New Medicine Assessment

PALIPERIDONE (6-MONTHLY INJECTION)

Recommendation: RED for the following indications:

Paliperidone palmitate 6-monthly injection is recommended as a treatment option for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products:

- where treatment is in line with the recommendations within NICE CG178 for the use of depot or long-acting injectable antipsychotic medication, and
- where treatment is in line with the Lancashire Care Guidance for Prescribing Second Generation Long Acting Antipsychotic Injections.

Summary of supporting evidence:

- Paliperidone palmitate prolonged release suspension for injection 1-monthly or 3-monthly has an existing LSCMMG RED RAG status for the indication of maintenance treatment of schizophrenia in adult patients.
- A Lancashire Care approval process for long-acting antipsychotic injections is in place.
- A double-blind, randomized, parallel-group study, found that 36 (7.5%) patients in the paliperidone 6 monthly (PP6M) group and 11 (4.9%) in the paliperidone 3 monthly (PP3M) group experienced a relapse event during the double-blind phase, thus PP6M was declared noninferior to PP3M for the primary efficacy endpoint.
- In the same study, 24/478 (5.0%) patients in the PP6M group and 15/224 (6.7%) in the PP3M group experienced serious adverse effects that were mostly related to worsening of psychiatric symptoms; schizophrenia was the most frequent (PP6M: 1.7%; PP3M: 0.4%). No serious side effects were reported.
- The most frequently reported side effects (which may affect more than 1 in 20 people) are headache, upper respiratory tract infection (infections of the throat and nose), reactions at the site of injection, parkinsonism (neurological symptoms including tremor and impaired muscular control) and increased weight.
- Due to the long-acting nature of Byannli the patient's response to an adjusted dose may not be apparent for several months.
- Plasma exposure to paliperidone after a single dose of Byannli is expected to remain for up to 4 years. This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding.
- 6 monthly paliperidone may provide benefits in patients with adherence issues and/or those with limited access to healthcare.
- The annual cost of paliperidone injections at the maximum doses is the same for all 3 strengths of injection; but at lower doses the 1-monthly and 3 -monthly injections are significantly less costly over the course of a year. However, this does not take into account the administration costs and frequency of appointments for the patient.

Details of Review

Name of medicine (generic & brand name)**:**

Produced: May 2022 NHS Midlands and Lancashire

Paliperidone palmitate

Strength(s) and form(s):

Byannli[a] 1000mg prolonged-release suspension for injection in pre-filled syringe
(1560 mg paliperidone palmitate equivalent to 1000 mg paliperidone)
Byannli 700mg prolonged-release suspension for injection in pre-filled syringe
(1092 mg paliperidone palmitate equivalent to 700 mg paliperidone)

Invega[b] 3 mg prolonged-release tablets
Invega 6 mg prolonged release tablets
Invega 9 mg prolonged-release tablets

Trevicta[c] 175mg prolonged release suspension for injection
(273 mg paliperidone palmitate equivalent to 175 mg paliperidone)
Trevicta 263mg prolonged release suspension for injection
(410 mg paliperidone palmitate equivalent to 263 mg paliperidone)
Trevicta 350mg prolonged release suspension for injection
(546 mg paliperidone palmitate equivalent to 350 mg paliperidone)
Trevicta 525mg prolonged release suspension for injection
(819 mg paliperidone palmitate equivalent to 525 mg paliperidone)

Xeplion[d] 100 mg prolonged-release suspension for injection
(156 mg paliperidone palmitate equivalent to 100 mg paliperidone)
Xeplion 150 mg prolonged-release suspension for injection
(234 mg paliperidone palmitate equivalent to 150 mg paliperidone)
Xeplion 50 mg prolonged-release suspension for injection
(78 mg paliperidone palmitate equivalent to 50 mg paliperidone)
Xeplion 75 mg prolonged-release suspension for injection
(117 mg paliperidone palmitate equivalent to 75 mg paliperidone)

Dose and administration:[1]

Byannli

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.

Transitioning from 1-monthly paliperidone

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

[a] Byannli is the six monthly preparation of paliperidone
[b] Invega is administered every day
[c] Trevicta is the three monthly preparation of paliperidone
[d] Xepilon is the monthly preparation of paliperidone, after initiation dosing of one dose repeated after seven days for the first two doses

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.

- If the last dose of 1-monthly paliperidone injection is 100mg, initiate Byannli at 700mg.
- If the last dose of 1-monthly paliperidone injection is 150mg, Initiate Byannli at 1000mg.

Transitioning from 3-monthly paliperidone

Byannli should be initiated in place of the next scheduled dose of 3-monthly paliperidone palmitate injection (± 14 days).

- If the last dose of 3-monthly paliperidone injection is 350mg, Initiate Byannli at 700mg.
- If the last dose of 3-monthly paliperidone injection is 525mg, initiate Byannli at 1000mg.

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.

If needed, dose adjustment of Byannli can be made every 6 months between the dose levels of 700 mg and 1000 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. If the patient remains symptomatic, they should be managed according to clinical practice.

Byannli is for gluteal intramuscular use only.

Each injection must be administered only by a healthcare professional giving the full dose in a single injection.

Byannli must be administered using only the thin wall needle that is provided in the Byannli pack.

BNF therapeutic class / mode of action:

Antipsychotics > second-generation > depot injections[2]

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.1

Paliperidone is the primary active metabolite of risperidone.[3]

Licensed indication(s):

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.

Invega is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older. Invega is indicated for the treatment of schizoaffective disorder in adults.

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

Xeplion is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous

responsiveness to oral paliperidone or risperidone, Xeplion may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

Proposed use (if different from, or in addition to, licensed indication above):

6-monthly injection, for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products.

Course and cost:

Prices not currently listed in drug tariff or BNF.

Price listed on SPS website (Feb 2022):

1 x 700mg PFS=£1884.42

1 x 1,000mg PFS = £2355.54

Annual cost of maintenance on is: £3768.84 - £4711.08

Current standard of care/comparator therapies:

Adults with a first episode of psychosis start treatment in early intervention in psychosis services within 2 weeks of referral.[4]

Drug therapy for schizophrenia should be accompanied by appropriate psychological therapy, including CBT.

The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees.[5]

At the start of antipsychotic treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British national formulary (BNF) or SPC.

Clozapine should be offered if schizophrenia is not controlled despite the sequential use of at least 2 different antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for an adequate duration.2

Long-acting depot injectable antipsychotic drugs can be considered for patients with psychosis and schizophrenia where it is a clinical priority to avoid non-adherence.

First-generation antipsychotic depot injections may give rise to a higher incidence of adverse effects such as extrapyramidal reactions. Extrapyramidal reactions occur less frequently with second-generation antipsychotic depot preparations, such as aripiprazole, paliperidone, risperidone and olanzapine embonate.

There are very few differences in efficacy between individual first-generation antipsychotic depot injections; zuclopenthixol decanoate may be more effective in preventing relapses than other first-generation antipsychotic depot preparations.

All of the second generation are currently RAG rated as RED which means that they cannot be passed back to the GP for prescribing and are not covered by the Shared Care Prescribing arrangements for Antipsychotics.[6]

For further details on the Lancashire Care approval process for long acting injections use the following link. Approval criteria includes:

- The patient has previously been prescribed a first generation antipsychotic (FGA) long acting injection (LAI) or a FGA LAI has been discussed as an option with the patient and the patient will not accept a FGA LAI
- The patient has experienced intolerable side effects to a FGA LAI or oral FGA, is expressing a clear preference for a second generation antipsychotic (SGA) LAI, or has a

history of positive response to oral aripiprazole or risperidone and the consultant psychiatrist therefore deems a SGA LAI the most appropriate pharmacological option for the patient

- The patient does not fulfil the criteria for prescribing clozapine or clozapine has been discussed with the patient and they are adamantly refusing to accept treatment or clozapine is contraindicated

Table 1. Table listing the available antipsychotics[7]

Oral first-generation (typical)	Oral second-generation (atypical)	Antipsychotic depot injections*
Benperidol	Amisulpride	Aripiprazole
Chlorpromazine	Aripiprazole	Flupentixol decanoate
Flupentixol	Clozapine	Fluphenazine decanoate
Haloperidol	Olanzapine	Haloperidol
Levomepromazine	Paliperidone	Olanzapine embonate
Pericyazine	Quetiapine	Paliperidone
Perphenazine	Risperidone	Pipotiazine palmitate
Pimozide		Risperidone
Prochlorperazine		Zuclopenthixol decanoate
Promazine		
Sulpiride		
Trifluoperazine		
Zuclopenthixol		

* Antipsychotic depot injections are used for maintenance therapy when adherence to oral treatment is unreliable. They are administered every 1–4 weeks.

Table 2. Atypical LAI antipsychotics containing paliperidone or risperidone licenced in the UK for the maintenance treatment of schizophrenia3

Agent	Product	Summary of indication	Frequency of administration
Paliperidone	BYANNLI	Maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products.	Once every 6 months
	TREVICTA	Maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable products.	Once every 3 months
	XEPLION	Maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.	Once a month

Risperidone	RISPERDAL CONSTA	Maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.	Once every 2 weeks

Relevant NICE guidance:

Psychosis and schizophrenia in adults: prevention and management CG178 (Feb 2014)

Psychosis and schizophrenia in adults QS80 (Feb 2015)

Background and context

Psychosis and the specific diagnosis of schizophrenia represent a major psychiatric disorder (or cluster of disorders) in which a person's perception, thoughts, mood and behaviour are significantly altered. The symptoms of psychosis and schizophrenia are usually divided into 'positive symptoms', including hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Each person will have a unique combination of symptoms and experiences.

Typically, there is a prodromal period, which precedes a first episode of psychosis and can last from a few days to around 18 months. The prodromal period is often characterised by some deterioration in personal functioning. The prodromal period is usually followed by an acute episode marked by hallucinations, delusions and behavioural disturbances, usually accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological, psychological and other interventions, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes that may need additional pharmacological, psychological and other interventions, as in previous episodes.[5]

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 1000 mg dose of BYANNLI.[1]

Summary of evidence

Summary of efficacy data in proposed use:

European Medicines Agency[8]

This medicine is similar to Xeplion and Trevicta, which are already authorised in the EU, but are available in different strengths. Scientific data from Xeplion was used during the initial authorisation of Byannli.

In a main study involving 702 patients with schizophrenia stabilised on monthly or three-monthly paliperidone injections, Byannli (given six-monthly) was as effective in preventing relapses as another paliperidone injections every 3 months (*see* Najarian et al, below for further details of study) . In this study, 92.5% of the patients receiving six-monthly Byannli treatment were relapse-free during a 12-month period. By comparison, 95.1% of the patients receiving three-monthly paliperidone palmitate injectable treatment were relapse-free during the same 12-month period.10

No serious side effects were reported. The longer dosing interval might also offer benefits to individuals with limited access to healthcare.

MHRA PAR[9]

When authorising Byannli, the MHRA relied on a European Commission (EC) decision on 22 November 2021, in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

Najarian et al[10]

This double-blind (DB), randomized, parallel-group study was designed to evaluate efficacy and safety of paliperidone palmitate 6-month (PP6M) formulation relative to paliperidone palmitate 3-month (PP3M) formulation in patients with schizophrenia. The study had 3 phases: (1) a screening phase (up to 28 days), (2) an open-label (OL) maintenance phase (duration of 1 or 3 months depending on treatment received [1 injection cycle of PP1M/ PP3M]), and (3) DB phase (12 months).

To maintain the blinding, patients treated with PP6M received injections of placebo at the 3-month time points between their 6-month doses.

The primary endpoint was time to relapse during the DB phase. This noninferiority primary endpoint was based on the difference in the Kaplan-Meier 12-month estimate of survival (i.e., percentage of patients remaining relapse free) between PP6M and PP3M. The relapse criteria were identical to those used in previous clinical studies of PP3M and PP1M.

Of the 838 patients enrolled and dosed in the OL phases, 702 (83.8%) completed the OL phases and were randomized (PP6M, n=478; PP3M, n=224) in the DB phase. All 702 patients were included in the ITT-DB set. Withdrawal by patient (57/838 [6.8%]) or adverse events (30/838 [3.6%]) were the common reasons for discontinuations in the OL phases. A total of 618 (88.0%) patients completed the DB phase, with similar percentages in both treatment groups (PP3M, n=202 [90.2%]; PP6M n=416 [87.0%]). Withdrawal by patient (54/702 [7.7%]) was the most common reason for discontinuation during the DB phase.

Patients (n=702) were a mean age of 40.8 (range, 18–69) years and were mostly men (68.4%), White (74.2%), non-Hispanic (84.6%), and ≤50 years of age (79.6%).

Thirty-six (7.5%) patients in the PP6M group and 11 (4.9%) in the PP3M group experienced a relapse event during the DB phase (ITT-DB). The Kaplan-Meier estimate of the difference (95% CI) between the treatment groups (PP6M − PP3M) in the percentages of patients who remained relapse free was −2.9% (−6.8%, 1.1%). Thus, PP6M was noninferior to PP3M based on the lower bound of the 95% CI being larger than the pre-specified noninferiority margin of −10%. Thus, PP6M was declared noninferior to PP3M for the primary efficacy endpoint. The median time to relapse (the time at which the cumulative survival function equals 0.5 [or 50%]) was not estimable for either the PP6M or PP3M groups due to the low number of relapses during the DB phase.

The most common reasons for relapses were an increase of ≥25% in PANSS total score (PP6M: 16 [3.3%]; PP3M: 5 [2.2%]), PANSS item (P1, P2, P3, P6, P7, G8) score of ≥5 after randomization (PP6M: 13 [2.7%]; PP3M: 5 [2.2%]), and psychiatric hospitalizations (PP6M: 11 [2.3%]; PP3M: 6 [2.7%]). The ratio (95% CI) of the instantaneous risk of relapse for a patient who received PP6M treatment vs the risk for a patient who received PP3M in the DB phase was 1.57 (0.80, 3.08).

The percentage of patients with ≥20% improvement from DB baseline to DB endpoint in PANSS total scores was numerically higher in the PP6M (38.9%) compared with PP3M (32.1%); similar percentage of patients in the PP6M and PP3M treatment groups showed an improvement of ≥30% and ≥40% in PANSS total score. More than 60% of patients in both treatment groups (PP6M: 66.3%; PP3M: 70.1%) achieved symptomatic remission during the DB phase.

Ostuzzi et al[11]

A meta-analysis of 92 studies, including 22,645 participants.

Two co-primary outcomes were analysed: relapse (i.e., the number of participants experiencing at least one relapse by the end of the trial, as a proportion of the total of randomized participants) and tolerability (i.e., the number of participants who dropped out by the end of the trial because of an adverse event, as a proportion of the total of randomized participants).

In terms of relapse prevention, all antipsychotics – with the exception of clopenthixol-oral (OS),

haloperidol-LAI and zuclopenthixol-LAI – were significantly more effective than placebo. “High” confidence was found for the following antipsychotics (ordered from the largest to the smallest point estimate): amisulpride-OS, olanzapine-OS, aripiprazole-LAI, olanzapine-LAI, aripiprazole-OS, paliperidone-OS, and ziprasidone-OS. “Moderate” confidence was found for the following antipsychotics (ordered from the largest to the smallest point estimate): paliperidone-LAI 1-monthly, iloperidone-OS, fluphenazine-OS, brexpiprazole-OS, paliperidone-LAI 1-monthly, asenapine-OS, haloperidol-OS, quetiapine-OS, cariprazine-OS, and lurasidone-OS.

Head-to-head comparisons showed relatively few statistically significant differences between antipsychotics.

This NMA did not detect clear advantages of LAIs over oral antipsychotic formulations in terms of relapse and re-hospitalisation.

Both oral and LAI formulations of olanzapine, aripiprazole and paliperidone proved to be effective and are supported by moderate-to-high confidence of evidence and should therefore be given priority when initiating a pharmacological maintenance treatment in people with schizophrenia-spectrum disorders, although differences in adverse effect profiles should also be considered in the decision-making process.

Summary of safety data:

Medicines and Healthcare Products Regulatory Agency[12]

Risperidone and paliperidone: risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery

Cases of intraoperative floppy iris syndrome (IFIS) during cataract surgery have been reported in patients taking the atypical antipsychotics risperidone or paliperidone.

European Medicines Agency8

The most frequently reported side effects (which may affect more than 1 in 20 people) are headache, upper respiratory tract infection (infections of the throat and nose), reactions at the site of injection, parkinsonism (neurological symptoms including tremor and impaired muscular control) and increased weight.

On 16 September 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Paliperidone Janssen-Cilag International, which will now be known as Byannli.

Food and Drug Administration[13]

The most common adverse reactions were upper respiratory tract infection, injection site reaction, weight increased, headache, and parkinsonism.

Najarian et al10

A total of 341 of 838 patients (40.7%) had ≥1 treatment-emergent adverse event (TEAE) in the OL phase; 23 (2.7%) patients had ≥1 serious TEAE, 31 (3.7%) had TEAEs leading to withdrawal of the study drug, and 1 (0.1%) death (due to completed suicide) was reported in the OL phase.

In the DB phase, TEAEs were reported in a comparable percentage of patients in the PP6M (297/478 [62.1%]) and PP3M (131/224 [58.5%]) groups. The most common TEAEs (≥5% in either group) were increased weight, injection-site pain, headache, upper respiratory tract infections, and nasopharyngitis. Most TEAEs were mild or moderate in severity. In total, 24/478 (5.0%) patients in the PP6M group and 15/224 (6.7%) in the PP3M group experienced serious TEAEs that were mostly related to worsening of psychiatric symptoms; schizophrenia was the most frequent (PP6M: 1.7%; PP3M: 0.4%).

Overall, 16/478 (3.3%) patients in the PP6M group and 6/224 (2.7%) in the PP3M group

discontinued the DB phase due to TEAEs that were mostly psychiatric in nature, with schizophrenia (PP6M: 8 [1.7%]; PP3M: 1 [0.4%]) being the most common.

Three deaths (PP6M: n=1 [cause not specified]; PP3M: n=2 [pulmonary embolism and sudden death, unknown cause, n=1 each]) were reported in the DB phase; investigators considered these deaths as not related to study medication.

The occurrences of TEAEs of special interest related to EPS (46 [9.6%] vs 19 [8.5%]), suicidality (5 [1.0%] vs 6 [2.7%]), agitation and aggression (3 [0.6%] vs none), somnolence (9 [1.9%] vs 3 [1.3%]), tachycardia (7 [1.5%] vs 1 [0.4%]), orthostatic hypotension (2 [0.4%] vs 2 [0.9%]) and QT prolongation (2 [0.4%] vs 2 [0.9%]), and diabetes mellitus and hyperglycemia (15 [3.1%] vs 6 [2.7%]) were generally similar between the treatment groups (PP6M vs PP3M). There were no reported TEAEs for neuroleptic malignant syndrome or post-injection delirium/sedation syndrome during the study.

Summary of product characteristics1

Special populations

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

The 1000 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).

Plasma exposure to paliperidone after a single dose of BYANNLI is expected to remain for up to 4 years. This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding.

Contraindications

Hypersensitivity to the active substance, to risperidone or to any of the excipients.

Warnings and precautions for use

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 has been reported to occur with paliperidone

Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia.

Events of leucopenia, neutropenia, and agranulocytosis have been reported with paliperidone.

Hypersensitivity reactions can occur even in patients who have previously tolerated oral risperidone or oral paliperidone.

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes, including diabetic coma and ketoacidosis, have been reported with paliperidone.

Significant weight change has been reported with BYANNLI use.

Paliperidone should be used with caution in patients with a pre-existing tumour that may be prolactin-dependent.

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).

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

BYANNLI is not recommended to treat elderly patients with dementia due to increased risk of overall mortality and cerebrovascular adverse reactions.

Antipsychotic medicinal products (including paliperidone) with alpha-adrenergic blocking effects have been reported to induce priapism.

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products.

Cases of VTE have been reported with antipsychotic medicinal products.

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicinal products with alpha 1a-adrenergic antagonist effect, such as BYANNLI.

Adverse reactions

System Organ Class	**Adverse reactions**				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
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		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		hyperglycaemia, weight increased, weight decreased, decreased appetite	diabetes mellitus, hyperinsulinaemia, increased appetite, anorexia, blood triglycerides increased, blood cholesterol increased	diabetic ketoacidosis, hypoglycaemia, polydipsia	water intoxication
Psychiatric disorders	insomnia	agitation, depression, anxiety	sleep disorder, mania, libido decreased, nervousness.	catatonia, confusional state, somnambulism, blunted affect.	sleep-related eating disorder

			nightmare	anorgasmia	
Nervous system disorders		parkinsonism, akathisia, sedation/somnolence, dystonia, dizziness, dyskinesia, 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, 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	ileus

				incontinence, faecaloma, cheilitis	
Hepatobiliary disorders		transaminases increased	gamma- glutamyl transferase 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
Reproductive system and breast disorders		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder, 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, 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		

Strengths and limitations of the evidence:

- Byannli (six monthly paliperidone) has been approved by the EMA, MHRA and FDA.
- LSCMMG has an exiting RED RAG status for other paliperidone long-acting injections.
- A double-blind, randomized, parallel-group study, found that 36 (7.5%) patients in the PP6M group and 11 (4.9%) in the PP3M group experienced a relapse event during the double-blind phase, thus PP6M was declared noninferior to PP3M for the primary efficacy endpoint.
- In the same study, 24/478 (5.0%) patients in the PP6M group and 15/224 (6.7%) in the PP3M group experienced serious adverse effects that were mostly related to worsening of psychiatric symptoms; schizophrenia was the most frequent (PP6M: 1.7%; PP3M: 0.4%).
- Data for the 6-monthly preparation is limited currently to one main study.
- The most frequently reported side effects (which may affect more than 1 in 20 people) are headache, upper respiratory tract infection (infections of the throat and nose), reactions at the site of injection, parkinsonism (neurological symptoms including tremor and impaired muscular control) and increased weight.
- Due to the long-acting nature of Byannli, the patient's response to an adjusted dose may not be apparent for several months.
- Theoretical risk of intraoperative floppy iris syndrome (IFIS) during cataract surgery.
- Safety is not established in patients >65 years of age.
- Not recommended in mild renal impairment.
- Head-to-head comparisons showed relatively few statistically significant differences between antipsychotics.

Summary of evidence on cost effectiveness:

Prices for 6-monthly product not currently listed in drug tariff or BNF.

Price listed on SPS website (Feb 2022):

1 x 700mg PFS=£1884.42

1 x 1,000mg PFS = £2355.54

Annual cost of maintenance on 6-monthly paliperidone injections: **£3768.84** - **£4711.08**

Annual cost of maintenance on 1-monthly paliperidone injections (drug tariff May 2022): **£2207.04** - **£4711.08**

Annual cost of maintenance on 3-monthly paliperidone injections (drug tariff May 2022): **£2207.04** - **£4711.08**

NB. These are drug cost prices only. Consideration should also be given to the cost of administration and appointment frequency.

Prescribing and risk management issues:

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.

Due to the large volume to be injected, Byannli should be administered into the gluteal muscle only, by a healthcare professional using the needle provided with the product.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
None identified.
Financial implications of the intervention:
The annual cost of paliperidone injections at the maximum doses is the same for all 3 strengths of injection; but at lower doses the 1-monthly and 3 -monthly injections are significantly less costly over the course of a year. However, this does not take into account the administration costs and frequency of appointments for the patient. Also, for some patients with adherence issues, there may be indirect savings due to fewer relapses.
Service Impact Issues Identified:
Potential reduction in frequency of administration could have a positive service impact by reducing appointment frequency.
Equality and Inclusion Issues Identified:
None identified.
Cross Border Issues Identified:
The **Pan Mersey APC** do not currently have the 6-monthly paliperidone injection listed in their formulary. The 1- and 3-monthly injections have RED RAG status. The **Greater Manchester Medicines Management Group** (GMMMG) have a shared care protocol for the 1-monthly preparation, which has AMBER RAG status. It is available only for those patients who are stable and if SCP available, or if under the care of a community psychiatric nurse. In some localities there may be commissioning arrangements in place to permit step down.
Legal Issues Identified:
None identified.
Media/ Public Interest:
None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Byannli 1000mg prolonged-release suspension for injection in pre-filled syringe", Janssen-Cilag Ltd, Feb 2022 [Online]. Available: https://www.medicines.org.uk/emc/product/13308/smpc#PHARMACOLOGICAL_PROPS

[2] British National Formulary, “Psychoses and related disorders” [Online]. Available: https://bnf.nice.org.uk/treatment-summary/psychoses-and-related-disorders.html [Accessed 16 May 2022]

[3] Janssen Neuroscience, “BYANNLI (paliperidone palmitate 6-monthly) Schizophrenia Formulary pack”, March 2022

[4] National Institute for Health and Care Excellence, "Quality Standard 80: Psychosis and schizophrenia in adults" Feb 2015. [Online]. Available: https://www.nice.org.uk/guidance/qs80/resources/psychosis-and-schizophrenia-in-adults-pdf-2098901855941

[5] National Institute for Health and Care Excellence, "Clinical Guideline 178: Psychosis and schizophrenia in adults: prevention and management" March 2014. [Online]. Available: https://www.nice.org.uk/guidance/cg178/resources/psychosis-and-schizophrenia-in-adults-prevention-and-management-pdf-35109758952133

[6] Lancashire Care NHS Foundation Trust, “Guidance for Prescribing Second Generation Long Acting Antipsychotic Injections” Oct 2021. [Online]. Available: https://www.lancsmmg.nhs.uk/media/1059/second-generation-long-acting-antipsychotic-injections-prescribing-guidance.pdf

[7] National Institute for Health and Care Excellence, "Clinical Knowledge Summaries: Psychosis and schizophrenia" September 2021. [Online]. Available: https://cks.nice.org.uk/topics/psychosis-schizophrenia/prescribing-information/available-antipsychotics/

[8] European Medicines Agency, “Byannli (paliperidone)” Nov 2021. [Online]. Available: https://www.ema.europa.eu/en/documents/overview/byannli-previously-paliperidone-janssen-cilag-international-epar-medicine-overview_en.pdf

[9] Medicines and Healthcare Products Regulatory Agency, “BYANNLI 700 mg prolonged release suspension for injection in pre-filled syringe BYANNLI 1000 mg prolonged release suspension for injection in pre-filled syringe (paliperidone palmitate)” March 2022

[10] Najarian D et al, “A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia”, *International Journal of Neuropsychopharmacology,* Vol. 25(3), pp 238–251, 2022

[11] Ostuzzi G et al, “Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: a network meta-analysis of 92 randomized trials including 22,645 participants”, *World Psychiatry,* Vol.21, pp 295–307, 2022

[12] Medicines and Healthcare Products Regulatory Agency, “Risperidone and paliperidone: risk of intraoperative floppy iris syndrome in patients undergoing cataract surgery”, Dec 2014

[13] US Food and Drug Admisitration, “Full prescribing information: INVEGA HAFYERA™ (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use” Aug 2021. [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207946s010lbl.pdf