ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BYANNLI 700 mg prolonged-release suspension for injection in pre-filled syringe
BYANNLI 1 000 mg prolonged-release suspension for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

700 mg prolonged-release suspension for injection

Each pre-filled syringe contains 1 092 mg paliperidone palmitate in 3.5 mL equivalent to 700 mg paliperidone

1 000 mg prolonged-release suspension for injection

Each pre-filled syringe contains 1 560 mg paliperidone palmitate in 5 mL equivalent to 1 000 mg paliperidone

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BYANNLI, a 6-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products (see section 5.1).

4.2 Posology and method of administration

Posology

Patients who are adequately treated with 1-monthly paliperidone palmitate injection at doses of 100 mg or 150 mg (preferably for four months or more) or 3-monthly paliperidone palmitate injection at doses of 350 mg or 525 mg (for at least one injection cycle) and do not require dose adjustment may be transitioned to 6-monthly paliperidone palmitate injection.

BYANNLI for patients adequately treated with 1-monthly paliperidone palmitate injection
BYANNLI should be initiated in place of the next scheduled dose of 1-monthly paliperidone palmitate injection (± 7 days). To establish a consistent maintenance dose, it is recommended that the last two doses of 1-monthly paliperidone palmitate injection be the same dose strength before starting BYANNLI. The BYANNLI dose should be based on the previous 1-monthly paliperidone palmitate injectable dose shown in the following table:

Transitioning to BYANNLI for patients adequately treated with 1-monthly paliperidone palmitate injection

If the last dose of 1-monthly paliperidone injection is	Initiate BYANNLI at the following dose*
100 mg	700 mg
150 mg	1 000 mg

* There are no equivalent doses of BYANNLI for the 25 mg, 50 mg or 75 mg doses of 1-monthly paliperidone palmitate injection, which were not studied.

BYANNLI for patients adequately treated with 3-monthly paliperidone palmitate injection
BYANNLI should be initiated in place of the next scheduled dose of 3-monthly paliperidone palmitate injection (± 14 days). The BYANNLI dose should be based on the previous 3-monthly paliperidone palmitate injectable dose shown in the following table:

Transitioning to BYANNLI for patients adequately treated with 3-monthly paliperidone palmitate injection

If the last dose of 3-monthly paliperidone injection is	Initiate BYANNLI at the following dose*
350 mg	700 mg
525 mg	1 000 mg

* There are no equivalent doses of BYANNLI for the 175 mg or 263 mg doses of 3-monthly paliperidone palmitate injection, which were not studied.

Following the initial BYANNLI dose, BYANNLI should be administered once every 6 months. If necessary, patients may be given the injection up to 2 weeks before or up to 3 weeks after the 6-month scheduled timepoint (see also *Missed dose* section).

If needed, dose adjustment of BYANNLI can be made every 6 months between the dose levels of 700 mg and 1 000 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of BYANNLI 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 BYANNLI should only be initiated after the patient is stabilised on 3-monthly or 1-monthly paliperidone palmitate injectable products.

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

Transitioning from BYANNLI to 1-monthly paliperidone palmitate injection
When transitioning from BYANNLI to 1-monthly paliperidone palmitate injection, the 1-monthly injection should be administered at the time of the next scheduled BYANNLI dose as shown in the following table. The initiation dosing as described in the prescribing information for 1-monthly paliperidone palmitate injection is not required. The 1-monthly paliperidone palmitate injection should then be dosed at monthly intervals as described within the prescribing information for that product.

Doses of 1-monthly paliperidone palmitate injectable for patients transitioning from BYANNLI

If the last dose of BYANNLI is	Initiate 1-monthly paliperidone injection 6 months later at the following dose
700 mg	100 mg
1 000 mg	150 mg

Transitioning from BYANNLI to 3-monthly paliperidone palmitate injectable
When transitioning patients from BYANNLI to 3-monthly paliperidone palmitate injection, the 3-monthly injection should be administered at the time of the next scheduled BYANNLI dose as shown in the following table. The initiation dosing regimen described in the prescribing information for 3-monthly paliperidone palmitate injection is not required. The 3-monthly paliperidone palmitate injection should then be dosed at 3-monthly intervals as described within the prescribing information for that product.

Doses of 3-monthly paliperidone palmitate injectable for patients transitioning from BYANNLI

If the last dose of BYANNLI is	Initiate 3-monthly paliperidone injectable 6 months later at the following dose
700 mg	350 mg
1 000 mg	525 mg

Transitioning from BYANNLI to oral daily paliperidone prolonged-release tablets
When transitioning patients from BYANNLI to paliperidone prolonged-release tablets, the daily dosing of paliperidone prolonged-release tablets should be started 6 months after the last BYANNLI dose and treatment should be continued with paliperidone prolonged-release tablets as described in the table below. Patients previously stabilised on different doses of BYANNLI can attain similar paliperidone exposure with paliperidone prolonged-release tablets according to the following conversion regimens:

Doses of paliperidone prolonged-release tablets for patients transitioning from BYANNLI*

If the last dose of BYANNLI is	Months after last BYANNLI dose		
	6 months to 9 months	More than 9 months to 12 months	More than 12 months
	Daily dose of paliperidone prolonged-release tablets		
700 mg	3 mg	6 mg	9 mg
1 000 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 transitioning, response to previous paliperidone treatment, severity of psychotic symptoms, and/or propensity for side effects.

Missed dose

Dosing window
BYANNLI should be injected once every 6 months. To avoid a missed dose of BYANNLI, patients may be given the injection up to 2 weeks before or up to 3 weeks after the scheduled 6-month time point.

Missed doses

If scheduled dose is missed and the time since last injection is	**Action**
up to 6 months and 3 weeks	The injection of BYANNLI should be administered as soon as possible and then resume the 6-monthly injection schedule.
> 6 months and 3 weeks up to < 8 months	The injection of BYANNLI should not be administered. Use the recommended re-initiation regimen with 1-monthly paliperidone palmitate injectable as shown in the table below.
≥ 8 months to ≤ 11 months	The injection of BYANNLI should not be administered. Use the recommended re-initiation regimen with 1-monthly paliperidone palmitate injectable as shown in the table below.
> 11 months	The injection of BYANNLI should not be administered. Re-initiate treatment with 1-monthly paliperidone palmitate injectable as described in the prescribing information for that product. BYANNLI 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 > 6 months and 3 weeks up to < 8 months of BYANNLI		
If the last dose of BYANNLI was	Administer 1-monthly paliperidone palmitate injectable (into deltoid[a] muscle)	Then administer BYANNLI (into gluteal muscle)
	Day 1	1 month after Day 1
700 mg	100 mg	700 mg
1 000 mg	150 mg	1 000 mg

Recommended re-initiation regimen after missing ≥ 8 months to ≤ 11 months of BYANNLI			
If the last dose of BYANNLI was	Administer 1-monthly paliperidone palmitate injectable (into deltoid[a] muscle)		Then administer BYANNLI (into gluteal muscle)
	Day 1	Day 8	1 month after Day 8
700 mg	100 mg	100 mg	700 mg
1 000 mg	100 mg	100 mg	1 000 mg

[a] See *Information intended for healthcare professionals* for the 1-monthly paliperidone palmitate injectable product 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 BYANNLI 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
While BYANNLI has not been systematically studied in patients with renal impairment, the plasma concentrations of orally administered paliperidone are increased in these patients (see sections 4.4 and 5.2).

Patients with mild renal impairment (creatinine clearance ≥ 50 to ≤ 80 mL/min) who are stabilised on either 100 mg 1-monthly paliperidone palmitate injectable or 350 mg 3-monthly paliperidone palmitate injectable can be transitioned to BYANNLI at the 700 mg dose only. The 1 000 mg dose of BYANNLI is not recommended for patients with mild renal impairment.

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

Hepatic impairment
BYANNLI 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 BYANNLI in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

BYANNLI is for gluteal 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 upper-outer quadrant of the gluteal muscle. A switch between the two gluteal muscles should be considered for future injections in the event of injection site discomfort (see section 4.8).

The needle for administration of BYANNLI is a thin wall 1½ inch, 20 gauge (0.9 mm × 38 mm) needle, regardless of body weight. BYANNLI must be administered using only the thin wall needle that is provided in the BYANNLI pack. Needles from the 3-monthly or 1-monthly paliperidone palmitate injectable pack or other commercially available needles must not be used when administering BYANNLI (see *Information intended for healthcare professionals*).

The contents of the pre-filled syringe should be inspected visually for foreign matter and discolouration prior to administration. This highly concentrated product requires specific steps to ensure complete resuspension.

It is important to **shake the syringe with the syringe tip cap pointing up** using a **very fast** up and down motion with a loose wrist **for at least 15 seconds. Rest briefly, then shake again** in the same way, using a **very fast** up and down motion with a loose wrist for a **further 15 seconds** to resuspend the medicinal product. **Proceed immediately to inject BYANNLI**. If more than five minutes passes before the injection is administered, shake the syringe again, as above to resuspend the medicinal product (see *Information intended for healthcare professionals*).

Incomplete administration
BYANNLI is a highly concentrated product that requires specific steps to ensure complete resuspension and prevent clogging of the needle during injection. Proper shaking can reduce the likelihood of an incomplete injection. Shipping and storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product. Follow the details in the *Information intended for healthcare professionals* to avoid an incomplete injection.

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 6-monthly injection of BYANNLI.

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

BYANNLI 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 (NMS)

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 BYANNLI.

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 BYANNLI.

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 (WBC) count or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of BYANNLI 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 $< 1 \times 10^9$/L) should discontinue BYANNLI and have their WBC followed until recovery. Consideration should be given to the long-acting nature of BYANNLI.

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 BYANNLI 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.

Body weight change

Significant weight change has been reported with BYANNLI use. Weight should be monitored regularly (see section 4.8).

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. BYANNLI 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

BYANNLI 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. Patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to ≤ 80 mL/min) who are stabilised on either 1-monthly paliperidone palmitate injectable or 3-monthly paliperidone palmitate injectable may be transitioned to BYANNLI (see section 4.2). The 1 000 mg dose of BYANNLI is not recommended for patients with mild renal impairment. BYANNLI 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

BYANNLI has not been studied in elderly patients with dementia. BYANNLI 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 (DLB)

Physicians should weigh the risks versus the benefits when prescribing BYANNLI to patients with Parkinson's disease or DLB since both groups may be at increased risk of NMS 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 BYANNLI 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 (VTE)

Cases of 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 BYANNLI 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 overdose 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 BYANNLI into a blood vessel.

Intraoperative floppy iris syndrome (IFIS)

IFIS has been observed during cataract surgery in patients treated with medicinal products with alpha 1a-adrenergic antagonist effect, such as BYANNLI (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 BYANNLI 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 BYANNLI 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), BYANNLI 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 BYANNLI 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 BYANNLI and lithium has been performed, however, a pharmacokinetic interaction is not likely to occur.

Potential for other medicines to affect BYANNLI

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 BYANNLI should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of BYANNLI should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of BYANNLI.

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 BYANNLI gluteal intramuscular injection. This interaction has not been studied with BYANNLI.

Concomitant use of BYANNLI with risperidone or oral paliperidone

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

Concomitant use of BYANNLI 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

Women of childbearing potential

Plasma exposure to paliperidone after a single dose of BYANNLI is expected to remain for up to 4 years (see section 5.2). This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding. BYANNLI should only be used in women planning to become pregnant if clearly necessary.

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.

Paliperidone has been detected in plasma up to 18 months after a single dose of the 3-monthly paliperidone palmitate injectable. Plasma exposure to paliperidone after a single dose of BYANNLI is expected to remain for up to 4 years (see section 5.2). Maternal exposure to BYANNLI before and during pregnancy may lead to adverse reactions in the newborn child. BYANNLI should not be used during pregnancy unless clearly necessary.

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 a single dose of BYANNLI is expected to remain for up to 4 years in plasma (see section 5.2), breast-fed infants may be at risk even from BYANNLI administration long before breast-feeding. Patients currently under treatment or who have been treated in the past 4 years with BYANNLI should not breast feed.

Fertility

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

4.7 Effects on ability to drive and use machines

Paliperidone has 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 BYANNLI is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions reported in ≥ 5% of patients in the randomised double-blind active controlled clinical trial of BYANNLI were upper respiratory tract infection, injection site reaction, weight increased, headache and Parkinsonism.

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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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 the clinical trial of BYANNLI, 10.7% of subjects reported injection site related adverse reaction (4.5% in subjects treated with the comparator 3-monthly paliperidone palmitate injectable). None of these events were serious or led to discontinuation. Based on the investigators' clinical 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 trial of BYANNLI, akathisia, dyskinesia, dystonia, parkinsonism, and tremor were reported in 3.6%, 1.5%, 0.6%, 5.0%, and 0.2% of subjects, respectively.

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 (includes 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 (includes tremor, action tremor).

Changes in body weight
In the 12-month clinical trial of BYANNLI, the number of subjects with abnormal weight percent change from double-blind baseline to double-blind end point is presented in the table below. The overall mean weight change from double-blind baseline to double-blind end point was +0.10 kg for the BYANNLI group and +0.96 kg for the 3-monthly paliperidone palmitate group. In subjects 18-25 years of age, mean (SD) weight change of -0.65 (4.955) kg was observed for the BYANNLI group and +4.33 (7.112) kg in the 3-monthly paliperidone palmitate group. For overweight subjects (BMI 25 to < 30), mean weight change of -0.53 kg in the BYANNLI group and +1.15 kg in the 3-monthly paliperidone palmitate group was observed.

Number of patients with abnormal weight percent change from (double-blind) baseline to end point

Weight percent change	PP3M[1] (N=219)	BYANNLI (N=473)
Decrease ≥ 7%	15 (6.8%)	43 (9.1%)
Increase ≥ 7%	29 (13.2%)	50 (10.6%)

[1] PP3M – 3-monthly paliperidone palmitate injectable

Hyperprolactinaemia
In the 12-month clinical trial of BYANNLI, the mean (SD) change from double-blind baseline in prolactin levels was -2.19 (13.61) µg/L for males and -4.83 (34.39) µg/L for females in the 6-monthly paliperidone palmitate group and in the 3-monthly paliperidone palmitate group it was 1.56 (19.08)◦µg/L for males and 9.03 (40.94) µg/L for females. During the double-blind phase, 3 females (4.3%) in the 3-monthly paliperidone palmitate group and 5 females (3.3%) in the 6-monthly paliperidone palmitate group experienced amenorrhoea.

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 VTE, 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

BYANNLI 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 BYANNLI for the treatment of schizophrenia in patients who had previously been adequately treated with either 1-monthly paliperidone palmitate injection for at least 4 months or 3-monthly paliperidone palmitate injectable for at least one 3-month injection cycle was evaluated in a Phase 3, randomised, double-blind, active-controlled, interventional, parallel-group, multicentre, non-inferiority study in adult patients. The primary outcome was time to relapse.

The study consisted of an open-label phase which included screening, transition and maintenance phases, followed by a 12-month double-blind phase in which patients were randomised to receive either BYANNLI or 3-monthly paliperidone palmitate injectable. 702 adequately treated patients were randomised in a 2:1 ratio to receive BYANNLI (478 patients) or 3-monthly paliperidone palmitate

injectable (224 patients). Patients received either 2 injection cycles of BYANNLI (4 injections in total; BYANNLI with alternating placebo) or 4 injections of 3-monthly paliperidone palmitate injection every 3 months with regular scheduled visits between injections over the 12-month study duration. Dose adjustment was not permitted during the double-blind phase. Patients remained in this phase until they experienced a relapse event, met discontinuation/withdrawal criteria, or study conclusion.

7.5% of patients in the BYANNLI treatment group and 4.9% of patients in the 3-monthly paliperidone palmitate injectable treatment group experienced a relapse event in the 12-month double-blind Phase with the Kaplan-Meier estimated difference (BYANNLI – 3-monthly paliperidone palmitate injection) of 2.9% (95% CI: -1.1% to 6.8%). The Kaplan-Meier plot (with 95% pointwise confidence bands) of time from randomisation to impending relapse during the 12-month double-blind, active-controlled Phase for BYANNLI 700 and 1 000 mg and 3-monthly paliperidone palmitate injectable 350 mg and 525 mg is shown in Figure 1.

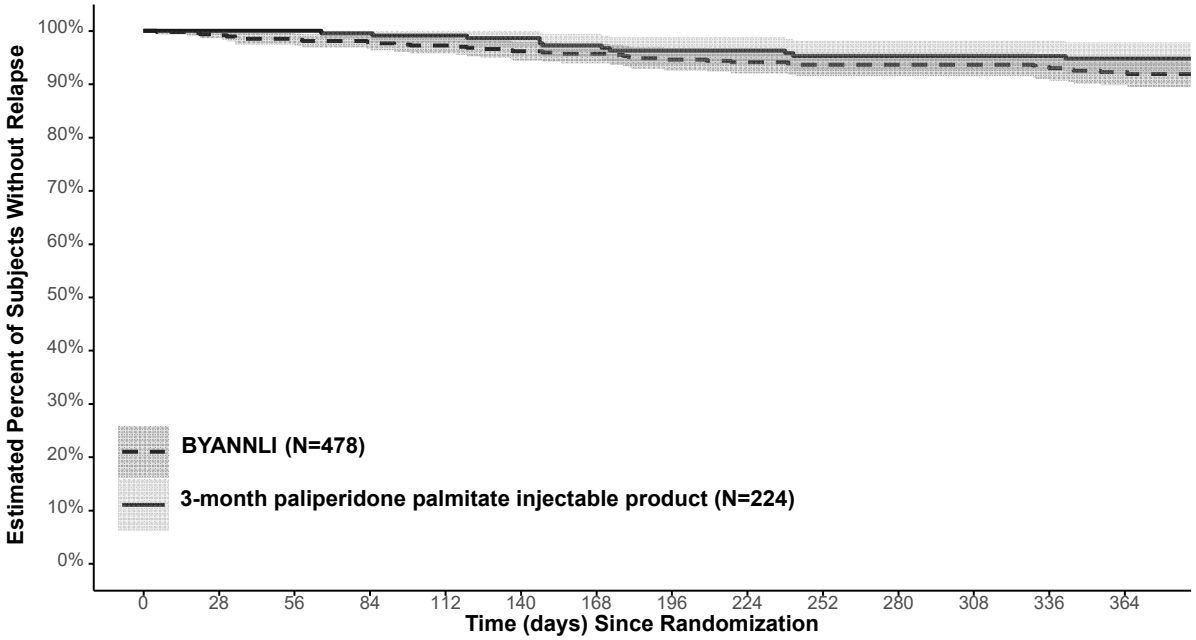


Figure 1: Kaplan-Meier Plot (with 95% pointwise confidence bands) of percentage of subjects without relapse

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

It was determined that the efficacy of BYANNLI was noninferior to the efficacy of 3-monthly paliperidone palmitate injection in adults with a DSM-5 diagnosis of schizophrenia. The upper bound of the 95% CI (6.8%) was less than 10%, the prespecified non-inferiority margin.

Paediatric population

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

5.2 Pharmacokinetic properties

The pharmacokinetics for BYANNLI are presented after gluteal administration only.

Absorption and distribution

Due to its extremely low water solubility, the 6-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 after a single dose of 3-monthly paliperidone palmitate injectable starts as early as day 1 and lasts for as long as 18 months. The release of BYANNLI is expected to last longer. Paliperidone plasma concentrations have only been studied up to 6 months after administration of BYANNLI. Based on population pharmacokinetic simulations paliperidone concentrations are expected to remain in plasma for up to approximately 4 years following a single 1 000 mg dose of BYANNLI. The concentration of paliperidone remaining in the circulation approximately 4 years after a single dose of 1 000 mg BYANNLI is expected to be low (< 1% of the average steady state levels).

The data presented in this paragraph are based on a population pharmacokinetic analysis. Following a single gluteal intramuscular injection of BYANNLI at doses of 700 and 1 000 mg, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations predicted on days 33 and 35, respectively. The release profile and dosing regimen of BYANNLI results in sustained therapeutic concentrations over 6 months. C_{max} and AUC_{6month} of BYANNLI were approximately dose-proportional in the range of 700-1 000 mg. The median steady-state peak:trough ratio is approximately 3.0.

The plasma protein binding of racemic paliperidone is 74%.

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 BYANNLI gluteal administration at doses of 700 and 1 000 mg is estimated to be 148 and 159 days, respectively.

Long-acting 6-monthly paliperidone palmitate injection versus other paliperidone formulations

BYANNLI is designed to deliver paliperidone over a 6-month period, compared to the 1-monthly or 3-monthly products which are administered every month or every three months, respectively. BYANNLI doses of 700 mg and 1 000 mg results in a range of paliperidone exposures similar to those obtained with corresponding doses of 1-monthly or 3-monthly paliperidone palmitate injections or corresponding once daily doses of paliperidone prolonged-release tablets (see section 4.2).

Hepatic impairment

Paliperidone is not extensively metabolised in the liver. Although BYANNLI 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

BYANNLI 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 BYANNLI, the trough concentrations were similar among normal, overweight, and obese subjects.

Race

Pharmacokinetic analysis showed no evidence of clinically relevant difference in pharmacokinetics between races.

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 BYANNLI. 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 1.6 times the exposure level in humans at the maximum recommended dose of 1 000 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 0.3 and 0.6 times the exposure level at the maximum recommended human 1 000 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 temperature storage conditions.
Ship and store in a horizontal position. See arrows on product carton for proper orientation.

6.5 Nature and contents of container

700 mg
3.5 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, plunger rod, backstop, and tip cap (bromobutyl rubber) with a thin wall 20G 1½ inch (0.9 mm × 38 mm) safety needle.

1 000 mg
5 mL suspension in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, plunger rod, backstop, and tip cap (bromobutyl rubber) with a thin wall 20G 1½ inch (0.9 mm × 38 mm) safety needle.

Pack sizes:
Pack contains 1 pre-filled syringe and 1 needle

6.6 Special precautions for disposal and other handling

Ship and store this product in a horizontal orientation to improve the ability to resuspend this highly concentrated product and prevent clogging of the needle.
Shake the syringe very fast for at least 15 seconds, rest briefly, then shake again for 15 seconds. The suspension should be visually inspected before injection. When mixed well the product is uniform,

thick and milky white. Full instructions for use and handling of BYANNLI are provided in the package leaflet (See *Information intended for healthcare professionals*).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1453/007
EU/1/20/1453/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 June 2020
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

BYANNLI 700 mg prolonged-release suspension for injection in pre-filled syringe
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 700 mg paliperidone (as paliperidone palmitate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection
1 pre-filled syringe of 3.5 mL
1 needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Gluteal intramuscular use

Administer every 6 months

Shake syringe VERY FAST in an up and down motion for 15 seconds, then repeat

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

Administer only using the needle provided in the pack.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Ship and store with THIS SIDE UP
LAY FLAT
UP
Inset upward pointing arrows
DOWN
Ship and store with THIS SIDE DOWN
LAY FLAT

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/1/20/1453/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BYANNLI 700 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 BLISTERS OR STRIPS

BLISTER TRAY LABEL

1. NAME OF THE MEDICINAL PRODUCT

BYANNLI 700 mg injection
paliperidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Requires specific shaking to prevent clogging.
Read *Information intended for healthcare professionals.*

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

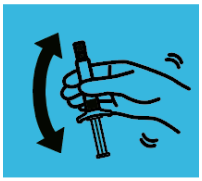
PRE-FILLED SYRINGE

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

BYANNLI 700 mg injection
paliperidone

2. METHOD OF ADMINISTRATION

Gluteal i.m



Shake fast

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

700 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD CARTON

1. NAME OF THE MEDICINAL PRODUCT

BYANNLI 1 000 mg prolonged-release suspension for injection in pre-filled syringe
paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 1 000 mg paliperidone (as paliperidone palmitate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection
1 pre-filled syringe of 5 mL
1 needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Gluteal intramuscular use

Administer every 6 months

Shake syringe VERY FAST in an up and down motion for 15 seconds, then repeat

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

Administer only using the needle provided in the pack.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Ship and store with THIS SIDE UP
LAY FLAT
UP
Inset upward pointing arrows
DOWN
Ship and store with THIS SIDE DOWN
LAY FLAT

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/1/20/1453/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BYANNLI 1 000 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 BLISTER OR STRIPS

BLISTER TRAY LABEL

1. NAME OF THE MEDICINAL PRODUCT

BYANNLI 1 000 mg injection
paliperidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Requires specific shaking to prevent clogging.
Read *Information intended for healthcare professionals.*

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

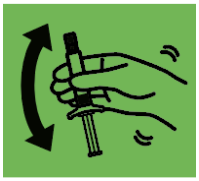
PRE-FILLED SYRINGE

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

BYANNLI 1 000 mg injection
paliperidone

2. METHOD OF ADMINISTRATION

Gluteal i.m



Shake fast

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

BYANNLI 700 mg prolonged-release suspension for injection in pre-filled syringe
BYANNLI 1 000 mg prolonged-release suspension for injection in pre-filled syringe
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 BYANNLI is and what it is used for

BYANNLI contains the active substance paliperidone which belongs to the class of antipsychotic medicines.

BYANNLI 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 or once every three months, your doctor may start treatment with BYANNLI.

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.

BYANNLI can help alleviate the symptoms of your disease and reduce the risk of your symptoms coming back.

2. What you need to know before you use BYANNLI

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

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using BYANNLI.
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 a type of dementia called "Lewy body dementia"
- 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 BYANNLI. 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 or loose weight. Significant changes in weight 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.

Cataract operations
If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine. This is because during a cataract operation on the eye for cloudiness of the lens:

- the pupil (the black circle in the middle of your eye) may not increase in size as needed
- the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage.

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 BYANNLI
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 medicines, opioids, antihistamines and sleep medicines.

Tell your doctor if you take this medicine while you are also taking oral risperidone or paliperidone for extended periods of time. You may require a change to your dose of BYANNLI.

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 risk of experiencing them. Other medicines that have this effect include some medicines used to treat depression or to treat infection, and other antipsychotics.

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

BYANNLI 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.

Women of childbearing potential
A single dose of this medicine is expected to remain within the body for up to 4 years, which may be a risk for the baby. BYANNLI should, therefore, only be used in women planning to have a baby if clearly necessary.

Pregnancy
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. Newborns should be monitored carefully and if your baby develops any of these symptoms seek medical attention for your baby.

Breast-feeding
This medicine can pass from mother to baby through breast milk. It may harm the baby, even a long time after the latest dose. Therefore, you should not breast-feed if you are using, or have used, this medicine in the past 4 years.

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.

BYANNLI 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 BYANNLI

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, make sure you call right away so another appointment can be made as soon as possible.

You will receive an injection of BYANNLI in the buttocks once every 6 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 if BYANNLI is appropriate based on the dose of 1-monthly or 3-monthly paliperidone palmitate injectable that you have been receiving. The 1 000 mg dose of BYANNLI is not recommended.
If you have moderate or severe kidney problems this medicine should not be used.

Elderly
Your doctor may adjust your dose of this medicine if your kidney function is reduced.

If you are given more BYANNLI 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 BYANNLI
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.

Serious side effects
If you get any of the following serious side effects, you may need immediate medical treatment. Tell your doctor or go to the nearest hospital straight away:

- Blood clots in the veins, especially in the legs. This is rare (may affect up to 1 in 1 000 people). Symptoms include:
    - swelling, pain, and redness in the leg – "deep vein thrombosis"
    - chest pain and difficulty breathing caused by blood clots that travelled through blood vessels to the lungs – "pulmonary embolism".
- Signs of a stroke, the frequency is not known (cannot be estimated from the available data). Symptoms include:
    - sudden change in your mental state
    - sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time.
- Neuroleptic malignant syndrome. This is rare (may affect up to 1 in 1 000 people). Symptoms include:
    - Fever, muscle stiffness, sweating or a lowered level of consciousness.
- Prolonged erection, which may be painful (priapism). This is rare (may affect up to 1 in 1 000 people).
- Twitching or jerking rhythmic movements that you cannot control in your tongue, mouth and face or other parts of your body (Tardive Dyskinesia). This is uncommon (may affect up to 1 in 100 people).
- Severe allergic reaction (anaphylactic reaction), the frequency is not known (cannot be estimated from the available data). Symptoms include:
    - fever,
    - swollen mouth, face, lip or tongue,
    - shortness of breath,
    - itching, skin rash and sometimes drop in blood pressure.

Even if you have previously tolerated oral risperidone or oral paliperidone, rarely allergic reactions occur after receiving injections of paliperidone.

- Floppy iris syndrome, when the iris (the coloured part of the eye) become floppy during eye cataract surgery. This may lead to eye damage (see also '*Cataract operations*' in section 2). The frequency is not known (cannot be estimated from the available data).
- Stevens-Johnson syndrome or toxic epidermal necrolysis. 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. The frequencies are not known (cannot be estimated from the available data).

Tell your doctor straight away or go to the nearest hospital immediately if you notice any of the serious side effects above.

- Agranulocytosis, dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood. The frequency of this is not known (cannot be estimated from the available data).

Other side effects

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.
- BYANNLI 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, missed menstrual periods, or other problems with your cycle.

- high blood sugar, weight gain, weight loss, decreased appetite.
- irritability, depression, anxiety.
- 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.
- feeling restless, 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.
- white blood cell count decreased.
- 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.
- 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, abscess under the skin, flaky, itchy scalp or skin.
- an increase of CPK (creatine phosphokinase), an enzyme in your blood.
- 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.
- 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.
- not moving or responding while awake (catatonia).
- sleep walking.
- lack of emotion.
- inability to reach orgasm.
- 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.
- head shaking that you cannot control.
- atrial fibrillation (an abnormal heart rhythm), irregular heartbeat.
- flushing.
- trouble breathing during sleep (sleep apnoea).
- lung congestion, congestion of breathing passages.
- crackly lung sounds.
- wheezing.
- 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.
- breakdown of muscle tissue (“rhabdomyolysis”).
- inability to pass urine.
- breast discomfort, enlargement of the glands in your breasts, breast enlargement.
- vaginal discharge.
- 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 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).
- skin discolouration.
- abnormal posture.
- newborn babies born to mothers who have taken BYANNLI during pregnancy may experience side effects of the medicine 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 BYANNLI

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.

Ship and store in a horizontal position. See arrows on product carton for proper orientation.

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 BYANNLI contains
The active substance is paliperidone.
Each BYANNLI 700 mg pre-filled syringe contains 1 092 mg paliperidone palmitate equivalent to 700 mg paliperidone in 3.5 mL.
Each BYANNLI 1 000 mg pre-filled syringe contains 1 560 mg paliperidone palmitate equivalent to 1 000 mg paliperidone in 5 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 BYANNLI looks like and contents of the pack
BYANNLI is a white to off-white prolonged-release suspension for injection in a pre-filled syringe. pH is approximately 7.0. The doctor or nurse will shake the syringe very fast to resuspend the suspension before it is given as an injection.

Each pack contains 1 pre-filled syringe and 1 needle.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11

България
”Джонсън & Джонсън България” ЕООД
Тел.:+359 2 489 94 00

Česká republika
Janssen-Cilag s.r.o.
Tel:+420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf: +45 4594 8282

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955

Eesti
UAB “JOHNSON & JOHNSON” Eesti filiaal
Tel.: +372 617 7410

Ελλάδα
Janssen-Cilag Φαρμακευτική Α.Ε.Β.Ε
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00

Lietuva
UAB “JOHNSON & JOHNSON”
Tel: +370 5 278 68 88

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: +32 14 64 94 11

Magyarország
Janssen-Cilag Kft.
Tel.:+36 1 884 2858

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor hf
Sími: +354 535 7000

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444
medinfo@its.jnj.com

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 healthcare professionals

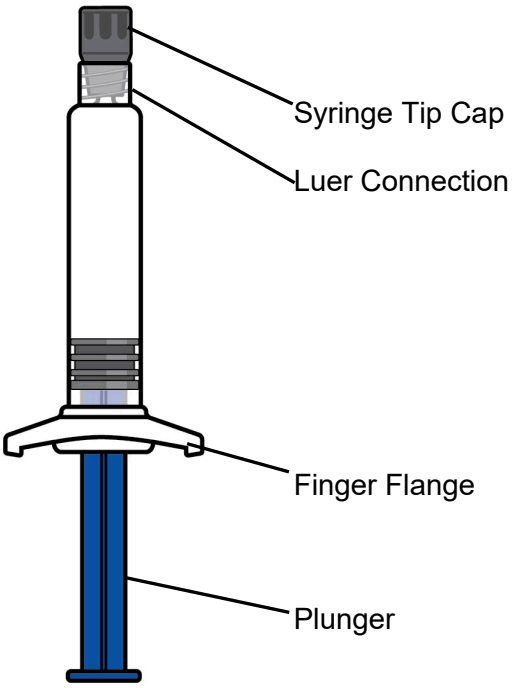
The following information is intended for healthcare professionals only and should be read by the healthcare professional in conjunction with the full prescribing information (Summary of Product Characteristics).

Important safety summary

	Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds.
Shipping and storing 	Shipping and storing the carton in a horizontal orientation improves the resuspendability of this highly concentrated product.
Preparation	BYANNLI (6-month paliperidone palmitate extended-release injectable suspension) requires longer and faster shaking than 1 month paliperidone palmitate extended-release injectable suspension. BYANNLI should be administered by a healthcare professional as a single injection. - Do not divide dose into multiple injections. BYANNLI is intended for gluteal intramuscular use only. - Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.
Dosing	Administer BYANNLI once every 6 months.
Thin wall safety needle	It is important to only use the thin wall safety needle (1½ inch, 20 gauge 0.9 mm × 38 mm) provided in the kit. It is designed to be used only with BYANNLI.

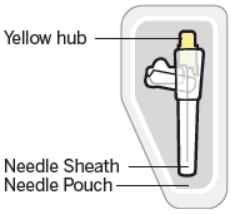
Dose pack contents

Prefilled Syringe



Thin wall safety needle

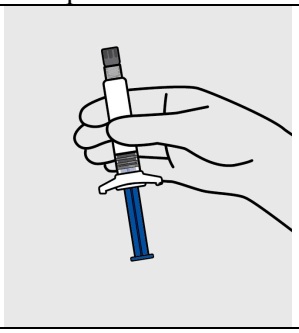
20G × 1½"
Only use the needle included in this kit



Thin Wall Safety Needle

1. Prepare for the injection.
This highly concentrated product requires specific steps to resuspend.

Always hold the syringe with the tip cap pointing up.

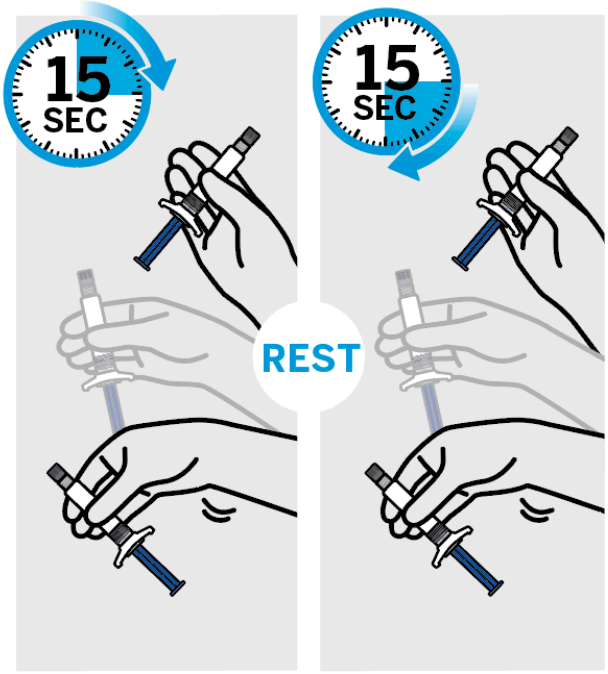


To ensure complete resuspension shake syringe with:

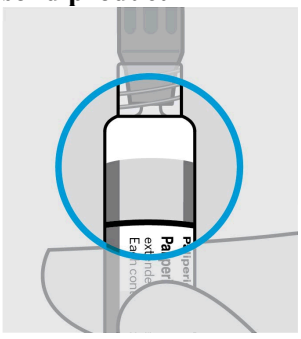
- Short VERY FAST up and down motion
- Loose wrist

Shake syringe VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds.

If more than <u>5 minutes</u> pass before injection, shake the syringe VERY FAST with the tip cap pointing up again for at least 30 seconds to resuspend the medication.



Check suspension for solid product



Mixed well

- Uniform, thick and milky white
- It is normal to see air bubbles

Not mixed well

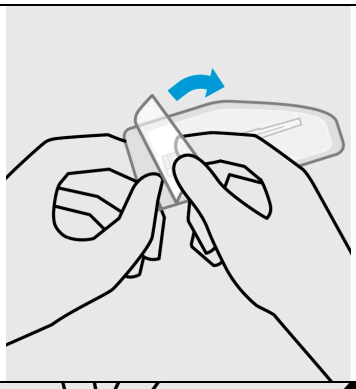
STOP

- Solid product on the sides and top of syringe
- Uneven mix
- Thin liquid

The product may clog. If this happens, shake the syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest, then shake again for 15 seconds.

Open needle pouch

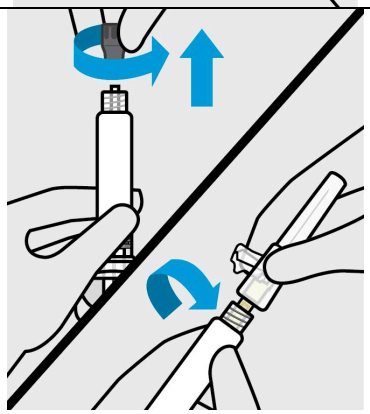
Peel off the pouch cover.
Place pouch with the needle inside on a clean surface.



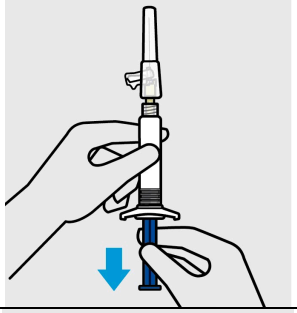
Remove syringe tip cap and attach needle

1. Hold the syringe with the tip cap pointing up.
2. Twist and pull the cap off.
3. 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.

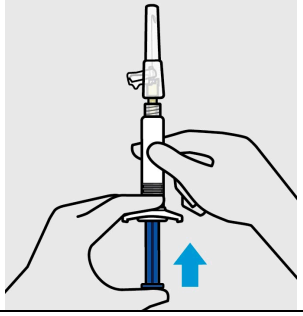
Only use the needle included in this kit.



1. Pull back plunger
2. Hold the syringe upright.
3. Gently pull back the plunger to clear the syringe tip of any solid product. This will make pressing the plunger easier during the injection.

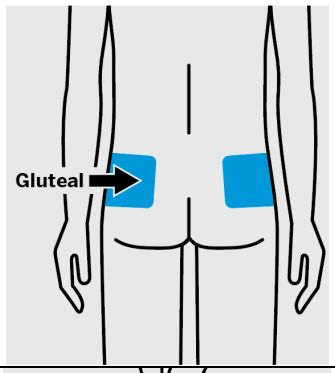


Remove air bubbles
Press the plunger carefully until a drop of liquid comes out of the needle tip.



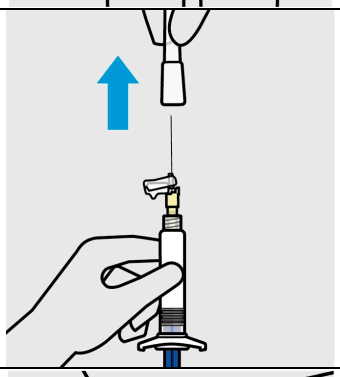
2. Slowly inject entire content and confirm

Select and clean an upper-outer quadrant gluteal injection site
Do not administer by any other route.
Wipe the injection site with an alcohol swab and allow it to dry.
Do not touch, fan or blow the injection site after you have cleaned it.



Remove needle sheath

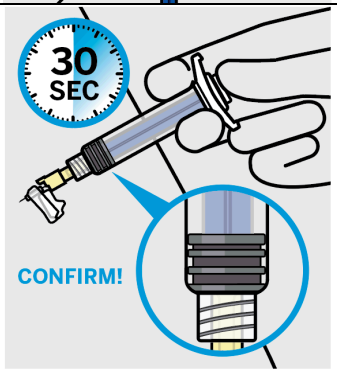
Pull the needle sheath away from the needle in a straight motion.
Do not twist the sheath, as this may loosen the needle from the syringe.



Slowly inject and confirm

Use slow, firm consistent pressure to press the plunger **completely**. This should take approximately 30-60 seconds.
Continue to press the plunger if you feel resistance. This is normal.

While the needle is in the muscle, confirm that the entire content of the syringe has been injected.

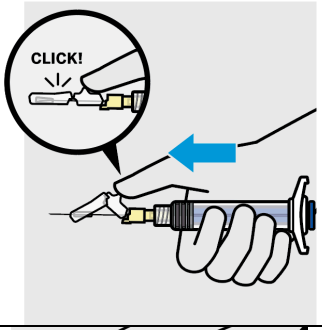


Remove needle from the muscle.

3. After the injection

Secure needle

After the injection is compete, use your thumb or a flat surface to secure the needle in the safety device.
The needle is secure when you hear a “click” sound.



Dispose of properly and check injection site

Dispose of the syringe in an approved sharps container.
There may be a small amount of blood or liquid at the injection site. Hold pressure over the skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage.