 adults with schizoaffective disorder, paliperidone was better than placebo in reducing symptoms after 6 weeks.

When paliperidone was approved, no information was available about long-term use in schizoaffective disorder. Thereafter, a long-term trial was completed for 667 adults with schizoaffective disorder.

VI.2.3 Unknowns relating to treatment benefits

There is limited information on the use of paliperidone in patients on kidney dialysis (a treatment for people whose kidneys no longer work), in pregnant women, or in breastfeeding women.

Benefits of paliperidone in schizophrenia have been studied in elderly patients as old as 81 years, and have been authorised in paediatric patients as young as 15 years. Clinical trials found no variability in the benefits of treatment for subpopulations by age, gender, race, geographic location, or body mass index.

Schizoaffective disorder

Benefits of paliperidone in schizoaffective disorder have not been established in elderly patients (aged >65 years) or paediatric patients (aged <18 years). Clinical trials found no variability in the benefits of treatment for subpopulations by age, gender, race, geographic location, or body mass index.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Stroke or "mini" stroke (Cerebrovascular accident)	In patients treated with paliperidone, a sudden loss of blood supply to the brain (stroke or "mini" stroke) has occurred in up to 1 in 1,000 patients. It is not known how often strokes occur in patients with schizophrenia or schizoaffective disorder who are not being treated with antipsychotic medicines. (See also the Important Potential Risk section below, regarding "Increased risk of stroke or mini-stroke in elderly patients with dementia".)	Doctors should monitor patients for early symptoms and control risk factors such as blood pressure, cholesterol, and diabetes.

Important potential risks:

Risk	What is know (Including reason why it is considered a potential risk)
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<p>Increased risk of developing certain types of cancer, including tumours in the pituitary gland in the brain, tumours in the pancreas, or breast cancer.</p> <p>(Carcinogenicity [pituitary adenomas, endocrine pancreas tumours, breast cancer])</p>	<p>In animal studies, an increase in certain types of cancer (including tumours in the pituitary gland in the brain, tumours in the pancreas, or breast cancer) was observed in animals who were given risperidone, a medicine very similar to paliperidone, and in animals receiving injections of paliperidone. These types of tumours are thought to be caused by or to be related to high levels of the hormone prolactin in the blood.</p> <p>Paliperidone treatment also increases prolactin levels in humans. However, information gathered with paliperidone and similar medicines has not shown any</p>
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	<p>sign that people who take them are at an increased risk of developing cancer compared with people who do not. It therefore seems unlikely that the animal studies are relevant to humans receiving paliperidone, but the risk cannot be totally ruled out.</p> <p>Paliperidone should be used carefully in patients who already have high levels of prolactin, or patients with certain types of tumours that may be affected by increases prolactin levels (e.g., breast cancer).</p>
<p>Increased risk of death in elderly patients with dementia</p> <p>(Overall increased mortality in elderly patients with dementia)</p>	<p>Paliperidone has not been studied in elderly patients with dementia.</p> <p>However, studies with other similar types of medicine have shown that elderly patients with dementia who are treated with these similar medicines may have an increased risk of death.</p>
<p>Increased risk of stroke or mini-stroke in elderly patients with dementia</p> <p>(Cerebrovascular adverse events in elderly patients with dementia)</p>	<p>Paliperidone has not been studied in elderly patients with dementia. However, studies with other similar types of medicine have shown that elderly patients with dementia who are treated with these similar medicines may have an increased risk of stroke or mini-stroke.</p> <p>Paliperidone should be used carefully in patients who have risk factors for stroke.</p> <p>See also the Important Identified Risk section above, regarding "Stroke or 'mini' stroke."</p>
<p>Problems with clear thinking or coordination</p> <p>(Cognitive and motor impairment)</p>	<p>Paliperidone can sometimes make people feel dizzy, sleepy, or less alert, and may make it difficult to concentrate or perform complicated tasks. These problems are more likely to happen if paliperidone is taken with other medicines (or alcohol) that affects brain function.</p> <p>It is still unclear if paliperidone has an effect on the ability to think clearly. Patients with schizophrenia often have problems thinking clearly, even without taking medicines. The effects of paliperidone on clear thinking abilities in adults have not been closely studied.</p>

<p>Suicide attempt or thoughts of committing suicide</p> <p>(Suicidality)</p>	<p>Suicide or thoughts of suicide are common in patients with schizophrenia or schizoaffective disorder, and high-risk patients (such as those with previous attempts or a history of substance abuse) should be closely supervised.</p> <p>So far, trials with paliperidone do not suggest that paliperidone increases the risk of suicide or suicidal thoughts in patients with schizophrenia or schizoaffective disorder.</p>
<p>Feelings of depression in patients with schizoaffective disorder</p> <p>(Depression in patients with affective disorders)</p>	<p>Some reports suggest that antipsychotic medicines such as paliperidone may cause a switch from manic ("high") symptoms to depression in patients with schizoaffective disorder.</p> <p>Although this has not been proven in patients who take paliperidone, patients with schizoaffective disorder who take paliperidone should be carefully monitored in case this does occur.</p>
<p>Increased effects of antipsychotics in patients who have a certain type of Parkinson's disease or dementia</p> <p>(Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy bodies)</p>	<p>Patients with Parkinson's disease or dementia with Lewy bodies (disorders of the brain that affect memory and ability to move) may be more likely to develop side effects of antipsychotic treatments like paliperidone, such as confusion, movement problems (shaking, stiffness, jerky movements) and unsteadiness when standing, which may lead to falls. These patients may also be at an increased risk of neuroleptic malignant syndrome.</p> <p>Paliperidone has not been studied in patients with Parkinson's disease or dementia with Lewy bodies.</p> <p>Patients should talk to their doctor before taking paliperidone if they have Parkinson's disease or dementia with Lewy bodies.</p>
<p>A blockage in the oesophagus (gullet), stomach, or bowel</p> <p>(Gastrointestinal obstruction in patients with preexisting severe gastrointestinal narrowing [pathologic or iatrogenic] or in patients with dysphagia or significant difficulty in swallowing tablets due to its nondeformable nature)</p>	<p>A paliperidone tablet releases its medicine at a constant rate over a 24-hour period. The medicine is contained in a shell that does not dissolve or change shape as it travels through the body. Paliperidone should not usually be given to patients who have a problem that reduces their ability to swallow or to pass foods by normal bowel movements, as there have been rare reports that paliperidone may cause a blockage in such patients.</p>

Decrease in bone strength/fragile bones (Decreased bone mineral density/osteoporosis)	There may be an increased risk of osteoporosis in patients with schizophrenia on atypical antipsychotic therapy, possibly because the high levels of prolactin over a long period of time can cause the bones to become weaker. It is still unclear if this increased risk is due to antipsychotic treatment or some other reason. This needs to be studied more before any conclusions can be made.
Children accidentally swallowing paliperidone that was not prescribed to them (Accidental exposure to product by child)	The packaging for paliperidone states that it should be kept out of the sight and reach of children. The blister packaging meets local requirements regarding opacity, such that children cannot see the tablets. Cases have been reported of children swallowing paliperidone that was not prescribed to them and medically serious events occurred as a result in some cases.

Missing information:

Risk	What is known
Limited information on use in patients who are on dialysis (a treatment for people whose kidneys no longer work) (Use in haemodialysis patients)	Paliperidone has been studied in patients who have mild or moderate-to- severe kidney disease, but it has not been studied in patients who have severe kidney disease that requires dialysis. Patients with severe kidney disease should not take paliperidone. Paliperidone is removed from the blood by the kidneys, so paliperidone should be used with caution in
Limited information on use in pregnant women (Exposure during pregnancy)	Paliperidone has not been studied in pregnant women. Women who are pregnant should not take paliperidone unless it has been discussed with their doctor.
Limited information on use in breastfeeding women (Exposure via breastfeeding)	Paliperidone has not been properly studied in women who are breastfeeding. Women who are breastfeeding should not take paliperidone. Paliperidone can pass into breast milk and may affect the baby.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first Risk management plan.