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.

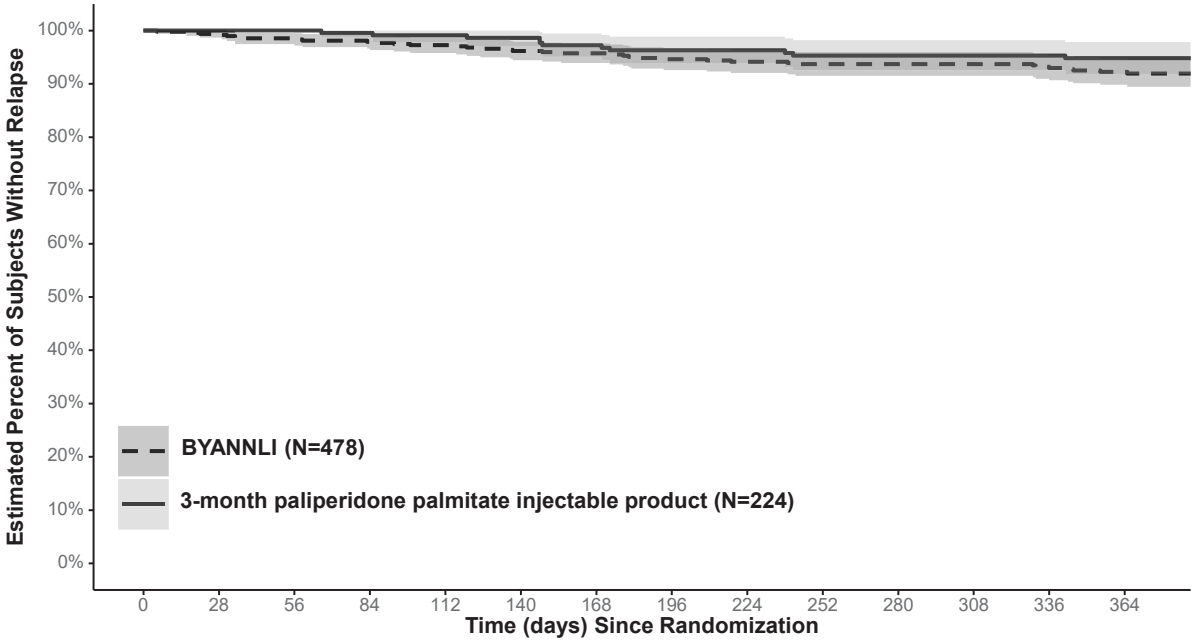

Figure 1: Kaplan-Meier Plot (with 95% pointwise confidence bands) of percentage of subjects without relapse

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.