ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TREVICTA 175 mg prolonged release suspension for injection
TREVICTA 263 mg prolonged release suspension for injection
TREVICTA 350 mg prolonged release suspension for injection
TREVICTA 525 mg prolonged release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

175 mg prolonged release suspension for injection

Each pre-filled syringe contains 273 mg paliperidone palmitate in 0.88 mL equivalent to 175 mg paliperidone.

263 mg prolonged release suspension for injection

Each pre-filled syringe contains 410 mg paliperidone palmitate in 1.32 mL equivalent to 263 mg paliperidone.

350 mg prolonged release suspension for injection

Each pre-filled syringe contains 546 mg paliperidone palmitate in 1.75 mL equivalent to 350 mg paliperidone.

525 mg prolonged release suspension for injection

Each pre-filled syringe contains 819 mg paliperidone palmitate in 2.63 mL equivalent to 525 mg paliperidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release suspension for injection.
The suspension is white to off-white. The suspension is pH neutral (approximately 7.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TREVICTA, a 3-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product (see section 5.1).

4.2 Posology and method of administration

Posology

Patients who are adequately treated with 1-monthly paliperidone palmitate injectable (preferably for four months or more) and do not require dose adjustment may be switched to 3-monthly paliperidone palmitate injection.

TREVICTA should be initiated in place of the next scheduled dose of 1-monthly paliperidone palmitate injectable (± 7 days). The TREVICTA dose should be based on the previous 1-monthly paliperidone palmitate injectable dose using a 3.5-fold higher dose shown in the following table:

TREVICTA doses for patients adequately treated with 1-monthly paliperidone palmitate injectable

If the last dose of 1-monthly paliperidone palmitate injectable is	Initiate TREVICTA at the following dose
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

There is no equivalent dose of TREVICTA for the 25 mg dose of 1-monthly paliperidone palmitate injectable which was not studied.

Following the initial TREVICTA dose, TREVICTA should be administered by intramuscular injection once every 3 months (± 2 weeks, see also *Missed dose* section).

If needed, dose adjustment of TREVICTA can be made every 3 months in increments within the range of 175 mg to 525 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of TREVICTA, the patient's response to an adjusted dose may not be apparent for several months (see section 5.2). If the patient remains symptomatic, they should be managed according to clinical practice.

Switching from other antipsychotic medicinal products
Patients should not be switched directly from other antipsychotics as 3-monthly paliperidone palmitate injectable should only be initiated after the patient is stabilised on the 1-monthly paliperidone palmitate injectable.

Switching from TREVICTA to other antipsychotic medicinal products
If TREVICTA is discontinued, its prolonged release characteristics must be considered.

Switching from TREVICTA to 1-monthly paliperidone palmitate injectable
For switching from TREVICTA to 1-monthly paliperidone palmitate injectable, 1-monthly paliperidone palmitate injectable should be administered at the time the next TREVICTA dose was to be administered using a 3.5-fold lower dose shown in the following table. The initiation dosing as described in the prescribing information for 1-monthly paliperidone palmitate injectable is not required. The 1-monthly paliperidone palmitate injectable should then continue to be dosed at monthly intervals as described within its prescribing information.

Doses of 1-monthly paliperidone palmitate injectable for patients switching from TREVICTA

If the last dose of TREVICTA is	Initiate 1-monthly paliperidone palmitate injectable 3 months later at the following dose
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

Switching from TREVICTA to oral daily paliperidone prolonged release tablets
For switching from TREVICTA to paliperidone prolonged release tablets, the daily dosing of paliperidone prolonged release tablets should be started 3 months after the last TREVICTA dose and treatment continued with paliperidone prolonged release tablets as described in the table below. The following table provides recommended dose conversion regimens to allow patients previously stabilised on different doses of TREVICTA to attain similar paliperidone exposure with paliperidone prolonged release tablets.

Doses of paliperidone prolonged release tablets for patients switching from TREVICTA*

Last TREVICTA dose (Week 0)	Week number after last TREVICTA dose		
	Week 12 to Week 18, inclusive	Week 19 to Week 24, inclusive	From Week 25 onwards
	Daily dose of paliperidone prolonged release tablets		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

* All doses of once daily paliperidone prolonged release tablets should be individualised to the specific patient, taking into consideration variables such as reasons for switching, response to previous paliperidone treatment, severity of psychotic symptoms, and/or propensity for side effects.

Missed dose

Dosing window
TREVICTA should be injected once every 3 months. To avoid a missed dose of TREVICTA patients may be given the injection up to 2 weeks before or after the 3-month time point.

Missed doses

If scheduled dose is missed and the time since last injection is	Action
> 3½ months up to 4 months	The injection should be administered as soon as possible and then resume the 3-monthly injection schedule.
4 months to 9 months	Use the recommended re-initiation regimen shown in the table below.
> 9 months	Re-initiate treatment with 1-monthly paliperidone palmitate injectable as described in the prescribing information for that product. TREVICTA can then be resumed after the patient has been adequately treated with 1-monthly paliperidone palmitate injectable preferably for four months or more.

Recommended re-initiation regimen after missing 4 months to 9 months of TREVICTA

If the last dose of TREVICTA was	Administer 1-monthly paliperidone palmitate injectable, two doses one week apart (into deltoid muscle)		Then administer TREVICTA (into deltoid[a] or gluteal muscle)
	Day 1	Day 8	1 month after day 8
175 mg	50 mg	50 mg	175 mg
263 mg	75 mg	75 mg	263 mg
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

[a] See also *Information intended for medical or healthcare professionals* for deltoid injection needle selection based on body weight.

Special populations

Elderly
Efficacy and safety in elderly > 65 years have not been established.

In general, recommended dosing of TREVICTA for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see *Renal impairment* below for dosing recommendations in patients with renal impairment.

Renal impairment
TREVICTA has not been studied in patients with renal impairment (see section 5.2). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), dose should be adjusted and the patient stabilised using 1-monthly paliperidone palmitate injectable, and then transitioned to TREVICTA.

TREVICTA is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Hepatic impairment
TREVICTA has not been studied in patients with hepatic impairment. Based on experience with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. As paliperidone has not been studied in patients with severe hepatic impairment, caution is recommended in such patients (see section 5.2).

Paediatric population
The safety and efficacy of TREVICTA in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

TREVICTA is intended for intramuscular use only. It must not be administered by any other route. Each injection must be administered only by a healthcare professional giving the full dose in a single injection. It should be injected slowly, deep into the deltoid or gluteal muscle. A switch from gluteal to deltoid (and *vice versa*) should be considered for future injection in the event of injection site discomfort (see section 4.8).

TREVICTA must be administered using only the thin wall needles that are provided in the TREVICTA pack. Needles from the 1-monthly paliperidone palmitate injectable pack or other commercially available needles must not be used when administering TREVICTA (see *Information intended for medical or healthcare professionals*).

The contents of the pre-filled syringe should be inspected visually for foreign matter and discolouration prior to administration. **It is important to shake the syringe vigourously with the tip up and a loose wrist for at least 15 seconds to ensure a homogeneous suspension. TREVICTA should be administered within 5 minutes after shaking.** If more than 5 minutes pass before injection, shake vigourously again for at least 15 seconds to re-suspend the medicinal product. (See *Information intended for medical or healthcare professionals*).

Deltoid muscle administration
The specified needle for administration of TREVICTA into the deltoid muscle is determined by the patient's weight.
- For those ≥ 90 kg, the thin wall 1½ inch, 22 gauge (0.72 mm x 38.1 mm) needle should be used.
- For those < 90 kg, the thin wall 1 inch, 22 gauge (0.72 mm x 25.4 mm) needle should be used.

It should be administered into the centre of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

Gluteal muscle administration
The needle to be used for administration of TREVICTA into the gluteal muscle is the thin wall 1½ inch, 22 gauge (0.72 mm x 38.1 mm) needle regardless of body weight. It should be administered into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

Incomplete administration
To avoid incomplete administration of TREVICTA, the pre-filled syringe must be shaken vigourously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension (see *Information intended for medical or healthcare professionals*).

However, in the event of an incompletely injected dose, the dose remaining in the syringe should not be re-injected and another dose should not be given since it is difficult to estimate the proportion of the dose actually administered. The patient should be closely monitored and managed as clinically appropriate until the next scheduled 3-monthly injection of TREVICTA.

4.3 Contraindications

Hypersensitivity to the active substance, to risperidone or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Use in patients who are in an acutely agitated or severely psychotic state

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

QT interval

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.

Neuroleptic malignant syndrome

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 paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, paliperidone should be discontinued. Consideration should be given to the long-acting nature of TREVICTA.

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. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including paliperidone, should be considered. Consideration should be given to the long-acting nature of TREVICTA.

Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medicinal products. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

Leucopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with paliperidone. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of TREVICTA 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 10^9/L) should discontinue TREVICTA and have their WBC followed until recovery. Consideration should be given to the long-acting nature of TREVICTA.

Hypersensitivity reactions

Hypersensitivity reactions can occur even in patients who have previously tolerated oral risperidone or oral paliperidone (see section 4.8).

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes, including diabetic coma and ketoacidosis, have been reported with paliperidone. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with TREVICTA 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 TREVICTA use. Weight should be monitored regularly.

Use in patients with prolactin-dependent tumours

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with a pre-existing tumour that may be prolactin-dependent.

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-adrenergic blocking activity. In the clinical trials of TREVICTA, 0.3% of subjects reported orthostatic hypotension related adverse reaction. TREVICTA 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 hypovolaemia).

Seizures

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

Renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), dose should be adjusted and the patient stabilised using 1-monthly paliperidone palmitate injectable, then transitioned to TREVICTA. TREVICTA is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). (See sections 4.2 and 5.2).

Hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if paliperidone is used in such patients.

Elderly patients with dementia

TREVICTA has not been studied in elderly patients with dementia. TREVICTA is not recommended to treat elderly patients with dementia due to increased risk of overall mortality and cerebrovascular adverse reactions.

The experience from risperidone cited below is considered valid also for paliperidone.

Overall mortality
In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

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.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing TREVICTA 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.

Priapism

Antipsychotic medicinal products (including paliperidone) 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 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 TREVICTA 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 risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with TREVICTA and preventative measures undertaken.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicinal products or of conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Administration

Care must be taken to avoid inadvertent injection of TREVICTA into a blood vessel.

Intraoperative floppy iris syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicinal products with alpha 1a-adrenergic antagonist effect, such as TREVICTA (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicinal products with alpha 1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing TREVICTA with medicinal products 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 antibiotics (e.g., fluoroquinolones), some other antipsychotics and some antimalarials (e.g., mefloquine). This list is indicative and not exhaustive.

Potential for TREVICTA to affect other medicines

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicinal products that are metabolised by cytochrome P450 isozymes.

Given the primary central nervous system (CNS) effects of paliperidone (see section 4.8), TREVICTA should be used with caution in combination with other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when TREVICTA is administered with other medicinal products that have this potential, e.g., other antipsychotics, tricyclics.

Caution is advised if paliperidone is combined with other medicinal products known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.).

Co-administration of oral paliperidone prolonged release tablets at steady-state (12 mg once daily) with divalproex sodium prolonged release tablets (500 mg to 2 000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

No interaction study between TREVICTA and lithium has been performed, however, a pharmacokinetic interaction is not likely to occur.

Potential for other medicines to affect TREVICTA

In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of oral paliperidone with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone.

Co-administration of oral paliperidone prolonged release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of TREVICTA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of TREVICTA should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of TREVICTA.

Co-administration of a single dose of an oral paliperidone prolonged release tablet 12 mg with divalproex sodium prolonged release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely as a result of increased oral absorption. Since no effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium prolonged release tablets and TREVICTA intramuscular injection. This interaction has not been studied with TREVICTA.

Concomitant use of TREVICTA with risperidone or oral paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when TREVICTA is co-administered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of TREVICTA with other antipsychotics is limited.

Concomitant use of TREVICTA with psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of paliperidone during pregnancy. Intramuscularly injected paliperidone palmitate and orally administered paliperidone were not teratogenic in animal studies, but other types of reproductive toxicity were seen (see section 5.3). Neonates exposed to paliperidone during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. TREVICTA should not be used during pregnancy unless clearly necessary.

Since paliperidone has been detected in plasma up to 18 months after a single dose of TREVICTA, consideration should be given to the long-acting nature of TREVICTA as maternal exposure to TREVICTA before and during pregnancy may lead to adverse reactions in the newborn child.

Breast-feeding

Paliperidone is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if therapeutic doses are administered to breast-feeding women. Since paliperidone has been detected in plasma up to 18 months after a single dose administration of TREVICTA, consideration should be given to the long-acting nature of TREVICTA as breastfed infants may be at risk even from TREVICTA administration long before breast-feeding. TREVICTA should not be used while breast-feeding.

Fertility

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Paliperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred (see section 4.8). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to TREVICTA is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions reported in ≥ 5% of patients in two double-blind controlled clinical trials of TREVICTA were weight increased, upper respiratory tract infection, anxiety, headache, insomnia, and injection site reaction.

Tabulated list of adverse reactions

The following are all adverse reactions that were reported with paliperidone by frequency category estimated from paliperidone palmitate clinical trials. The following terms and frequencies are applied: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1 000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1 000); *very rare* (< 1/10 000); and *not known* (cannot be estimated from the available data).

System Organ Class	**Adverse reactions**				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known[a]**
Infections and infestations		upper respiratory tract infection, urinary tract infection, influenza	pneumonia, bronchitis, respiratory tract infection, sinusitis, cystitis, ear infection, tonsillitis, onychomycosis, cellulitis, subcutaneous abscess	eye infection, acarodermatitis	
Blood and lymphatic system disorders			white blood cell count decreased, anaemia	neutropenia, thrombocytopenia, eosinophil count increased	agranulocytosis
Immune system disorders			hypersensitivity		anaphylactic reaction

Endocrine disorders		hyperprolactinaemia[b]		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		hyperglycaemia, weight increased, weight decreased, decreased appetite,	diabetes mellitus[d], hyperinsulinaemia, increased appetite, anorexia, blood triglycerides increased, blood cholesterol increased	diabetic ketoacidosis, hypoglycaemia, polydipsia	water intoxication
Psychiatric disorders	insomnia[e]	agitation, depression, anxiety	sleep disorder, mania, libido decreased, nervousness, nightmare	catatonia, confusional state, somnambulism, blunted affect, anorgasmia	sleep-related eating disorder
Nervous system disorders		parkinsonism[c], akathisia[c], sedation/ somnolence, dystonia[c], dizziness, dyskinesia[c], tremor, headache	tardive dyskinesia, syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion[e], balance disorder, coordination abnormal, head titubation	diabetic coma
Eye disorders			vision blurred, conjunctivitis, dry eye	glaucoma, eye movement disorder, eye rolling, photophobia, lacrimation increased, ocular hyperaemia	floppy iris syndrome (intraoperative)
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders		tachycardia	atrioventricular block, conduction disorder, electrocardiogram QT prolonged, postural orthostatic tachycardia syndrome, bradycardia, electrocardiogram abnormal, palpitations	atrial fibrillation, sinus arrhythmia	
Vascular disorders		hypertension	hypotension, orthostatic hypotension	pulmonary embolism, venous thrombosis, flushing	ischaemia
Respiratory, thoracic and mediastinal disorders		cough, nasal congestion	dyspnoea, pharyngolaryngeal pain, epistaxis	sleep apnoea syndrome, pulmonary congestion, respiratory tract congestion, rales, wheezing	hyperventilation, pneumonia aspiration, dysphonia

Gastrointestinal disorders		abdominal pain, vomiting, nausea, constipation, diarrhoea, dyspepsia, toothache	abdominal discomfort, gastroenteritis, dysphagia, dry mouth, flatulence	pancreatitis, intestinal obstruction, swollen tongue, faecal incontinence, faecaloma, cheilitis	ileus
Hepatobiliary disorders		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased		jaundice
Skin and subcutaneous tissue disorders			urticaria, pruritus, rash, alopecia, eczema, dry skin, erythema, acne	drug eruption, hyperkeratosis, seborrhoeic dermatitis, dandruff	Stevens-Johnson syndrome/toxic epidermal necrolysis, angioedema, skin discolouration
Musculoskeletal and connective tissue disorders		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, muscular weakness	rhabdomyolysis, joint swelling	posture abnormal
Renal and urinary disorders			urinary incontinence, pollakiuria, dysuria	urinary retention	
Pregnancy, puerperium and perinatal conditions					drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder[e], gynaecomastia, galactorrhoea, sexual dysfunction, breast pain	priapism, breast discomfort, breast engorgement, breast enlargement, vaginal discharge	
General disorders and administration site conditions		pyrexia, asthenia, fatigue, injection site reaction	face oedema, oedema[e], body temperature increased, gait abnormal, chest pain, chest discomfort, malaise, induration	hypothermia, chills, thirst, drug withdrawal syndrome, injection site abscess, injection site cellulitis, injection site cyst, injection site haematoma	body temperature decreased, injection site necrosis, injection site ulcer
Injury, poisoning and procedural complications			fall		

[a] The frequency of adverse reactions is qualified as "not known" because they were not observed in paliperidone palmitate clinical trials. They were either derived from spontaneous post-marketing reports and frequency cannot be determined, or they were derived from risperidone (any formulation) or oral paliperidone clinical trials data and/or post-marketing reports.

[b] Refer to 'Hyperprolactinaemia' below.

[c] Refer to 'Extrapyramidal symptoms' below.

[d] In placebo-controlled trials, diabetes mellitus was reported in 0.32% in subjects treated with 1-monthly paliperidone palmitate injectable compared to a rate of 0.39% in placebo group. Overall incidence from all clinical trials was 0.65% in all subjects treated 1-monthly paliperidone palmitate injectable.

[e] **Insomnia includes:** initial insomnia, middle insomnia; **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema; **Menstrual disorder includes:** menstruation delayed, menstruation irregular, oligomenorrhoea.

Undesirable effects noted with risperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another.

Description of selected adverse reactions

Anaphylactic reaction
Rarely, cases of anaphylactic reaction after injection with 1-monthly paliperidone palmitate injectable have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone (see section 4.4).

Injection site reactions
In clinical trials of TREVICTA, 5.3% of subjects reported injection site related adverse reaction. None of these events were serious or led to discontinuation. Based on the investigators' ratings, induration, redness, and swelling were absent or mild in ≥ 95% of the assessments. Subject-rated injection site pain based on a visual analogue scale was low and decreased in intensity over time.

Extrapyramidal symptoms (EPS)
In the clinical trials of TREVICTA, akathisia, dyskinesia, dystonia, parkinsonism, and tremor were reported in 3.9%, 0.8%, 0.9%, 3.6%, and 1.4% of subjects, respectively.

Extrapyramidal symptoms (EPS) included a pooled analysis of the following terms: parkinsonism (includes extrapyramidal disorder, extrapyramidal symptoms, on and off phenomenon, Parkinson's disease, parkinsonian crisis, salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, glabellar reflex abnormal, and parkinsonian rest tremor), akathisia (includes akathisia, restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, chorea, movement disorder, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, cervical spasm, emprosthotonus, oculogyric crisis, oromandibular dystonia, risus sardonicus, tetany, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor.

Weight gain
In the long-term randomised withdrawal study, abnormal increases of ≥ 7% in body weight from double-blind baseline to double-blind end point were reported for 10% subjects in the TREVICTA group and 1% subjects in the placebo group. Conversely, abnormal decreases in body weight (≥ 7%) from double-blind baseline to double-blind end point were reported for 1% subjects in the TREVICTA group and 8% subjects in the placebo group. The mean changes in body weight from double-blind baseline to double-blind end point were +0.94 kg and -1.28 kg for the TREVICTA and placebo groups, respectively
Hyperprolactinaemia
During the double-blind phase of the long-term randomised withdrawal study, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) were noted in a higher percentage of males and females in the TREVICTA group than in the placebo group (9% vs. 3% and 5% vs. 1%, respectively). In the TREVICTA group, the mean change from double-blind baseline to double-blind end point was +2.90 ng/mL for males (vs. -10.26 ng/mL in the placebo group) and +7.48 ng/mL for females (vs. -32.93 ng/mL in the placebo group). One female (2.4%) in the TREVICTA group experienced an adverse reaction of amenorrhea, while no potentially prolactin related adverse reactions were noted among females in the placebo group. There were no potentially prolactin related adverse reactions among males in either group.

Class effects

QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest, and Torsade de pointes may occur with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic medicinal products (frequency unknown).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone. In the case of acute overdose, the possibility of multiple drug involvement should be considered.

Management

Consideration should be given to the long-acting nature of the medicinal product and the long elimination half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics. ATC code: N05AX13

TREVICTA contains a racemic mixture of (+)- and (-)-paliperidone.

Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT2- and dopaminergic D2-receptors. Paliperidone also blocks alpha 1-adrenergic receptors and slightly less, H1-histaminergic and alpha 2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D2-antagonist, which is believed to relieve the symptoms of schizophrenia, it causes less catalepsy and

decreases motor functions less than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

Clinical efficacy

The efficacy of TREVICTA in the maintenance treatment of schizophrenia in subjects who have been adequately treated for at least four months with 1-monthly paliperidone palmitate injectable and the last two doses of the same dosage strength was evaluated in one long-term randomised withdrawal double-blind, placebo-controlled study and one long-term double-blind, active-controlled, non-inferiority study. For both studies, the primary outcome was based on relapse.

In the long-term randomised withdrawal study, 506 adult subjects who met DSM-IV criteria for schizophrenia were enrolled into the open-label transition phase and treated with flexible doses of 1-monthly paliperidone palmitate injectable administered into the deltoid or gluteal muscle (50-150 mg) for 17 weeks (dose adjustments occurred at weeks 5 and 9). A total of 379 subjects then received a single dose of TREVICTA in either the deltoid or gluteal muscle in the open-label stabilisation phase (dose was a 3.5 multiple of the last dose of 1-monthly paliperidone palmitate). Subjects who were considered clinically stable at the end of the 12-week stabilisation phase were then randomised 1:1 to TREVICTA or placebo in a variable duration double-blind phase (the dose of TREVICTA was the same as the last dose received during the stabilisation phase; this dose remained fixed throughout the double-blind phase). In this period, 305 symptomatically stable subjects were randomised to continue treatment with TREVICTA (n = 160) or placebo (n = 145) until relapse, early withdrawal, or the end of study. The primary efficacy variable was time to first relapse. The study was terminated on the basis of a pre-planned interim analysis conducted when 283 subjects had been randomised and 42 relapse events had been observed.

Based on the final analysis (N = 305), 42 subjects (29.0%) in the placebo group and 14 subjects (8.8%) in the TREVICTA group had experienced a relapse event during the double blind phase. The hazard ratio was 3.81 (95% CI: 2.08, 6.99) indicating a 74% decrease in relapse risk with TREVICTA compared to placebo. A Kaplan Meier plot of time to relapse by treatment group is shown in Figure 1. There was a significant difference ($p < 0.0001$) between the two treatment groups in the time to relapse in favour of TREVICTA. The time to relapse of the placebo group (median 395 days) was significantly shorter than for the TREVICTA group (the median could not be estimated due to the low percentage of subjects with relapse [8.8%]).

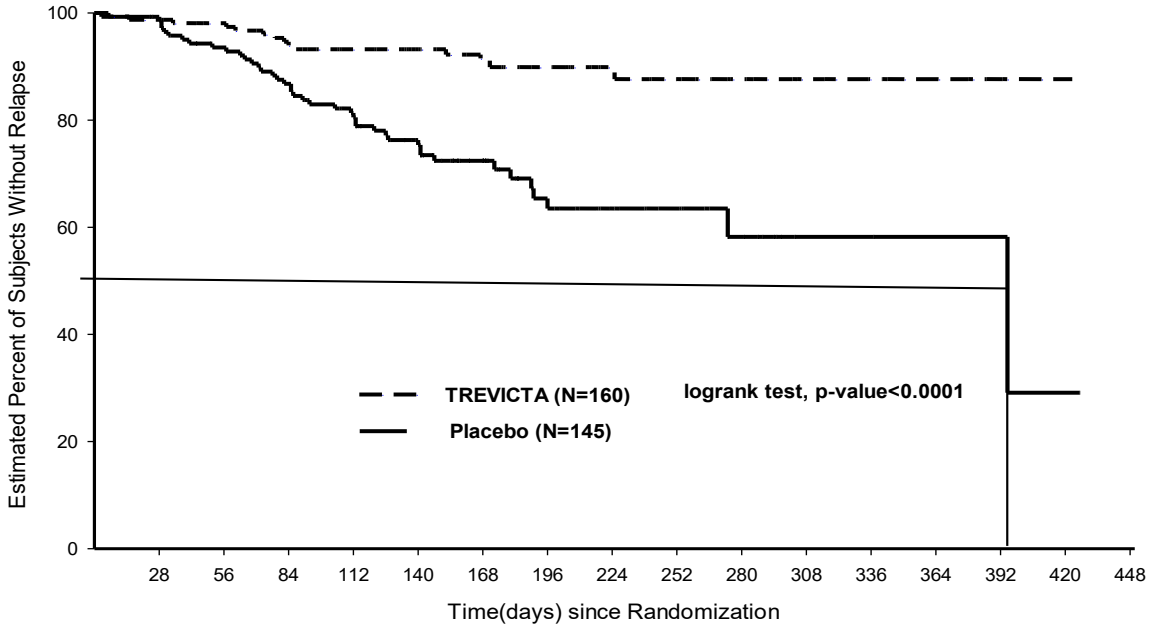

Figure 1: Kaplan-Meier plot of time to relapse – Final analysis

In the non-inferiority study, 1,429 acutely ill subjects (baseline mean PANSS total score: 85.7) who met DSM-IV criteria for schizophrenia were enrolled into the open-label phase and treated with 1-monthly paliperidone palmitate injectable for 17 weeks. The dose could be adjusted (i.e., 50 mg, 75 mg, 100 mg, or 150 mg) at the week 5 and 9 injections and the injection site could be deltoid or gluteal. For subjects that met randomisation criteria at weeks 14 and 17, 1,016 were randomised in a 1:1 ratio to continue on monthly injections of 1-monthly paliperidone palmitate injectable or to switch to TREVICTA with a 3.5 multiple of the week 9 and 13 dose of 1-monthly paliperidone palmitate injectable for 48 weeks. Subjects received TREVICTA once every 3 months and received placebo-injectable medication for the other months to maintain the blind. The primary efficacy endpoint of the study was the percentage of subjects who had not relapsed at the end of the 48-week double-blind phase based on the Kaplan-Meier 48-week estimate (TREVICTA: 91.2%, 1-monthly paliperidone palmitate injectable: 90.0%). The median time to relapse in either group could not be estimated due to low percentage of subjects with relapse. The difference (95% CI) between the treatment groups was 1.2% (-2.7%, 5.1%), meeting non-inferiority criterion based on a margin of -10%. Thus, the TREVICTA treatment group was non-inferior to 1-monthly paliperidone palmitate injectable. Improvements in functioning, as measured by the Personal and Social Performance scale (PSP), which was observed during the open-label stabilisation phase were maintained during the double-blind phase for both treatment groups.

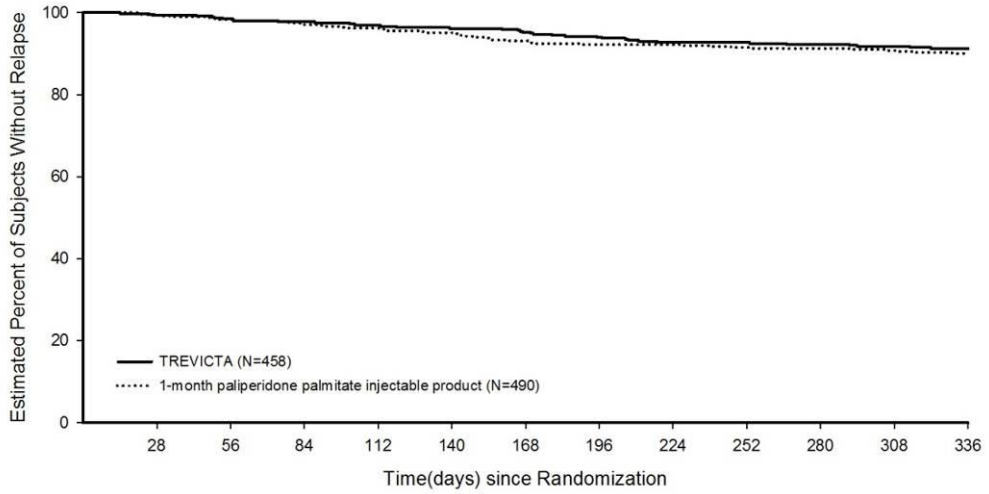

Figure 2: Kaplan-Meier plot of time to relapse comparing TREVICTA and 1-monthly paliperidone palmitate injectable

The efficacy results were consistent across population subgroups (gender, age, and race) in both studies.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TREVICTA in all subsets of the paediatric population in schizophrenia. (See section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and distribution

Due to its extremely low water solubility, the 3-monthly formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolysed to paliperidone and absorbed into the systemic circulation. The release of the active substance starts as early as day 1 and lasts for as long as 18 months.

The data presented in this paragraph are based on a population pharmacokinetic analysis. Following a single intramuscular dose of TREVICTA, the plasma concentrations of paliperidone gradually rise to

reach maximum plasma concentrations at a median T_{max} of 30-33 days. Following intramuscular injection of TREVICTA at doses of 175-525 mg in the deltoid muscle, on average, an 11-12% higher C_{max} was observed compared with injection in the gluteal muscle. The release profile and dosing regimen of TREVICTA results in sustained therapeutic concentrations. The total exposure of paliperidone following TREVICTA administration was dose-proportional over a 175-525 mg dose range, and approximately dose-proportional for C_{max}. The mean steady-state peak:trough ratio for a TREVICTA dose was 1.6 following gluteal administration and 1.7 following deltoid administration.

The plasma protein binding of racemic paliperidone is 74%.

Following administration of TREVICTA, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.7-1.8.

Biotransformation and elimination

In a study with oral immediate release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Based on population pharmacokinetic analysis, the median apparent half-life of paliperidone following TREVICTA administration over the dose range of 175-525 mg ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections.

Long-acting 3-monthly paliperidone palmitate injection versus other paliperidone formulations

TREVICTA is designed to deliver paliperidone over a 3-month period, while 1-monthly paliperidone palmitate injection is administered on a monthly basis. TREVICTA, when administered at doses that are 3.5-fold higher than the corresponding dose of 1-monthly paliperidone palmitate injection (see section 4.2), results in paliperidone exposures similar to those obtained with corresponding monthly doses of 1-monthly paliperidone palmitate injection and corresponding once daily doses of paliperidone prolonged release tablets. The exposure range for TREVICTA is encompassed within the exposure range for the approved dose strengths of paliperidone prolonged release tablets.

Hepatic impairment

Paliperidone is not extensively metabolised in the liver. Although TREVICTA was not studied in patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment.

Renal impairment

TREVICTA has not been systematically studied in patients with renal impairment. The disposition of a single oral dose of a paliperidone 3 mg prolonged release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8-fold, respectively, compared to healthy subjects.

Elderly

Population pharmacokinetics analysis showed no evidence of age related pharmacokinetics differences.

Body mass index (BMI)/body weight

Lower C_{max} was observed in overweight and obese subjects. At apparent steady-state with TREVICTA, the trough concentrations were similar among normal, overweight, and obese subjects.

Race

Population pharmacokinetics analysis showed no evidence of race related pharmacokinetics differences.

Gender

Population pharmacokinetics analysis showed no evidence of gender related pharmacokinetics differences.

Smoking status

Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Effect of smoking on the pharmacokinetics of paliperidone was not studied with TREVICTA. A population pharmacokinetic analysis based on data with oral paliperidone prolonged release tablets showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is not likely to be of clinical relevance.

5.3 Preclinical safety data

Repeat-dose toxicity studies of intramuscularly injected paliperidone palmitate (the 1-monthly formulation) and orally administered paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. In animals treated with paliperidone palmitate an inflammatory reaction was seen at the intramuscular injection site. Occasionally abscess formation occurred.

In rat reproduction studies with oral risperidone, which is extensively converted to paliperidone in rats and humans, adverse effects were seen on the birth weight and survival of the offspring. No embryotoxicity or malformations were observed following intramuscular administration of paliperidone palmitate to pregnant rats up to the highest dose (160 mg/kg/day) corresponding to 2.2 times the exposure level in humans at the maximum recommended dose of 525 mg. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

Paliperidone palmitate and paliperidone were not genotoxic. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas

adenomas (rat), and mammary gland adenomas (both species) were seen. The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 0.6 and 1.2 times the exposure level at the maximum recommended human 525 mg dose. These tumours can be related to prolonged dopamine D2-antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Polyethylene glycol 4 000
Citric acid monohydrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

175 mg
0.88 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a thin wall 22G 1½ inch (0.72 mm x 38.1 mm) safety needle and a thin wall 22G 1 inch (0.72 mm x 25.4 mm) safety needle.

263 mg
1.32 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a thin wall 22G 1½ inch (0.72 mm x 38.1 mm) safety needle and a thin wall 22G 1 inch (0.72 mm x 25.4 mm) safety needle.

350 mg
1.75 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a thin wall 22G 1½ inch (0.72 mm x 38.1 mm) safety needle and a thin wall 22G 1 inch (0.72 mm x 25.4 mm) safety needle.

525 mg
2.63 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a thin wall 22G 1½ inch (0.72 mm x 38.1 mm) safety needle and a thin wall 22G 1 inch (0.72 mm x 25.4 mm) safety needle.

Pack sizes:
Pack contains 1 pre-filled syringe and 2 needles

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Full instructions for use and handling of TREVICTA are provided in the package leaflet (See *Information intended for medical or healthcare professionals*).

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/971/007
EU/1/14/971/008
EU/1/14/971/009
EU/1/14/971/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 December 2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD CARTON

1. NAME OF THE MEDICINAL PRODUCT

TREVICTA 175 mg prolonged release suspension for injection
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 175 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, polyethylene glycol 4 000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection
1 pre-filled syringe of 0.88 mL
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/971/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trevicta 175 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TREVICTA 175 mg injection
paliperidone
IM

2. METHOD OF ADMINISTRATION

Shake vigorously

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

175 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD CARTON

1. NAME OF THE MEDICINAL PRODUCT

TREVICTA 263 mg prolonged release suspension for injection
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 263 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, polyethylene glycol 4 000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection
1 pre-filled syringe of 1.32 mL
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/971/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trevicta 263 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TREVICTA 263 mg injection
paliperidone
IM

2. METHOD OF ADMINISTRATION

Shake vigorously

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

263 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD CARTON

1. NAME OF THE MEDICINAL PRODUCT

TREVICTA 350 mg prolonged release suspension for injection
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 350 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, polyethylene glycol 4 000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection
1 pre-filled syringe of 1.75 mL
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/971/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trevicta 350 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TREVICTA 350 mg injection
paliperidone
IM

2. METHOD OF ADMINISTRATION

Shake vigorously

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

350 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD CARTON

1. NAME OF THE MEDICINAL PRODUCT

TREVICTA 525 mg prolonged release suspension for injection
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 525 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, polyethylene glycol 4 000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection
1 pre-filled syringe of 2.63 mL
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/971/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trevicta 525 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TREVICTA 525 mg injection
paliperidone
IM

2. METHOD OF ADMINISTRATION

Shake vigorously

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

525 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TREVICTA 175 mg prolonged release suspension for injection
TREVICTA 263 mg prolonged release suspension for injection
TREVICTA 350 mg prolonged release suspension for injection
TREVICTA 525 mg prolonged release suspension for injection
paliperidone

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TREVICTA is and what it is used for

TREVICTA contains the active substance paliperidone which belongs to the class of antipsychotic medicines and is used as a maintenance treatment for the symptoms of schizophrenia in adult patients.

If you have responded well to treatment with paliperidone palmitate injection given once a month, your doctor may start treatment with TREVICTA.

Schizophrenia is a disease with “positive” and “negative” symptoms. Positive means an excess of symptoms that are not normally present. For example, a person with schizophrenia may hear voices or see things that are not there (called hallucinations), believe things that are not true (called delusions), or feel unusually suspicious of others. Negative means a lack of behaviours or feelings that are normally present. For example, a person with schizophrenia may appear withdrawn and may not respond at all emotionally or may have trouble speaking in a clear and logical way. People with this disease may also feel depressed, anxious, guilty, or tense.

TREVICTA can help alleviate the symptoms of your disease and reduce the chance of your symptoms coming back.

2. What you need to know before you use TREVICTA

Do not use TREVICTA
- if you are allergic to paliperidone or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to another antipsychotic medicine including the substance risperidone.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using TREVICTA.
This medicine has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death (see section 4).

All medicines have side effects and some of the side effects of this medicine can worsen the symptoms of other medical conditions. For that reason, it is important to discuss with your doctor any of the following conditions which can potentially worsen during treatment with this medicine:

- if you have Parkinson's disease
- if you have ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome)
- if you have ever experienced twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body (Tardive Dyskinesia)
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines)
- if you are diabetic or prone to diabetes
- if you have had breast cancer or a tumour in the pituitary gland in your brain
- if you have a heart disease or heart disease treatment that makes you prone to low blood pressure
- if you have low blood pressure when you stand up or sit up suddenly
- if you have a history of seizures
- if you have kidney problems
- if you have liver problems
- if you have prolonged and/or painful erection
- if you have problems with controlling body temperature or overheating
- if you have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour
- if you or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose or monitor you for a while.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking this medicine, your doctor may check your white blood cell counts.

Even if you have previously tolerated oral paliperidone or risperidone, rarely allergic reactions occur after receiving injections of TREVICTA. Seek medical attention right away if you experience a rash, swelling of your throat, itching, or problems breathing as these may be signs of a serious allergic reaction.

This medicine may cause you to gain weight. Significant weight gain may be bad for your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking this medicine, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

Since this medicine may reduce your urge to vomit, there is a chance that it may mask the body's normal response to ingestion of toxic substances or other medical conditions.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

Children and adolescents
Do not use this medicine in children and adolescents under 18 years of age. It is not known if it is safe and effective in these patients.

Other medicines and TREVICTA
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Taking this medicine with carbamazepine (an anti-epileptic and mood stabiliser) may require a change to your dose of this medicine.

Since this medicine works primarily in the brain, using other medicines that work in the brain can cause an exaggeration of side effects such as sleepiness or other effects on the brain such as other psychiatric medications, opioids, antihistamines and sleep medication.

Since this medicine can lower blood pressure, care should be taken when this medicine is used with other medicines that lower blood pressure.

This medicine can reduce the effect of medicines against Parkinson's disease and restless legs syndrome (e.g., levodopa).

This medicine may cause an electrocardiogram (ECG) abnormality demonstrating a long time for an electrical impulse to travel through a certain part of the heart (known as "QT prolongation"). Other medicines that have this effect include some medicines used to treat the rhythm of the heart or to treat infection, and other antipsychotics.

If you have a history of seizures, this medicine may increase your chance of experiencing them. Other medicines that have this effect include some medicines used to treat depression or to treat infection, and other antipsychotics.

TREVICTA should be used with caution with medicines that increase the activity of the central nervous system (psychostimulants such as methylphenidate).

TREVICTA with alcohol
Alcohol should be avoided.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not use this medicine during pregnancy unless this has been discussed with your doctor. The following symptoms may occur in newborn babies of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms seek medical attention for your baby.

This medicine can pass from mother to baby through breast milk and may harm the baby. Therefore, you should not breast-feed when using this medicine.

Driving and using machines
Dizziness, extreme tiredness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

TREVICTA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use TREVICTA

This medicine is administered by your doctor or other healthcare professional. Your doctor will tell you when you need your next injection. It is important not to miss your scheduled dose. If you cannot

keep your appointment with the doctor, make sure you call him right away so another appointment can be made as soon as possible.

You will receive an injection of TREVICTA in the upper arm or buttocks once every 3 months.

Depending on your symptoms, your doctor may increase or decrease the amount of medicine you receive at the time of your next scheduled injection.

Patients with kidney problems
If you have mild kidney problems your doctor will determine the appropriate dose of TREVICTA based on the dose of 1-monthly paliperidone palmitate injectable that you have been receiving. If you have moderate or severe kidney problems this medicine should not be used.

Elderly
Your doctor will determine your dose of this medicine if your kidney function is reduced.

If you are given more TREVICTA than needed
This medicine will be given to you under medical supervision; it is, therefore, unlikely that you will be given too much.

Patients who have been given too much paliperidone may experience the following symptoms: drowsiness or sedation, fast heart rate, low blood pressure, an abnormal electrocardiogram (electrical tracing of the heart), or slow or abnormal movements of the face, body, arms or legs.

If you stop using TREVICTA
If you stop receiving your injections, your symptoms of schizophrenia may get worse. You should not stop using this medicine unless told to do so by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you:
- experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately.
- have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.
- experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called “Neuroleptic Malignant Syndrome”). Immediate medical treatment may be needed
- are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed.
- experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed.
- experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an ‘anaphylactic reaction’). Even if you have previously tolerated oral risperidone or oral paliperidone, rarely allergic reactions occur after receiving injections of paliperidone.
- are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine. During an operation on the eye for cloudiness of the lens (cataract), the iris (the coloured part of the eye) may become floppy during surgery (known as “floppy iris syndrome”) that may lead to eye damage.

- are aware of having dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood.

The following side effects may happen:

Very common side effects: may affect more than 1 in 10 people
- difficulty falling or staying asleep.

Common side effects: may affect up to 1 in 10 people
- common cold symptoms, urinary tract infection, feeling like you have the flu
- TREVICTA can raise your levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include: (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction; (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle.
- high blood sugar, weight gain, weight loss, decreased appetite
- irritability, depression, anxiety
- feeling restless
- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- restlessness, feeling sleepy, or less alert
- dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw.
- dizziness
- dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching.
- tremor (shaking)
- headache
- rapid heart rate
- high blood pressure
- cough, stuffy nose
- abdominal pain, vomiting, nausea, constipation, diarrhoea, indigestion, toothache
- increased liver transaminases in your blood
- bone or muscle ache, back pain, joint pain
- loss of menstrual periods
- fever, weakness, fatigue (tiredness)
- a reaction at the injection site, including itching, pain or swelling.

Uncommon side effects: may affect up to 1 in 100 people
- pneumonia, infection of the chest (bronchitis), infection of the breathing passages, sinus infection, bladder infection, ear infection, tonsillitis, fungal infection of the nails, infection of the skin, abscess under the skin
- white blood cell count decreased, decrease in the type of white blood cells that help to protect you against infection, anaemia
- allergic reaction
- diabetes or worsening of diabetes, increased insulin (a hormone that controls blood sugar levels) in your blood
- increased appetite
- loss of appetite resulting in malnutrition and low body weight
- high blood triglycerides (a fat), increased cholesterol in your blood
- sleep disorder, elated mood (mania), decreased sexual drive, nervousness, nightmares

- tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of this medicine may be needed.
- fainting, a restless urge to move parts of your body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin
- blurry vision, eye infection or "pink eye", dry eye
- sensation of spinning (vertigo), ringing in the ears, ear pain
- an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, rapid heartbeat upon standing, slow heart rate, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)
- low blood pressure, low blood pressure upon standing (consequently, some people taking this medicine may feel faint, dizzy, or may pass out when they stand up or sit up suddenly)
- shortness of breath, sore throat, nosebleeds
- abdominal discomfort, stomach or intestinal infection, difficulty swallowing, dry mouth, excessive passing of gas or wind
- increased GGT (a liver enzyme called gamma-glutamyltransferase) in your blood, increased liver enzymes in your blood
- hives (or "nettle rash"), itching, rash, hair loss, eczema, dry skin, skin redness, acne
- an increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown
- muscle spasms, joint stiffness, muscle weakness
- incontinence (lack of control) of urine, frequent passing of urine, pain when passing urine
- erectile dysfunction, ejaculation disorder, missed menstrual periods or other problems with your cycle (females), development of breasts in men, sexual dysfunction, breast pain, leakage of milk from the breasts
- swelling of the face, mouth, eyes, or lips, swelling of the body, arms, or legs
- an increase in body temperature
- a change in the way you walk
- chest pain, chest discomfort, feeling unwell
- hardening of the skin
- fall.

Rare side effects: may affect up to 1 in 1,000 people
- eye infection
- skin inflammation caused by mites, flaky, itchy scalp or skin
- increase in eosinophils (a type of white blood cell) in your blood
- decrease in platelets (blood cells that help you stop bleeding),
- inappropriate secretion of a hormone that controls urine volume
- sugar in the urine
- life threatening complications of uncontrolled diabetes
- low blood sugar
- excessive drinking of water
- confusion
- shaking of the head
- not moving or responding while awake (catatonia)
- sleep walking
- lack of emotion
- inability to reach orgasm
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness), blood vessel problems in the brain, including sudden loss of blood supply to brain (stroke or "mini" stroke), unresponsive to stimuli, loss of consciousness, low level of consciousness, convulsion (fits), balance disorder

- abnormal coordination
- glaucoma (increased pressure within the eyeball)
- problems with movement of your eyes, eye rolling, oversensitivity of the eyes to light, increased tears, redness of the eyes
- atrial fibrillation (an abnormal heart rhythm), irregular heartbeat
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg). If you notice any of these symptoms seek medical advice immediately
- blood clot in the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- flushing
- trouble breathing during sleep (sleep apnoea)
- lung congestion, congestion of breathing passages, wheezing
- crackly lung sounds
- inflammation of the pancreas, swollen tongue, stool incontinence, very hard stool
- a blockage in the bowels
- chapped lips
- rash on skin related to drug, thickening of skin, dandruff
- joint swelling
- inability to pass urine
- breast discomfort, enlargement of the glands in your breasts, breast enlargement
- vaginal discharge
- priapism (a prolonged penile erection that may require surgical treatment
- very low body temperature, chills, feeling thirsty
- symptoms of drug withdrawal
- accumulation of pus caused by infection at injection site, deep skin infection, a cyst at the injection site, bruising at injection site

Not known: frequency cannot be estimated from the available data
- dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood
- severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure
- dangerously excessive intake of water
- sleep-related eating disorder
- coma due to uncontrolled diabetes
- fast, shallow breathing, pneumonia caused by inhaling food, voice disorder
- decreased oxygen in parts of your body (because of decreased blood flow)
- lack of bowel movement that causes blockage
- yellowing of the skin and the eyes (jaundice)
- severe or life-threatening rash with blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body (Stevens-Johnson syndrome or toxic epidermal necrolysis)
- serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing
- skin discolouration
- abnormal posture
- newborn babies born to mothers who have taken TREVICTA during pregnancy may experience side effects of the drug and/or withdrawal symptoms, such as irritability, slow, or sustained muscle contractions, shaking, sleepiness, breathing, or feeding problems
- a decrease in body temperature
- dead skin cells at injection site, an ulcer at injection site

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TREVICTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What TREVICTA contains
The active substance is paliperidone.
Each TREVICTA 175 mg pre-filled syringe contains 273 mg paliperidone palmitate in 0.88 mL.
Each TREVICTA 263 mg pre-filled syringe contains 410 mg paliperidone palmitate in 1.32 mL.
Each TREVICTA 350 mg pre-filled syringe contains 546 mg paliperidone palmitate in 1.75 mL.
Each TREVICTA 525 mg pre-filled syringe contains 819 mg paliperidone palmitate in 2.63 mL.

The other ingredients are:
Polysorbate 20
Polyethylene glycol 4 000
Citric acid monohydrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

What TREVICTA looks like and contents of the pack
TREVICTA is a white to off-white prolonged release suspension for injection in a pre-filled syringe that your doctor or nurse will shake vigorously to resuspend the suspension before it is given as an injection.

Each pack contains 1 pre-filled syringe and 2 needles.

Not all pack sizes may be marketed.

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Manufacturer
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Information intended for medical or healthcare professionals

The following information is intended for medical or healthcare professionals only and should be read by the medical or healthcare professional in conjunction with the full prescribing information (Summary of Product Characteristics).

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

For intramuscular injection only. Do not administer by any other route.

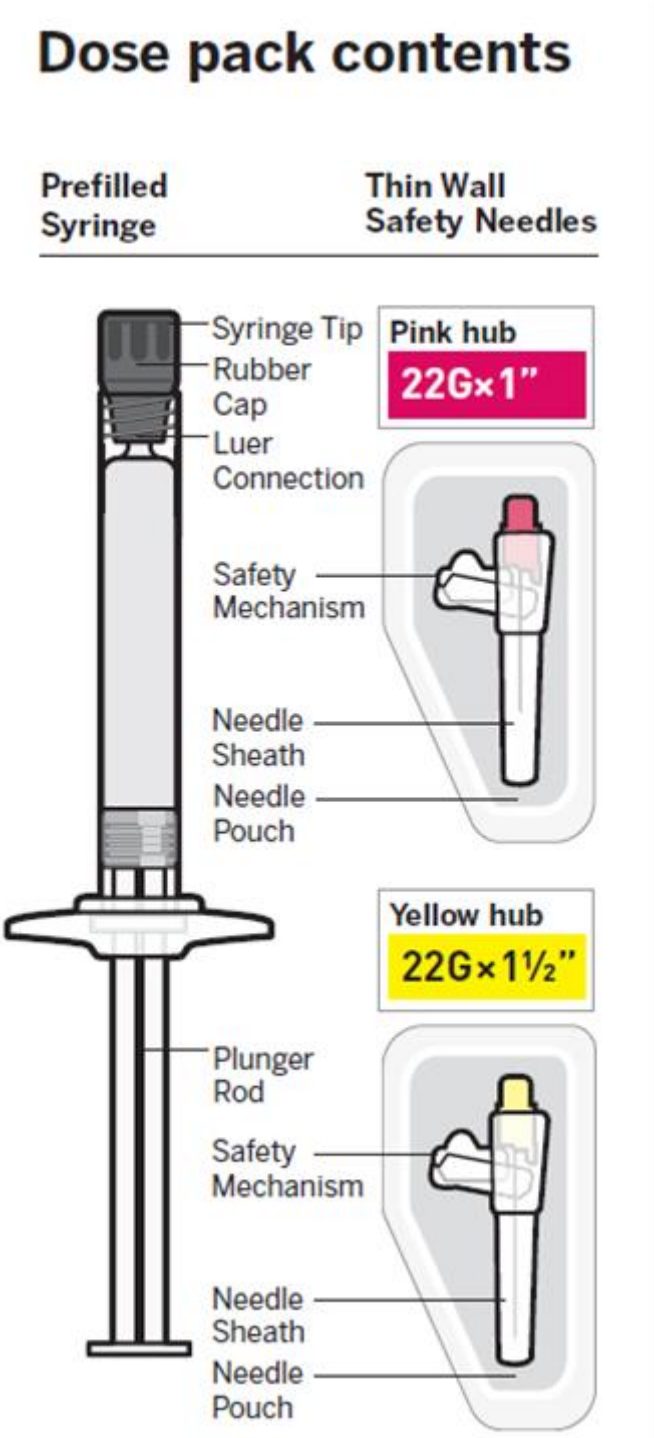
Important
Read complete instructions prior to use. TREVICTA requires close attention to these step-by-step Instructions for Use to help ensure successful administration.
TREVICTA should be administered by a healthcare professional as a single injection. **DO NOT** divide dose into multiple injections.
TREVICTA is intended for intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.

Dosing
TREVICTA should be administered **once every 3 months**.

Preparation
Peel off the tab label from the syringe and place in patient record.
TREVICTA requires **longer and more vigorous shaking** than 1-monthly paliperidone palmitate injectable. Shake the syringe vigorously, with the syringe tip pointing up, for **at least 15 seconds within 5 minutes prior to administration** (see Step 2).

Thin Wall Safety Needle Selection
Thin wall (TW) safety needles are designed to be used with TREVICTA. It is important to **only use the needles provided in the TREVICTA pack**.

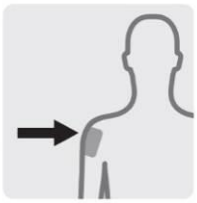
Dose pack contents



1 Select needle

Needle selection is determined by injection site and patient weight.

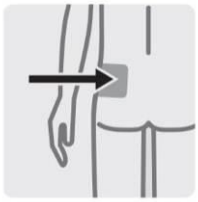
If administering a **Deltoid** injection



If patient weighs:
Less than 90 kg
pink hub
22G × 1"

90 kg or more
yellow hub
22G × 1½"

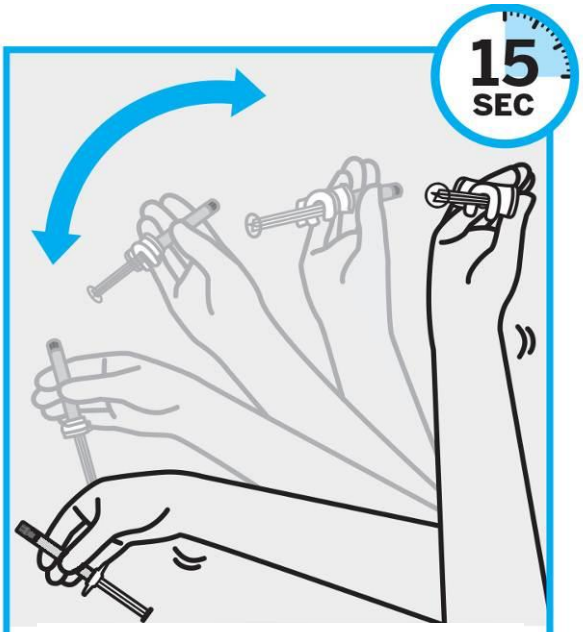
If administering a **Gluteal** injection



Regardless of patient weight:
yellow hub
22G × 1½"

Immediately discard the unused needle in an approved sharps container. Do not save for future use.

2 Prepare for injection



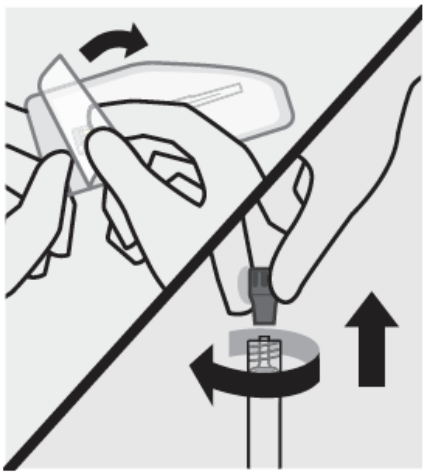
SHAKE VIGOROUSLY for at least 15 seconds
With the syringe tip pointing up, SHAKE VIGOROUSLY with a **loose wrist** for at least 15 seconds to ensure a homogeneous suspension.
NOTE: This medicine requires longer and more vigorous shaking than 1-monthly paliperidone palmitate injectable.

Proceed to the next step immediately after shaking. **If more than <u>5 minutes</u> pass before injection, shake vigorously, with the syringe tip pointing up, again** for at least 15 seconds to re-suspend the medication.

Check suspension

After shaking the syringe for at least 15 seconds, check the appearance of the suspension in the viewing window.
The suspension should appear uniform and milky white in colour.
It is also normal to see small air bubbles.

Open needle pouch and remove cap

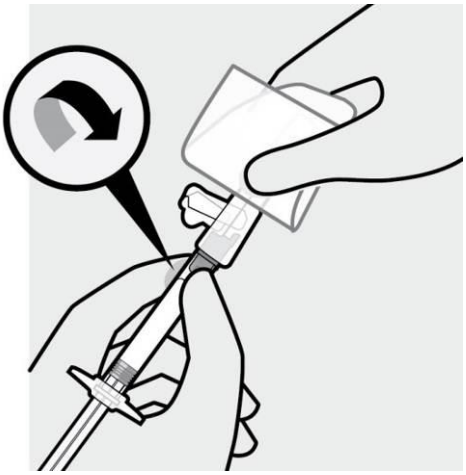


First, open needle pouch by peeling the cover back half way. Place on a clean surface.
Then, holding the syringe upright, twist and pull the rubber cap to remove.

Grasp needle pouch

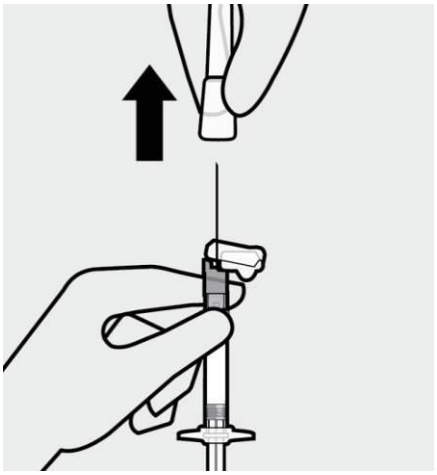
Fold back needle cover and plastic tray. Then, firmly grasp the needle sheath through the pouch, as shown.

Attach needle



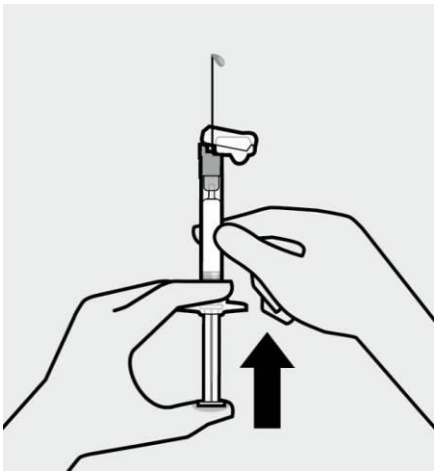
Hold the syringe pointing up. Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leakage prior to administration.

Remove needle sheath



Pull the needle sheath away from the needle in a straight motion.
Do not twist the sheath, as this may loosen the needle from the syringe.

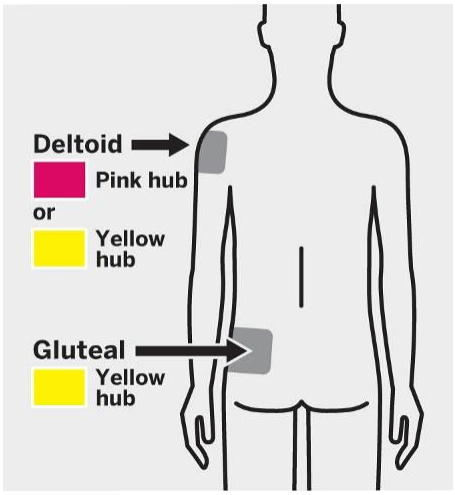
Remove air bubbles



Hold the syringe upright and tap gently to make any air bubbles rise to the top.
Slowly and carefully press plunger rod upward to remove air.

3 Inject

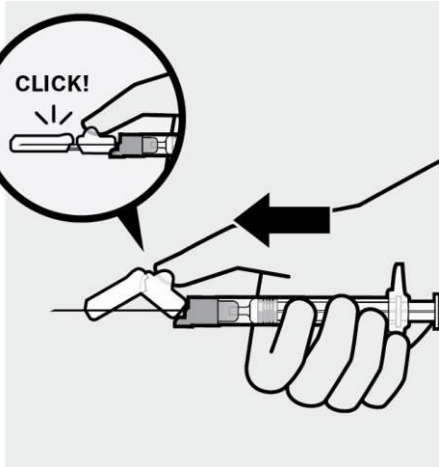
Inject dose



Slowly inject the entire contents of the syringe intramuscularly, deep into the selected deltoid or gluteal muscle.
Do not administer by any other route.

4 After injection

Secure needle



After the injection is complete, use your thumb or a flat surface to secure the needle in the safety mechanism. The needle is secure when a “click” sound is heard.

Dispose properly

Dispose of the syringe and unused needle in an approved sharps container.

Thin wall safety needles are designed specifically for use with TREVICTA. Unused needle should be discarded and not saved for future use.