Paliperidone

Essential medicine status

Section: 24. Medicines for mental and behavioural disorders > 24.1. Medicines for psychotic disorders

ATC codes: N05AX13

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A4Z
INN	Paliperidone
Medicine type	Chemical agent
List type	Core
Formulations	Parenteral > General injections > IM: 25 mg in pre-filled syringe (as palmitate) ; 50 mg in pre-filled syringe (as palmitate) ; 75 mg in pre-filled syringe (as palmitate) ; 100 mg in pre-filled syringe (as palmitate) ; 150 mg in pre-filled syringe (as palmitate)
EML status history	First added in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	risperidone (ATC codes: N05AX08) Parenteral > General injections > IM:
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Paliperidone
DrugBank	Paliperidone

Expert Committee recommendation

The Expert Committee recognized that long-acting injectable antipsychotic medicines were an important treatment option for some patients with schizophrenia, and recalled the recommendation made by the 2021 Expert Committee to include PP1M long-acting injection on the EML for this indication, with risperidone long-acting injection as a therapeutic alternative among second-generation antipsychotics. The Committee also noted the separate application to the 2023 meeting proposing therapeutic alternatives to long-acting injections of first-generation antipsychotics. The Committee noted that compared with the 1-month formulation (PP1M), the 3-month formulation (PP3M) had evidence of similar clinical efficacy and safety and may offer advantages to patients in terms of fewer injections. However, the Committee noted that PP3M was recommended for use only in patients who have been adequately treated with PP1M and demonstrate benefit from and tolerance to it for at least 4 months. The Committee was therefore concerned that both strength formulations would need to be available for appropriate treatment and considered that the more limited availability of PP3M in low- and middle-income countries would be problematic. In addition, the Committee noted that PP3M was more highly priced and was not yet available in generic forms. The Committee also noted that PP3M long-acting injection was not currently included in WHO mhGAP guidelines. Based on these considerations, the Expert Committee did not recommend inclusion of PP3M long-acting injection on the EML for maintenance treatment of schizophrenia.

Background

In 2021, the Expert Committee recommended the addition of PP1M long-acting injection to the core list of the EML for maintenance treatment of schizophrenia in adults stabilized on oral therapy. A square box listing was recommended specifying risperidone long-acting injection as a therapeutic alternative (1). The 2021 Committee considered that long-acting injectable antipsychotic medicines are a valuable treatment option to increase adherence to treatment and reduce relapse in adults with schizophrenia and related psychotic disorders. The Committee also noted with concern the uncertainty of current and future

availability of fluphenazine injection, which was the only long-acting injectable antipsychotic medicine included on the EML at that time and considered that the availability of alternative medicines would be important to meet the public health need for such treatments. The Committee noted that long-acting injectable antipsychotic medicines are an established treatment option for schizophrenia and are recommended in existing WHO Mental Health Gap Action Programme (mhGAP) guidelines. In particular, the Committee acknowledged that long-acting injectable antipsychotic medicines are useful in low-resource settings, where many factors might impede regular monitoring and follow-up of patients. The 2021 Committee noted that the available data suggested benefits of long-acting injectable antipsychotic medicines versus oral antipsychotic medicines in preventing hospitalization or relapse, especially in populations with low treatment adherence. The effectiveness and overall safety of first-generation and second-generation antipsychotic medicines were similar. The availability of agents with different side-effect profiles may support the selection of one treatment over another given a patient's clinical status and vulnerabilities. In consideration of the application for inclusion of PP1M, the 2021 Committee noted that although PP3M was shown to be effective and acceptable, the applicants decided not to include this formulation in the proposal for the following reasons. • PP3M had become available only relatively recently, was not yet commonly used in clinical practice and its worldwide availability might be limited. • Some concerns had been raised about a randomized study comparing PP3M and placebo (2) in which study participants underwent a stabilization phase with PP1M before randomization which might have inflated the effect size in favour of paliperidone. • More research was needed to rule out possible unintended consequences of PP3M, including the effects of reduced doctors' visits due to the longer dosing interval. • The cumulative monthly dosing of PP3M was slighter higher than that of PP1M and this may affect toxicity and tolerability (3).

Public health relevance

Schizophrenia is a debilitating mental disorder that typically starts in late adolescence or early adulthood (4–6). In 2019, nearly 24 million people worldwide were estimated to have schizophrenia (7). The global burden of mental disorders, including schizophrenia, has been increasing over time (4,7). Between 1990 and 2019, the number of disability-adjusted life years (DALYs) due to mental disorders rose from 80.8 million to 125.3 million, accounting for almost 5% of all DALYs (7). The incident cases and DALYs of schizophrenia also increased during this period, reaching 1.13 million persons and 12.66 million DALYs, a 37% increase in incident cases and a 62% increase in DALYs compared with 1990 (4). In low- and middle-income countries, a significant treatment gap exists, with about two thirds of individuals with schizophrenia not receiving adequate treatment (8). People with schizophrenia also have a reduced life expectancy of about 15 years compared with the general population, which is partly due to physical diseases such as cardiovascular disease (9,10). Schizophrenia is a significant economic burden and is projected to cost the global economy trillions of dollars by 2030 (11–13). The costs include direct expenses of treatment, rehabilitation and social welfare, as well as indirect costs such as reduced productivity, unemployment and the financial impact on families. The burden is exacerbated by the limited global coverage of mental health care (14–17). Long-term treatment is crucial in managing schizophrenia, and long-acting injectable medicines are commonly prescribed for patients who are non-compliant or experience persistent symptoms (18–21).

Benefits

The R092670-PSY-3011 study was a company-sponsored non-inferiority phase III study that compared PP3M with PP1M in adults with schizophrenia (22). Participants received PP1M during a 17-week open-label phase before being randomized to receive the same dose of PP1M or the corresponding equivalent dose of PP3M for 48 weeks. The primary efficacy endpoint was the percentage of participants who had not relapsed at the end of the double blind phase based on the Kaplan–Meier 48-week cumulative estimate of survival. The per-protocol analysis showed similar rates of relapse in both treatment groups after 48 weeks (37/458 (8.1%) for PP3M versus 45/490 (9.2%) for PP1M; estimated difference (PP3M – PP1M) 1.2%, 95% confidence interval (CI) –2.7% to 5.1%). It was concluded that PP3M was non-inferior to PP1M as the lower bound of the CI was larger than the prespecified non-inferiority margin of –15%. The hazard ratio (HR) for risk of relapse when switching from PP1M to PP3M versus remaining on PP1M was 0.87 (95% CI 0.56 to 1.34). Subgroup analyses also supported the non-inferiority of PP3M in different age groups, sexes, races, baseline body mass index groups and geographic regions (23–25). The R092670-PSY-3012 study was a company-sponsored long-term, placebo-controlled phase III randomized withdrawal study with PP3M in adults with schizophrenia (2). The study consisted of four phases and evaluated the efficacy of PP3M in delaying relapse of symptoms in adult participants with schizophrenia who had achieved symptom control with PP1M. The study used a randomized withdrawal design to assess whether the discontinuation of PP3M treatment after stabilization with PP1M would affect the course of the disease. The fixed-dose regimen of PP3M was based on the conversion from the effective dose of PP1M. The primary endpoint was the time to relapse during the double-blind phase. At the preplanned interim analysis, conducted after 42 relapse events, 23.0% (31/135) of participants who switched from open-label

PP3M to double-blind placebo experienced a relapse event, compared with 7.4% (11/148) of participants who remained on PP3M. Participants who continued treatment with PP3M in the double-blind phase experienced a significantly longer time to relapse compared with those who switched to placebo (P < 0.001 based on a log-rank test). The median time to the first relapse was 274 days in the placebo group, while it was not estimable in the PP3M group. At the final analysis, after 56 relapse events, 29.0% (42/145) of participants in the double-blind placebo group experienced a relapse event versus 8.8% (14/160) of participants in the double-blind PP3M group. A significant difference was seen in the time to relapse which favoured PP3M (P < 0.001 based on a log-rank test). The median time to the first relapse event was 395 days for the placebo group, while it was not estimable for the PP3M group. A 2021 systematic review and network meta-analysis of 78 randomized controlled trials (11 505 participants) compared relapse prevention and acceptability of long-acting injectable antipsychotics in the maintenance treatment of non-affective psychoses in adults (26). PP1M and PP3M were among the long-acting antipsychotics included in the analysis. The primary outcomes were the proportion of patients who experienced at least one relapse, and the proportion of patients who dropped out of the trial for any reason (acceptability). The ranking probability was assessed by surface under the cumulative ranking curve (SUCRA) and the certainty of evidence was assessed by Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). The primary analysis found that most long-acting injectable antipsychotics evaluated were significantly more effective than placebo in preventing relapse, including PP3M (relative risk (RR) 0.27, 95% CI 0.17 to 0.42; SUCRA 80.2%, high-certainty evidence) and PP1M (RR 0.39, 95% CI 0.30 to 0.50; SUCRA 46.8%, high-certainty evidence). There was also moderate-certainty evidence of no significant difference for the comparison between PP3M and PP1M (RR 1.44, 95% CI 0.95 to 2.19). Additionally, most long-acting injectable antipsychotics evaluated were significantly more acceptable than placebo, including PP3M (0.60, 95% CI 0.43 to 0.84; SUCRA 62.5%, high-certainty evidence) and PP1M (0.70, 95% CI 0.85 to 0.85; SUCRA 39.5%, moderate-certainty evidence). Exploratory secondary analyses showed significantly lower hospitalization rates for several long-acting injectable antipsychotics including PP3M (RR 0.26, 95% CI 0.10 to 0.65) and PP1M (RR 0.37, 95% CI 0.16 to 0.87). The authors concluded that long-acting injectable formulations of paliperidone (PP3M and PP1M) were among those that demonstrated the highest effectiveness and acceptability in preventing relapse in non-affective psychoses. A 2022 systematic review and network meta-analysis of 92 randomized controlled trials (22 645 participants) evaluated the differences in the effectiveness and tolerability of oral antipsychotics and long-acting injectable antipsychotics for maintenance treatment of schizophrenia-spectrum disorders (27). The two coprimary outcomes were the proportion of participants who experienced at least one relapse, and the proportion of participants who dropped out of the trial due to an adverse event. There was moderate-certainty evidence that PP3M was superior to placebo for the prevention of relapse (RR 0.24, 95% CI 0.13 to 0.42; SUCRA 80.3%). A more recent 2022 systematic review and network meta-analysis of 100 randomized controlled trials (16 812 participants) compared the efficacy and tolerability of 32 antipsychotics as maintenance treatment for non-treatment-resistant patients with schizophrenia. No clear evidence for the superiority of specific antipsychotics for relapse prevention was observed and the authors concluded that the choice of medicine should be guided mainly by tolerability (28). A retrospective observational study used claims data from the Hungarian National Health Insurance Fund database to compare the effectiveness of long-acting injectable antipsychotics versus oral antipsychotics (29). The study included 5400 patients who started treatment with a second-generation antipsychotic as monotherapy (1423 given injectable medicines, and 3977 given oral medicines) including PP1M and PP3M. The primary outcome was the all-cause discontinuation of the antipsychotic medication over a 1-year and 1.5-year period. The results showed that long-acting injectable antipsychotics had higher continuation rates compared with oral antipsychotics. Patients given PP3M (n = 627) had the highest continuation rates of all antipsychotics, with 79% and 76% of patients continuing treatment for 1 year and 1.5 years, respectively. Adjusted analyses showed that the risk of discontinuation was significantly higher for oral antipsychotics compared with PP3M and aripiprazole long-acting injection (P < 0.01 for all). Compared with PP1M, the risk of discontinuation was significantly higher for all oral antipsychotics except olanzapine and paliperidone. Risperidone long-acting injection had a lower risk of discontinuation compared with oral risperidone (P < 0.001). All other long-acting injectable antipsychotics had a significantly higher risk of discontinuation than PP3M (P < 0.05). The study limitations included the lack of randomization and control group, potential misclassification of diagnoses, and selection bias of different treatments (29). A company-sponsored prospective, multinational, single-arm, open-label phase IIIb study (305 participants) evaluated the efficacy and safety of converting patients with schizophrenia stabilized with PP1M to PP3M in a naturalistic clinical setting over 52 weeks (30). The primary efficacy endpoint was symptomatic remission at last observation carried forward. Symptomatic remission was achieved by 56.8% (172/303) of patients at the last observation carried forward endpoint, while symptomatic remission was achieved by 60.7% (184/303) of patients during the 12-month treatment period. Among these, 4.0% (12/303) patients had met the criteria for symptomatic remission during the treatment period, then subsequently did not. Over the PP3M treatment period, the proportion of patients

hospitalized for psychiatric reasons fell from 13.5% at baseline to 4.6%, and the mean number of days of hospitalization fell from 33.2 days to 15.2 days. Additionally, the number of patients visiting the emergency department for psychiatric reasons decreased from 11 to 3 during the PP3M treatment period compared with the 12 months before baseline.

Harms

PP3M and PP1M have the same active moiety, route of administration and nanoparticle aqueous suspension technology, although they differ in particle size and concentration (31). When used within the recommended dose range, PP3M results in similar exposure to paliperidone as PP1M, without accumulation over time (32). Safety findings from the long-term PP3M studies R092670 PSY 3011 (22) and R092670 PSY 3012 (2) were comparable to previous studies with PP1M, with no clinically meaningful differences in the safety profile between the two products. The warnings and precautions for PP3M are in line with those for other second-generation antipsychotics. In the United States, PP3M carries a black box warning on the increased risk of death associated with cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis (33). The types and incidences of adverse events are consistent between PP3M and PP1M. Weight gain was the most frequently reported treatment-emergent adverse event in both groups. The incidence of adverse events related to tardive dyskinesia/extrapyramidal symptoms, QT prolongation, hyperglycaemia and diabetes mellitus, weight gain, hyperprolactinaemia and prolactin-related adverse events, as well as injection site reactions and discontinuations due to these events, were generally similar between PP3M and PP1M. Neuroleptic malignant syndrome was not reported. While injection-site adverse events were infrequently reported in completed studies with PP3M, they occurred more frequently than with PP1M. Subgroup analyses based on geographical regions (east Asian, European/non-European and Latin American) did not show any unique safety signals associated with PP3M compared with PP1M (23–25). The 2021 network meta-analysis showed that PP1M had a higher risk of adverse events (RR 1.87, 95% CI 1.02 to 3.40) and weight gain (RR 2.51, 95% CI 1.55 to 4.05) compared with placebo. Point estimates for these outcomes also showed a higher risk for PP3M, however they were not statistically significant. PP3M had a lower risk of QTc prolongation than PP1M (based on results from a single study). Both PP1M and PP3M showed significantly higher risk of hyperprolactinaemia (RR 3.25, 95% CI 1.24 to 8.51 and RR 2.99, 95% CI 1.11 to 8.05, respectively) (27). An observational review of the French pharmacovigilance database found that adverse drug reactions associated with paliperidone palmitate were similar to those reported for other atypical antipsychotics (34). Another observational cohort study of 90 patients with schizophrenia spectrum disorders found that increased appetite and weight were more common with PP3M (40.9%) and PP1M (76.5%) compared with haloperidol decanoate (17.6%), but there were no significant differences in sedation, extrapyramidal symptoms, decreased libido or body mass index (35). A large retrospective cohort study involving 92 075 patients with schizophrenia or schizoaffective disorder reported no increased risk of all-cause death, completed suicide or suicidal behaviour/attempts in users of various long-acting injectable antipsychotics, including PP3M and PP1M (36). Likewise, an observational, cross-sectional study in 431 non-institutionalized patients with schizophrenia, psychosis, and schizoaffective, delusional, bipolar or personality disorders found similar results (37). A 12-month cohort study in outpatients with non-affective first episode psychosis found no statistically significant differences in treatment side-effects between PP3M and PP1M (38). Studies examining the switch from PP1M or clozapine to PP3M did not report any new safety concerns (30,39–43).

Cost / cost effectiveness

PP3M is available in different dose levels. The cost per patient for PP3M can vary depending on the dose and country. In the Netherlands (Kingdom of the), Portugal and Sweden, the publicly available list prices for PP3M range from €565 to €1868 per prefilled syringe or €2259 to €7471 a year (45). These prices can vary based on factors such as country-specific assessments of value, population coverage, local pricing and reimbursement negotiations, and local regulations. Despite potentially higher drug acquisition costs, PP3M and PP1M have been found to be cost-saving for maintenance treatment in resource-limited settings based on evidence from Rwanda and South Africa. Additionally, compared with standard oral antipsychotics, PP3M and PP1M have the potential for cost offsets. In the context of Rwanda, where health care resources are limited and patients must often travel long distances for treatment, a 1-year cost consequence model study showed that PP3M and PP1M led to longer treatment duration, fewer relapses, and fewer hospital days compared with haloperidol, the standard of care. This resulted in reduced indirect costs by almost 50%, including travel expenses and improved productivity (46,47). Real-world evidence and simulation studies also suggest that early use of long-acting injectable antipsychotics can improve long-term patient outcomes and potentially lead to cost offsets (48,49). These include a reduction in hospital admissions, reduced use of disability benefits, and increases in independent living and competitive employment. An analysis of the R092670-PSY-3012 study found that in terms of direct costs, PP3M decreased the

likelihood of hospitalization and emergency room visits, resulting in lower costs (49). The odds ratio for hospitalization for psychiatric and social reasons during the double-blind phase for placebo versus PP3M was 7.74 (95% CI 2.39 to 25.05). Total health-related health care resource utilization costs, mental health-related costs and hospitalization/emergency room visit costs were significantly lower for the PP3M group versus the placebo group.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a conditional recommendation that long-acting injection antipsychotic medicines (fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol) should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects and individual preference (moderate certainty of evidence) (44).

Availability

PP3M is approved and registered in 90 countries worldwide. It is not currently available on the market in all 90 countries in which it is registered. Generic brands are not currently available, with patent protection for the innovator brand not due to expire until 2036.

Other considerations

The WHO department of Mental Health and Substance Use reviewed the application. The technical department made the following comments. • Preliminary findings on the safety profile of PP3M are yet to be substantiated by evidence coming from long-term and pharmacovigilance studies. • The long half-life of PP3M has implications for the possibility of seeking prompt assistance in the event of treatment-emergent adverse effects in rural settings • The requirement to use PP3M after at least 4 months treatment with paliperidone palmitate 1-month (PP1M) may hinder its use due to limited or no availability in many low- and middle-income settings. • Price information is lacking from low- and middle-income countries, and no generics are currently available. • PP3M is not currently recommended for use in WHO guidelines.

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