



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Paliperidone

Proprietary Product Name: Invega

Sponsor: Janssen-Cilag Pty Ltd

May 2013

TGA Health Safety
Regulation

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I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	Extension of indications
<i>Decision:</i>	Withdrawn
<i>Date of Decision:</i>	22 October 2012
<i>Active ingredient:</i>	Paliperidone
<i>Product Name:</i>	Invega
<i>Sponsor's Name and Address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
<i>Dose form:</i>	Modified release tablet
<i>Strength:</i>	3 mg, 6 mg, 9 mg and 12 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	7, 28 or 56 tablets per pack
<i>Approved Therapeutic use:</i>	Unchanged
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Unchanged
<i>ARTG Numbers:</i>	130502, 130714, 130717, 130732

Product background

Paliperidone belongs to the atypical antipsychotic class of psychotropic drugs. It is the major active metabolite of risperidone, which is registered for the treatment of schizophrenia. Paliperidone is a monoaminergic antagonist with a high affinity for serotonergic (5-hydroxytryptamine Type 2A) and dopaminergic Type 2 receptors. Paliperidone binds also to α_1 -adrenergic receptors, and, with lower affinity, to H₁-histaminergic and α_2 -adrenergic receptors. It has no affinity for cholinergic, muscarinic or β_1 - or β_2 -adrenergic receptors.

Invega is currently approved in Australia for the following indication:

Invega is indicated for the treatment of schizophrenia, including acute treatment and recurrence prevention. Invega is indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate).

The sponsor proposes to amend the indications to include use of paliperidone for the treatment of schizophrenia in adolescents aged from 12 to 17 years. The proposed amendments to the approved indications are shown in bold font below:

*Invega is indicated for the treatment of schizophrenia **in adults**, including acute treatment and recurrence prevention.*

Invega is indicated for the treatment of schizophrenia in adolescents (ages 12-17 years).

*Invega is indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate) **in adults**.*

The current dosing recommendation [for adults] is a range of 3 to 12 mg daily. For individuals aged < 18 years, the current Invega Product Information states that Invega has not been studied in this patient group and should not be used in this age group.

For the proposed indication of schizophrenia in adolescents, the initial dose is 3 mg daily, and dosing may be adjusted within the dose range of 3-12 mg daily. The proposed initial dose is half the initial dose currently recommended for adults but the dose range of 3-12 mg daily proposed for adolescents is the same as that currently recommended for adults.

Quetiapine (Seroquel) was granted Australian approval for treatment of schizophrenia in adolescents (13 to 17 years of age, inclusive) in 2009. Risperidone is approved for treatment of schizophrenia in adolescents aged from 15 years and clozapine for adolescents aged from 16 years. Thus, if approved as proposed in the current application, paliperidone would be the only antipsychotic in Australia with a specific indication for treatment of schizophrenia in 12 year old children.

Regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) in September 2007. At the time of the current application, paliperidone was approved for the treatment of schizophrenia in adolescents (ages 12-17 years) in approximately 10 countries including the USA (April 2011) and was under evaluation for this indication in Canada.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

To support this application, the sponsor provided one new repeat dose toxicity study with paliperidone conducted using juvenile rats (Sprague Dawley strain, 3 weeks of age at commencement of 7 week study). The overall quality of this study was generally adequate and the observed effects were consistent with those seen in adult animal studies that have been previously evaluated by the TGA for other applications concerning paliperidone. The study also encompassed a fertility and early developmental study in subgroups of rats kept for an additional recovery period.

Toxicity

Repeat-dose toxicity

The new juvenile repeat dose toxicity study in rats and the related previously evaluated studies using risperidone were generally adequate and supportive of the proposal to extend the patient group using paliperidone to include adolescent patients (12–17 years). The studies were compliant with principles of Good Laboratory Practice. The duration of the new study, although relatively short (7 weeks) compared to typical repeat dose toxicity studies, was lengthy enough to ascertain effects that might arise in early adolescence (3 weeks of age at time of study commencement) and sexual maturation. Following the recovery period, reproductive function was assessed in a fertility and early embryonic study. Findings in the new repeat-dose toxicity study were generally consistent with those previously observed in earlier studies (re-submitted with the current application) conducted using risperidone.

The major toxicities/treatment-related effects noted in the new study were central nervous system (CNS)-related (for example, sedation, ptosis and dopamine-related enhanced prolactin levels) which, because of the pharmacological effects of paliperidone, were anticipated and consistent with those seen in previous studies with paliperidone (and risperidone).

Histopathology examinations indicated some instances of cortical scarring in the kidney, although this observation was confined to males treated with low and mid doses only. As well, there were histopathological and gross changes to the reproductive organs of treated females (for example, persistent corpora lutea, vaginal epithelial mucification and significant reductions in combine uterine and cervical weights) that were likely associated with treatment-dependent elevations in prolactin levels. Body weight gain preferentially seen in females might be associated with the growth effects of prolactin. The change in ulna length was slightly but significantly increased in females (but not males) over the treatment period (post natal day (PND) 24-65), which was consistent with similar effects in an earlier study with risperidone over the latter part of the treatment period (PND 29-50). (In the risperidone study, the change in long bone growth was reduced in both sexes when drug exposure occurred in an earlier treatment period (PND 12-22), but the paliperidone study did not investigate effects during this period).

Elevated prolactin levels also induced pseudopregnancies and altered oestrus cycles; however, these effects did not impact on overall reproductive function as evidenced by the lack of effect on the fertility index and conception rate in treated groups during the recovery/reproductive phase. Treatment caused increases in the number of corpora lutea, which resulted in slightly but not significantly higher numbers of implantations and live embryos.

Relative exposure

Exposure ratios for paliperidone were calculated using adolescent human area under the plasma concentration versus time curve (AUC) values extrapolated from a clinical modelling study, which deduced that a maximum clinical oral dose of 12 mg/day paliperidone in adolescents (with the youngest patient being < 51 kg) will give rise to AUC over time zero to 24 h (AUC_{0-24 h}) values of 1440 ng.h/mL. As well, exposures were also estimated as doses based on body surface area (BSA; mg/m²), since reference was made to comparisons against human (adolescent) exposures in the proposed PI. Relative exposures based on AUC were similar to estimates based on mg/m² doses in this study and are tabulated below (Tables 1 and 2).

From the new studies, a no observed adverse effect level (NOAEL) could not be established on the basis of observed CNS-related toxicities (for example, heightened sedation and ptosis [expected class effects]), as well as a prolactin-induced

pseudopregnant state in females. Furthermore, the exposures attained in the new repeat dose toxicity study were similar to or below the clinical range, and given the lack of established NOAEL, a comfortable safety margin was not attained. However, many of the observed adverse, treatment related effects were class-dependent, reversible, and known from previous studies with risperidone. It is also worth noting that human adolescent AUC values were extrapolated from a modelling study based on a maximum clinical dose of 12 mg/day. This is a conservative choice of dose for this nonclinical safety assessment; the proposed PI recommends a usual adolescent dose of 3 mg/day, and animal/human exposure comparisons would be correspondingly increased at this clinical dose level.

Table 1. Relative exposure in repeat-dose toxicity studies for paliperidone (based on toxicokinetic analysis from report TOX8691).

Species	Sex	Dose (mg/kg/day)	AUC _{0-24h} (ng·h/mL)	Exposure ratio [#]
Rat 7 week study	Male	0.16	76.7	0.05
		0.63	385	0.3
		2.5	1543	1.1
	Female	0.16	131	0.1
		0.63	525	0.4
		2.5	2056 [†]	1.4
Human* (maximum clinical dose in adolescents)	Male and female	12 mg per day	1440	–

*Data extrapolated from a human population pharmacokinetic modelling study provided in the clinical part of the dossier; [†] AUC_{0-8h}; # = animal:human plasma AUC_{0-24h}

Table 2. Relative exposure to paliperidone when estimated by BSA (mg/m²) dose.

Species	Dose (mg/kg/day)	Dose (mg/m ²)	Exposure ratio [#]
Rat 7 week study	0.16	0.96	0.1
	0.63	3.78	0.4
	2.5	15	1.6
Human (Adolescent 12 years, 40 kg)	0.3*	9.3	–

* Maximum daily dose of 12 mg; # = animal:human dose (mg/m²) [Conversion factors: rat – 6, human adolescent – 31]

Earlier studies that examined the effects of risperidone in juvenile beagles did approach higher exposure multiples (11 times the human dose at 5 mg/kg); however, no NOAEL was established on the basis of effects on bone density in females and delays to sexual maturity in both males and females. Relative exposure to risperidone and paliperidone, respectively, based on data from previously evaluated studies are shown in Tables 3 and 4.

Table 3. Relative exposure to risperidone active moiety in repeat-dose toxicity studies for risperidone.*

Species	Sex	Dose (mg/kg/day)	AUC _{0-24h} [^] (ng·h/mL)	Exposure ratio [#]
Rat 7 week study (JAB0074)	Male	0.04	23	0.02
		0.16	270	0.2
		0.63	751	0.5
	Female	0.04	26	0.02
		0.16	258	0.2
		0.63	888	0.6
Dog (Beagle) 40 wk study (EDMS-PSDB-9769000)	Male and female	0.31	1361	0.9
		1.25	5842	3.8
		5	16722	11
Human (maximum clinical dose in adolescents)	Male and female	6 mg per day	1524	–

*From previously evaluated nonclinical studies; # = animal:human plasma AUC_{0-24 h}; NOAEL values are bolded; ^ AUC of active moiety (risperidone plus paliperidone)

It is worth noting that in the earlier risperidone studies in juvenile rats and dogs, animal/human exposure margins were based on the AUC of active moiety (risperidone plus paliperidone) in the test species. The kinetic data from these studies indicate that approximately 70% (rat) and 90% (dog) of the active moiety was paliperidone. Hence, these nonclinical studies have also assessed the toxicological profile of paliperidone in juvenile animals.

Table 4. Relative exposure to paliperidone in juvenile dog repeat-dose study with risperidone.*

Species	Sex	Dose (mg/kg/day)	AUC _{0-24h} [^] (ng·h/mL)	Exposure ratio [#]
Dog (Beagle) 40 week study (EDMS-PSDB-9769000)	Male and female	0.31	1267	0.9
		1.25	5468	3.8
		5	15305	11
Human (maximum clinical dose in adolescents)	Male and female	12 mg per day	1440	–

*From previously evaluated nonclinical studies; # = animal:human plasma AUC_{0-24h}; ^ AUC of paliperidone only

The animal/human exposure margins for paliperidone achieved in the previous juvenile dog study are the same as those determined for risperidone active moiety (risperidone + paliperidone) in the earlier risperidone evaluation (the majority of the active moiety in this dog study was paliperidone).

The uncertainties concerning extrapolation of findings in juvenile animal studies to potential adverse effects in paediatric patients were considered in a previous TGA nonclinical evaluation report for risperidone, in which juvenile animal studies with risperidone were evaluated. Compared with rodents, humans are substantially more developed at birth, and much more so by 12 years of age, and it is likely that the adult human is a better model for effects in adolescents than juvenile rats, as there are no interspecies differences to confound interpretation of observations. Thus, although regulatory guidance¹ indicates that such nonclinical studies can provide useful insights into potential toxicological issues for paediatric populations, the exacerbated interspecies differences for juveniles in the present situation mean that any findings should be interpreted with caution. This caution is reflected in the recommended wording for the 'Paediatric use' section of the PI.²

Nonclinical summary and conclusions

- Janssen-Cilag Pty Ltd has applied to extend the patient population for paliperidone (Invega) to include adolescents (12–17 years). Supporting nonclinical data included a new oral repeat dose toxicity study in juvenile rats, and previously evaluated oral repeat dose toxicity studies with risperidone in juvenile rats and dogs.
- The findings in the new (GLP) study with paliperidone were consistent with those previously observed with this compound in adult animals and with those of its active prodrug, risperidone, in juvenile and adult animals. These included anticipated CNS class effects such as sedation and ptosis, as well as elevations in prolactin levels; the consequences of these effects prevented determination of a NOAEL. In a subset of rats allocated to a recovery/reproductive phase, no overall effects on mating, conception or the fertility index were observed.
- The findings in the new, juvenile rat repeat dose toxicity study occurred at systemic exposures (plasma AUC) similar to or less than the exposure anticipated in adolescent patients receiving the maximal recommended dose (12 mg/day). The exposure margins would be greater at the (more usual) clinical dose of 3 mg/day.
- It is likely that the juvenile rat is a poor toxicological model for adolescent humans, as discussed in a previous evaluation of juvenile animal studies supporting a risperidone submission.
- The exposure to paliperidone achieved in a previous juvenile dog study with risperidone was up to 11-fold the maximal anticipated paliperidone exposure in adolescents receiving 12 mg/day.

Recommendation

Based on the submitted nonclinical data, and in view of the approved use of risperidone (the active prodrug) in adolescents (and children > 5 years of age), there are no nonclinical objections to extending the population for paliperidone treatment to include adolescents of ages 12–17 years.

The proposed PI statements should be amended as recommended (details of these recommendations are beyond the scope of this AusPAR).

¹ EMEA/CHMP/SWP/169215/2005: *Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications*, 1 August 2008.

² Details of recommended revisions to the PI are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

Introduction

Background and rationale

The sponsor's clinical rationale included the following and is considered to be acceptable:

- Schizophrenia is a complex and severe neurodevelopmental brain disorder with a chronic course resulting in significant long-term morbidity and functional impairment. The lifetime morbidity risk of schizophrenia was estimated to be 7.2 per 1000 individuals. An estimated 1 in 10,000 children and adolescents worldwide develop full Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for the diagnosis of schizophrenia. Furthermore, many young people are thought to have sub-threshold symptomatology well before they meet the formal diagnostic criteria for the disorder.
- The onset of schizophrenia often occurs in adolescence, with close to one-third of patients diagnosed with schizophrenia developing their first positive symptoms of psychosis during adolescence. These symptoms are generally similar to those in adults. Schizophrenia has also been described in children but is considered uncommon in patients less than 12 years of age. It has been estimated that only 0.1% to 1% of all schizophrenic disorders present before 10 years of age, with 4% occurring before 15 years of age.
- Although the phenomenology and diagnostic criteria are similar in the adolescent and adult populations, an earlier age of onset is associated with a poorer prognosis and a more negative impact of the disease on personality and relationship development, cognitive functioning, educational and work attainment, and social functioning. There is also evidence to suggest a younger age of onset of schizophrenia is associated with a form of the illness that may be more resistant to treatment than adult-onset illness, especially with regard to treatment with typical antipsychotics. As in adults, adolescent-onset schizophrenia is a lifelong illness with no known cure.

Scope of the clinical dossier

The clinical dossier documented a development program of pharmacokinetic (PK), efficacy and safety studies relating to the proposed extension of indications. The submission was well presented and contained the following clinical information:

- One key PK study (PSZ-1001).
- One population-PK (pop-PK) analysis (based on 10 adult studies, PSZ-1001 and sparse PK data from PSZ-3001).
- One pivotal efficacy/safety study (PSZ-3001).
- Two ongoing efficacy/safety studies (PSZ-3002 and PSZ-3003).
- Literature references provided for background information.

No bioavailability or bioequivalence studies were submitted.

Evaluator comment: The sponsor nominated Study PSZ-3002 as pivotal but the evaluator does not agree. In brief, the study does not qualify as pivotal because efficacy is only regarded as a secondary outcome variable, multiplicity is unadjusted for, and the open-label design, without a comparator or placebo group, may introduce significant bias.

Guidance

There are no TGA-adopted guidelines relating specifically to schizophrenia. However, there is a general adopted *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia* (CPMP/EWP/559/95). The sponsor complied with TGA guidance.

Good clinical practice

The submitted studies were stated to have been conducted in compliance with Good Clinical Practice and according to appropriate ethical standards.

Pharmacokinetics**Studies providing pharmacokinetic data**

The submission included PK data from one Phase I study (25 subjects) and one pop-PK study, including pooled sampling data from a total of 137 subjects from one Phase III study in the target population and 153 subjects from three Phase I adult trials.

No PK study had deficiencies that excluded their results from consideration.

Evaluator's overall summary and conclusions on pharmacokinetics

Pharmacokinetics parameters for oral paliperidone extended release (ER) tablets in children and adolescents aged ≥ 10 to < 18 years appear to be similar to those found in adults in the dose-range 6 to 12 mg/day. Although the PK findings were similar to adults, adolescents had reduced apparent clearance as well as higher plasma exposure in low weight subjects. Such findings may impact upon the tolerability and safety of paliperidone in an adolescent population.

The PK results do not support a dosage regimen below 6 mg/day in children and adolescents. The weight based dosing schedule employed in Study PSZ-1001 appeared to assume older children and adolescents will require a 6 mg/day clinical dose, that is, the recommended adult starting dose. This is reflected in the way PK parameters were dose-normalised to 6mg/day.

According to the clinical study report (CSR), older heavier subjects (80% ≥ 15 years and 80% ≥ 51 kg) were recruited into the study. The actual dose range employed in this study was 4 to 12mg/day, with only five (20%) subjects (all weighing < 51 kg) receiving paliperidone < 6 mg/day. No subject received a 3 mg/day dose, the recommended proposed starting paliperidone ER dosage regimen in adolescents.

Given paliperidone ER dose proportionality in adults for the range 3-12mg/day (with further evidence down to 1.5 mg) and the similarity in PK parameters between adolescents and adults, extrapolation of the results to include a 3 mg dosing regimen in adolescents in a clinical setting is proposed. A 3 mg/day dosage regimen is not well supported based on the data provided in this report. There is no comparison of the PK of the proposed 3 mg daily dose in adolescents with the 6 mg dose in adults. It appears 6 mg daily leads to higher exposure and 3 mg daily to lower exposure in children and adolescents compared with adults.

The paliperidone paediatric PK study, PSZ-1001, has many significant design flaws. Firstly, it has an ill-defined study base. The selection of 25 subjects from thirteen centres in six countries, only one of which was English-speaking, raises the issue of the standardisation of medical practices across these countries, and the investigators' experiences of schizophrenia and related disorders in a cultural context. Recruitment of subjects from such a wide study base has the potential to introduce significant selection bias into the

study. Furthermore, subject numbers were too small to provide high statistical power in the PK parameters measured. Only descriptive statistics were reported. The sponsor justified this action *“in order to limit the exposure in paediatric subjects while providing sufficient data to develop a population PK model”*. The higher paliperidone dosages this study employed do not support this statement. From earlier statements, it appeared patients were at home during the steady state assessment phase. This raises the possibility of lack of strict adherence to the dosing schedule.

The results of this study need to be interpreted in terms of the dosage study participants received by a Push-Pill formulation (assumed to be equivalent to the Osmotic controlled Release Oral delivery System; OROS). There is no marketed 1 mg OROS preparation and patient dosages were rounded to the nearest 1 mg, which raises concerns over the suitability of the 1mg tablet and the accuracy of dosing for each individual patient (16 subjects, that is, 64%, received the 1 mg tablet). The sponsor provided dissolution data in support of the use of a 1 mg OROS-equivalent tablet formulation. However, examination of the dissolution data reveals a profile that suggests a quicker release of drug for the 1 mg tablet compared to the 3 mg and 6 mg tablets. In the sponsor’s *Paediatric Investigation Plan*, it is stated that: *“Current OROS technology does not allow reliable production of doses less than 1.5 mg”*. Hence, the findings of PSZ-1001 need to be considered carefully in view of this fact.

The sponsor did not report upon several key PK parameters in Study PSZ-1001, that is, elimination half-life and volume of distribution. Furthermore, no single dose PK parameter results are provided. Such omissions should be justified.

The proportion of study protocol violations was unreasonably high. Furthermore, eight subjects (equating to more than 30% of total participants) received olanzapine or quetiapine concomitantly. Although no drug interactions with paliperidone have been demonstrated, one cannot rule out the possibility of an effect on the PK and pharmacodynamic properties of paliperidone, as well as the reported adverse events.

Despite an adult pop-PK model that identified lean body mass as a significant predictor of apparent oral clearance of paliperidone, the sponsor chose body weight (BW) instead. Body weight was considered a more practical covariate on clearance for dose adaptation in adolescents. The sponsor cites Reigner and Welker 1996³, yet these authors refer to a meta-analysis that showed a linear increase in volume of distribution over systemic availability with lean body weight not body weight per se. An accurate assessment of weight is particularly pertinent in paediatric populations. Using BW instead of lean body mass (or lean body weight) appears a crude measure, again questioning the validity and applicability of the study findings.

While the sponsor investigated the higher plasma concentration and lower clearance of paliperidone found in low weight subjects (< 51 kg) compared with those ≥ 51 kg, no specific analysis by gender was reported. This was despite the recognised effect of female gender on paliperidone pharmacokinetics as declared in the Invega PI: *“The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in {adult} women than men”*. The latter may be explained largely by gender differences in lean body mass and creatinine clearance, again highlighting the need of applying lean body mass in PK modelling.

No separate PK data from Study PSZ-3001 were presented in this report.

³ Reigner BG and Welker HA. Factors influencing elimination and distribution of fleroxacin: Meta-analysis of individual data from 10 pharmacokinetic studies. *Antimicrobial Agents and Chemotherapy* 1996;40:575-580.

Conclusion

The study objectives of characterising the single and multiple dose PK of paliperidone in a paediatric population were only partially met. No single PK data are presented in this report. Furthermore, the multiple dose PK data (at steady state) were only characterised for a 6 mg daily dose, not a 3 mg daily dose as proposed in the PI. Elimination half-life and volume of distribution data were omitted from this report making it difficult to fully evaluate the submitted data.

The 3 mg/day dosage regimen in the proposed PI is not based on the submitted PK data or other paediatric dose-ranging paliperidone studies. The sponsor justifies its proposed regimen based on PK data from risperidone in children and adolescents, as well as paliperidone dose-proportionality studies in adults. This evaluator suspects the AUC at the proposed 3 mg/day dose will be substantially lower for most children and adolescents, depending most on their body weight. In addition, the mechanism for the apparent reduction in active secretion of paliperidone in children and adolescents has not been explored. Caution is required when extrapolating data from other sources.

The evaluator would recommend rejection of the proposed extension of indications for paliperidone use in adolescents with schizophrenia, if such indication relied solely on the submitted PK data. Even though the sponsor failed to provide a dose-ranging study in adolescents or demonstrate similar PK to adults at doses below 6 mg/day, the risk to the adolescent subject, provided they do not have renal impairment, is not regarded as high by the evaluator. Adult data clearly demonstrates consistency in PK parameters from 3-12 mg/day. Furthermore, based on PK data from risperidone in children and adolescents, the evaluator is confident the risk of administering paliperidone ER to the 15-17 year age group (representing 80% of the study population) is acceptable, especially given the lower expected toxicity for a 3 mg/day dosing regimen.

Pharmacodynamics

No new pharmacodynamic data are included in this submission.

Efficacy and safety

Dosage selection for the pivotal study

The following justification for dosing in the pivotal efficacy study, PSZ-3001, was provided in the sponsor's *Paediatric Investigation Plan*:

Based upon Study PALIOROS-PSZ-1001, the single and multiple dose PK of paliperidone in paediatric subjects (10-17 years of age, inclusive) are in the same range as adults. The study also showed that the safety profile of paliperidone ER in paediatric subjects was similar to that observed in adults: Paliperidone ER was well tolerated in doses up to 12 mg in both populations. Doses starting with paliperidone ER 3 mg administered once daily have been shown to be effective in adults with schizophrenia.

Recently, a pharmacokinetic study (Study R076477-SCH-1015) was completed to assess the dose proportionality of the 1.5 and 3 mg doses of paliperidone ER. Both doses were well tolerated by adult men. Dose proportionality was shown from paliperidone ER 1.5 to 3 mg for the maximum plasma concentration (C_{max}) and AUC extrapolated from time zero to infinite time (AUC_{0-∞}). In the previous Phase I Study R076477-P01-1010, dose proportionality was shown over the 3-15 mg dose range. Hence it can be concluded that all doses between 1.5 and 15 mg behave in a dose-proportional manner.

Based upon the combined PK and tolerability dose range data from these studies and the efficacy and safety data from the Phase II studies in adults, the sponsor intends to study paliperidone ER 1.5 to 12 mg daily for the efficacy and safety Study R076477-PSZ-3001 and the long-term safety Study R076477-PSZ-3002.

The doses (1.5-12 mg/day) selected for the paediatric studies will allow exploration of the entire dose range and determination of the benefit-to-risk ratio at each dose level. Maximum exposure to paliperidone observed in Study PALIOROS-PSZ-1001 was comparable to exposure at the doses established to be safe in adults.

In risperidone paediatric studies, the maximum dose (6 mg/day) of risperidone was equivalent to paliperidone ER 18 mg/d and was well tolerated. Thus, while the maximum possible doses (6 mg for a 29 kg subject [0.2069 mg/kg], and 12 mg for a 51 kg subject [0.2353 mg/kg]) in Study R076477-PSZ-3001 slightly exceed the maximum dose (0.171 mg/kg) used in Study PALIOROS-PSZ-1001 on a mg per kg basis, they are within the limits of safety established for paliperidone ER. Study results will include analysis of exposure based on weight that will allow [the sponsor] to maximise the risk-benefit ratio for dose recommendations.

The sponsor considered lowering the dose to a maximum of 0.171 mg/kg for the low-weight paediatric group; however, on reviewing data in adults weighing between 30 and 50 kg, there was no difference in the incidence or severity of adverse events between subjects of low weight and high weight. While there was a dose dependent increase in adverse events, it was not dependent on weight. Furthermore, paliperidone ER studies in adults included doses from 3 to 15 mg. The 15 mg dose did not have a significant therapeutic advantage over the 12 mg dose; however, there was an increase in adverse events at the higher dose. The maximum recommended dose of paliperidone ER in adults is 12 mg.

Dosing on a mg per kg basis is generally recommended for young paediatric patients or infants, using liquid preparations for improved accuracy. The sponsor is planning to recruit adolescents with a majority of patients in the adult weight range, where fixed dosing is preferable.

Study drug was taken in the morning, standardised in relation to food intake. That is, the patient was instructed to always take the study drug in the fasting state in the morning or always take it with breakfast. Invega must be swallowed whole, not chewed, divided or crushed.

Evaluator comment: There are no formal dose ranging studies for paliperidone in paediatric or adolescent subjects. Given a half-life approximating 24 h, the dose interval is appropriate for the pivotal study. The proposed PI cites 3 mg/day as the recommended dose in adolescents (12-17 years of age). Dosage selection based on adolescent PK data only applies to the 6-12 mg/day range (similar to adult PK data). This is discussed further under *First Round Clinical Summary and Conclusions Benefit risk assessment*, below.

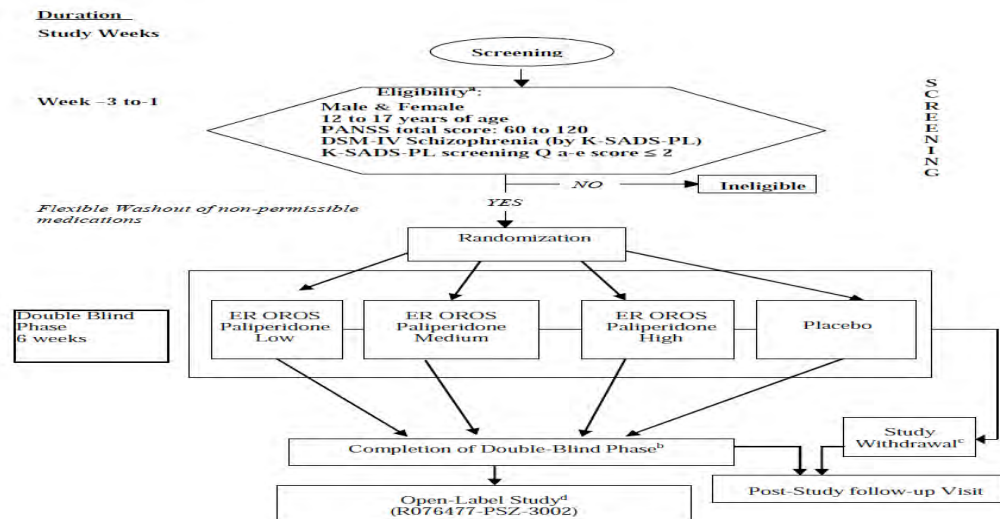
Given “*The sponsor is planning to recruit adolescents with a majority of patients in the adult weight range, where fixed dosing is preferable*” this raises a question of selection bias at the screening phase of the pivotal study. The sponsor did not provide further details on this aspect of subject recruitment.

Summary of studies

Pivotal efficacy study: Study PSZ-3001

The study design was a 6 week Phase III, randomised, multicentre, multinational, double-blind, weight-based, fixed-dose, parallel-group, placebo-controlled trial conducted in an outpatient setting at 35 centres in five countries. A summary of the design is shown below:

Figure 1: Design for Study PSZ-3001.



Study objectives

The primary objectives were to evaluate the efficacy, safety and tolerability of three weight-based, fixed-dose groups of ER paliperidone compared to placebo in adolescent subjects 12-17 years of age, inclusive, with schizophrenia.

The secondary objectives were to: assess the change in the global impression of severity of illness associated with the use of paliperidone compared to placebo as measured by the Clinical Global Impression-Severity Scale (CGI-S); assess the benefits in psychological, social and school functioning associated with treatment with paliperidone compared to placebo as measured by the Children's Global Assessment Scale (CGAS); assess the effect on sleep associated with treatment with paliperidone as measured by the sleep Visual Analog Scale (VAS); explore the PK of paliperidone; explore the relationships between its PK and results of efficacy parameters (for example, Positive and Negative Syndrome Scale [PANSS]) and safety parameters (including extrapyramidal symptoms (EPS) and adverse events (AEs) of interest).

Study treatments

Eligible subjects were randomised into one of four treatment groups: Placebo, paliperidone ER Low (the "Low group"), paliperidone ER Medium (the "Medium group") and paliperidone ER High (the "High group"). Dosing of paliperidone depended on baseline bodyweight. Table 5 shows the weight-based, fixed-doses administered for each randomisation dose group. Paliperidone ER or placebo was taken daily before 10 a.m.

Table 5. Weight-Based Fixed-Dose Treatment Groups for Study PSZ-3001.

	Weight-Based Fixed Dose to be Given			
	Randomization Group			
	Placebo	Paliperidone ER Low (0.0150 to 0.0517 mg/kg)	Paliperidone ER Medium (0.0589 to 0.1176 mg/kg)	Paliperidone ER High (0.1179 to 0.2353 mg/kg)
Body weight ≥29 to <51 kg	placebo	paliperidone ER 1.5 mg (0.0295 to 0.0517 mg/kg)	paliperidone ER 3 mg (0.0589 to 0.1034 mg/kg)	paliperidone ER 6 mg (0.1179 to 0.2069 mg/kg)
Body weight ≥51 to ≤100 kg	placebo	paliperidone ER 1.5 mg (0.0150 to 0.0294 mg/kg)	paliperidone ER 6 mg (0.0600 to 0.1176 mg/kg)	paliperidone ER 12 mg (0.1200 to 0.2353)
Analysis	placebo	paliperidone ER 1.5 mg	paliperidone ER 3 mg and paliperidone ER 6 mg combined	paliperidone ER 6 mg and paliperidone ER 12 mg combined

ER: Extended Release

Other efficacy study: PSZ-3002

This study only provided secondary efficacy outcome data and these outcomes are considered exploratory (only descriptive statistics are supplied with no adjustment for multiplicity). In view of the exploratory nature and the open-label design, which does not include an active comparator or placebo group, the usefulness of the study findings is limited. Furthermore, while this study forms a partial extension study from the pivotal Study PSZ-3001, the findings cannot be directly compared in view of the differences in subject populations, methodology, dosage and the study limitations. For these reasons, Study PSZ-3002 is not considered a pivotal study.

In summary, PSZ-3002 was an ongoing, Phase III, two year, open-label, multinational, multicentre, single-arm, safety study of flexibly-dosed ER paliperidone (1.5-12 mg/day) in the treatment of adolescents (12-17 years of age) with schizophrenia. It was conducted in an outpatient setting between 29 June 2007 and the 30 July 2009 cut-off date (for all safety and efficacy data). The original 6 month protocol was amended to two years to investigate any study treatment effects on growth and maturation. Those enrolled into the 6 month study were considered to have completed the study at 6 months and were offered the option of participating in the amended study.

Study objectives

The primary objective was to evaluate the long term safety and tolerability of paliperidone in at least 100 adolescents (12-17 years, inclusive) with schizophrenia. This study was commenced before the pivotal efficacy Study PSZ-3001. Secondary objectives assessed the effect of paliperidone on the long-term symptoms of schizophrenia as measured by changes in: PANSS scores (total and subscales); CGI-S scores; CGAS scores; VAS scores (quality of sleep and daytime drowsiness) and modified measurements and treatment research to improve cognition in schizophrenia cognition assessment battery (MATRICS; this test examines the changes in multiple domains of cognitive functioning associated with paliperidone treatment).

Study treatments

The single-arm study comprised three treatment groups. These were investigated and reported upon singly and combined: Placebo/Paliperidone (Placebo/Pali) (from Study PSZ-3001, who withdrew due to lack of efficacy after 21 days, n =39); Pali [DB]/Pali (from study PSZ-3001, who completed double-blind treatment and received one of the treatment

doses, n = 117)⁴; Pali [No DB]/Pali (who entered this study directly, n = 122). The dosing regimen is summarised in Table 6, below.

Table 6: Summary of dosing regimen: Study PSZ-3002.

	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Mode dose (days on drug only)*	39	118	125	282
1.5 mg	1 (3)	4 (3)	0	5 (2)
3 mg	5 (13)	11 (9)	14 (11)	30 (11)
6 mg	18 (46)	55 (47)	49 (39)	122 (43)
7.5 mg	1 (3)	0	0	1 (<1)
9 mg	7 (18)	20 (17)	34 (27)	61 (22)
12 mg	7 (18)	28 (24)	27 (22)	62 (22)
13.5 mg	0	0	1 (1)	1 (<1)

* This dose represents the dose that was most frequently taken during the open-label study.

Based on data up to 30 July 2009 cut-off date for subjects enrolled prior to that date.

Evaluator's overall summary and conclusions on clinical efficacy

It is considered that the submitted data have not satisfactorily established the efficacy of paliperidone ER tablets in the treatment of adolescents (12-17 years of age) with schizophrenia.

The submission included one 6 week pivotal Phase III efficacy and safety study (PSZ-3001). Analysis showed that PANSS total score (the primary efficacy endpoint) was statistically reduced in the Medium treatment arm compared with placebo. This group (of 48 subjects) represents 3 mg/day dosing for subjects < 51 kg (n = 16) and 6 mg/day for those ≥ 51 kg (n = 32). Treatment reduced PANSS total score by 17.3 points (p = 0.006, confidence interval (CI) -16.58 to -3.67) compared to 7.9 points for placebo. Given the sponsor's pre-determined level of a 13.2 point reduction compared to placebo to show a clinically meaningful result, these results suggest borderline clinical significance in just the one treatment arm.

The High treatment group (receiving 6 mg/day for < 51 kg and 12 mg/day for ≥ 51 kg) achieved borderline statistical significance in terms of PANSS total score reduction (-13.8, p = 0.086, CI -13.07 to -0.09) and onset of therapeutic effect.

Clinical dosing recommendations can only be made on the findings in relation to the Medium group. Hence, efficacy data supports 3 mg/day as the minimum effective dose in adolescents with schizophrenia. The sponsor has proposed a starting dose of 3 mg/day. This is acceptable to the evaluator on efficacy grounds and is discussed further under *First Round Clinical Summary and Conclusions Benefit risk assessment*, below.

Failure of the High group to maintain therapeutic dosing throughout the 6 week study period or show statistical separation in the primary efficacy variable has not proven the 12 mg/day dosage regimen to be an effective treatment option (for those weighing at least 51 kg) in adolescents with schizophrenia. Furthermore, as no 9 mg dosage regimen was employed in this study, the evidence presented here does not support such inclusion. While a dose response relationship exists for paliperidone in adults, at least between 3-12 mg/day, such a dose-response relationship has not been demonstrated in this submission for adolescents. Hence, the efficacy data does not support a dosage above 6 mg/day. This is at odds with the pharmacokinetic data in children and adolescents, which does not support a dosage regimen below 6 mg/day.

The dosing regimens employed in the efficacy trials conducted in adolescents (PSZ-3001 and PSZ-3003) appear to have been derived empirically from adult studies, rather than

⁴ The three active treatment groups (Low, Medium and High) were analysed together as one group (protocol deviation without explanation)

from adolescent PK studies. While the pivotal efficacy study attempted to individualise dose according to bodyweight (less than or greater than 51 kg) this appears a crude measure and contrary to the way most paediatric doses are calculated. The longer-term, open-label safety study based dosage on clinical response and tolerability to paliperidone, in preference to a bodyweight dosing schedule. Furthermore, the higher doses used in those entering Study PSZ-3002 (as well as the ongoing Phase III Study PSZ-3003) reflect the sponsor's assumption that the predicted minimum effective dose in adolescents for paliperidone would be 6 mg/day irrespective of baseline body weight, age, gender and race. This assumption appears to be partially correct only for those subjects weighing at least 51 kg.

In PSZ-3001, the sponsor attempted to investigate the effect of paliperidone on age by dividing the adolescent group into 12-14 year and 15-17 year age groups. The study appeared to have insufficient power to detect meaningful differences in the parameters examined. The Medium group comprised just 15 subjects in the 12-14 year age-group, eight receiving the 3 mg/day dosage. In view of the small numbers of subjects in this age-group, the difficulty diagnosing schizophrenia in very young children and the lack of efficacy data, the evaluator does not recommend dosing in the 12-14 year age-group.

Analyses of the secondary efficacy endpoints and pre-specified "other" efficacy endpoints against placebo supported the findings of the primary efficacy endpoint for the Medium group, although these analyses did not adjust for multiplicity effects. Exploratory post hoc analyses of efficacy endpoints versus placebo also supported the primary efficacy findings for the Medium group and suggested statistical separation for the High treatment group across several parameters.

The submission included no supportive randomised, double-blind, placebo-controlled studies. It did include one ongoing two year Phase III, open-label, single-arm, partial extension study in the target population (PSZ-3002). The results appeared to show some symptom and functional improvement over the 6 months' study period analysed, which are encouraging, but the data from this study are not considered relevant to the current application. The effect of paliperidone on efficacy has not been established beyond six weeks.

Overall, it is considered that the efficacy of paliperidone ER for the proposed extension of indication is not supported by the one confirmatory pivotal study. The TGA adopted Guideline *Points to Consider on Application with 1. Meta-analysis; 2. One Pivotal study*; (CPMP/EWP/2330/99, 31 May 2001) discusses applications that include only one pivotal study. This Guideline discusses the "*general demand for replication of scientific results*", but notes that "*clinical drug development differs from the situation with strictly experimental studies*". The Guideline states that where confirmatory evidence is provided by only one pivotal study "*this study will have to be exceptionally compelling*", but goes on to state "*there is no formal requirement to include two or more studies in the Phase III program*".

The Guideline lists factors that should be considered when determining whether the confirmatory evidence from one pivotal study is "*exceptionally compelling*". Applying these factors to Study PSZ-3001 leads to the following conclusions:

- The internal validity may be compromised from potential biases in subject selection (in and out of the study), lack of blinding of investigators, the quality of the randomisation process (generated by the sponsor) and hence the potential to introduce confounding into the results, the use of a modified intention to treat (ITT) population in preference to an "all randomised population" and the loss of almost 50% of the placebo (control) group. Study PSZ-3001 did not use any robust objective measure of compliance. Although the sponsor took blood samples to assess PK variables, no information relating these values to study medication was provided. The study was undertaken primarily on an outpatient basis and medication supervised by

family members. To achieve such high compliance rates in subjects purported to have acute psychosis, which tend to be a problematic group in terms of medication adherence, raises concern over the measures the sponsor used to ensure and assess compliance.

- The external validity is uncertain as the results of the efficacy study may not be extrapolated to the general population of adolescent Australians with schizophrenia. The body mass index (BMI) distribution in the study population may differ considerably from the heavier Australian population, which could give rise to dosing issues. The age of first diagnosis (as young as 3 years of age) is cause for concern as is how a definitive of schizophrenia diagnosis was established. A large proportion of participants had never been hospitalised for psychosis and hence diagnosis was made in an outpatient setting. This may be at odds with how diagnosis is made in Australia. Furthermore, it is unclear from the submitted data what non-pharmacological interventions occurred during the study. The approaches used may differ considerably from those used in Australia. The findings in US subjects, that is, the population that most closely resembles the Australian population (of those countries participating) were inconclusive, and indeed, did not appear to show efficacy at any dosage regimen (*albeit* small numbers recruited), giving rise to generalisability concerns. Furthermore, no family history of mental illness, and schizophrenia in particular, was provided. This information has relevance to establishing the diagnosis of schizophrenia. In addition, numbers of hospitalisations for schizophrenia were not provided.
- To be clinically relevant the estimated size of treatment benefit must be large enough to be clinically valuable. In the Medium group, the net reduction in PANSS total score was 9.4 points. This, according to the sponsor's pre-determined level of a 13.2 point reduction compared to placebo, is of doubtful clinical meaningfulness. The efficacy findings for the 12-14 year age-group (27% of the study population) were not clearly established and hence any extrapolation of study results to this population should be approached with caution.
- The degree of statistical significance achieved in the Medium group for PANSS total score reduction was $p = 0.006$ (CI -16.58 to -3.67). While the statistical result for this group is reasonably strong, the CIs are not particularly narrow.
- The data quality was acceptable and quality assurance audits/study monitoring processes appeared to be completed satisfactorily.
- The study revealed a reasonable degree of internal consistency in that the secondary and other efficacy variables supported the primary efficacy analysis for the Medium treatment group (showing efficacy over placebo). In terms of PANSS total score, baseline by country there was wide variation and the endpoints by country also showed a marked degree of variance. In sub-group analyses, especially by age-group (12-14 years; 15-17 years), race and geographical location, results were inconsistent and the data had wide distribution (*albeit* from small numbers in sub-groups).
- In regards to centre effects, the sponsor reports no treatment-by-country treatment effect. The evaluator is concerned by the numbers of centres and countries used in selecting its study subjects (especially the lack of involvement of Western European countries). These numbers may reflect the difficulty in finding suitable subjects for the adolescent age group. However, Romania for instance, in Study PSZ-3001, had one centre, yet recruited ten subjects (all of much higher PANSS total score baselines than other participating countries), whereas the ratio was more like one centre for every three subjects in the US. Indeed, all countries recruited relatively more subjects than the US. This trend was also noted in Study PSZ-3002. This raises an issue over the selection of subjects in terms of assessment and diagnosis of schizophrenia *per se*.

Heterogeneity in the population base is demonstrated by the wide distribution of baseline PANSS total scores among the participating constituent countries in both PSZ-3001 and PSZ-3002. In PSZ-3001, a large decrease in PANSS total score for the placebo group was evident in US subjects. The sponsor claims this effect was not statistically significant as a baseline treatment-by-country category interaction and refers to a similar response in an olanzapine study. No further explanation or supporting data is provided, particularly for paliperidone in adults or risperidone in adolescents. Dismissing this finding as an anomaly of the US population effectively negates the generalisability of US research to the Australian environment. The apparent “lack of placebo effect” in many participating countries in PSZ-3001 is of grave concern and suggests inappropriate selection of subjects and/or errors in applying diagnostic assessment to subjects.

- The plausibility of the hypothesis that paliperidone ER improves schizophrenia symptoms in adolescents with established disease is medically plausible.

In conclusion, the submitted data does not provide exceptionally compelling evidence to support the application for the extension of indication.

Safety

Studies providing evaluable safety data

The submission included a comprehensive Summary of Clinical Safety (SCS), which assessed the safety of 339 subjects from one completed 6 week, double-blind, placebo-controlled Phase III study (PSZ-3001), one completed Phase I PK study (PSZ-1001), and 6 month safety data from one ongoing, open-label, long-term extension study (PSZ-3002). For the ongoing Phase III, randomised, double-blind, active-controlled, parallel-group, multicentre study (PSZ-3003), deaths and serious AEs (SAEs) through a cut-off date of 8 July 2010 are included. Studies PSZ-3001 and PSZ-3002 assessed safety as a primary outcome, although only descriptive statistics are provided for each of these studies.

Patient exposure

Of the 314 adolescent subjects with schizophrenia who received at least one dose of paliperidone ER (comprising 282 subjects in PSZ-3002 and 32 subjects in PSZ-3001, who did not enter the open-label study), the mean duration of exposure was 209.7 days. One hundred and sixty nine subjects received paliperidone for 6 months (180 days) or more as of 30 July 2009.

A further 25 subjects (aged 10-17 years) with schizophrenia, schizoaffective disorder or schizophreniform disorder received up to eight doses of paliperidone in Study PSZ-1001. All but one subject received multiple-dose administration of paliperidone.

Evaluator’s overall summary and conclusion on clinical safety

The results of the Phase III studies, PSZ-3001 and PSZ-3002, were not pooled because of differences in their design and duration. However, many findings were similar across the studies and generally consistent to those found in paliperidone use in adults with schizophrenia and similar conditions, as well as those with risperidone and quetiapine in adolescents. However, higher incidences of dystonia, hyperkinesia, tremor and Parkinsonism were found in adolescents compared to adults receiving paliperidone. Furthermore, the incident rate of EPS related AEs appears to be related to duration of exposure to paliperidone. In PSZ-1001, subjects were exposed for up to 9 days and experienced 20% EPS (comparable to the rate found in adult populations receiving paliperidone in longer-term studies). In the 6 week efficacy study this rate rose to 31%

(46/150) and in the 6 month safety study the rate rose to 40% (114/282). However, these rates are based on the number of subjects experiencing at least one AE, not the number of events *per se*.

Study PSZ-3001 revealed an apparent dose related trend in all categories of treatment emergent adverse events (TEAEs). This study also revealed an apparent dose relationship for the incidence of somnolence, akathisia, tremor, dystonia and tachycardia, as well as an apparent dose-related trend in the incidence of EPS (supported by increased use of anti-EPS medication). These have implications for dosing (see under *First Round Clinical Summary and Conclusions Benefit risk assessment*, below).

In Study PSZ-3002, most of the serious TEAEs and those that led to study discontinuation occurred in the newly exposed groups to study medication, that is, the Placebo/Pali and Pali (No DB)/Pali groups. Higher incidences of many TEAEs, for example, akathisia and potential-suicide-related AEs, occurred in the Pali (No DB)/Pali group (8%), which may reflect a more severe patient population (supported by baseline PANSS total scores and CGI-S scores).

Whereas laboratory findings for haematology, urinalysis, endocrine, renal, hepatic, thyroid and electrolytes were generally unaffected by paliperidone treatment, prolactin levels rose in every study, as predicted by its effect on dopamine D2 receptors. Study PSZ-3001 showed dose-related increases in prolactin levels in males and females. Only female subjects had the potential for prolactin related AEs. In the open-label safety Study PSZ-3002, the highest prolactin levels were achieved in the Placebo/Pali and Pali (No DB)/Pali groups, that is, those more recently exposed to study drug. Again, female subjects experienced much more potentially prolactin-related AEs (14.7%) than their male counterparts (2.4%), with 7.4% incidence overall. Prolactin levels for Seroquel (quetiapine) in adolescents with schizophrenia were greater than 10% overall and higher than levels seen in adults (see Seroquel PI). Hyperprolactinemia may have long-term effects on pubertal development and sexual maturation.

No effect on growth and sexual maturation was demonstrated in this submission based on Tanner staging.⁵ However, such an effect cannot be ruled out without more long-term data. The findings for reduced insulin like growth factor (IGF) and IGF binding protein-3 (IGFBP-3) levels in these studies suggest a possible effect on growth hormone. Further study is required. The effect of paliperidone on testosterone levels in males has not yet been established.

No consistent effect on QT interval⁶ or vital sign parameters was demonstrated in these studies, other than an effect on heart rate, which is predicted based on the pharmacology of paliperidone. Study PSZ-3001 showed dose related increases in standing and supine pulse rate, particularly in 15-17 year olds. Study PSZ-3002 supports this finding in this age-group and the effects have been observed in adult studies as well as in olanzapine in adolescents (see Zyprexa PI).

Orthostatic hypotension occurred primarily in the Pali (No DB)/Pali group in Study PSZ-3002 (10%) and 12% incidence in Study PSZ-1001. Hence, this needs to be monitored in patients receiving paliperidone, especially with initial dose titration or when used concurrently with anti-hypertensive medication.

A relationship to baseline bodyweight category (< 51 kg or ≥ 51 kg) was demonstrated. Study PSZ-3001 revealed an apparent dose-response relationship in TEAE incidence for those weighing at least 51 kg, which represented a majority of the study population.

⁵ The Tanner Scale is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics.

⁶ QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

Incidence of TEAEs was generally higher in heavier subjects except for the High group in Study PSZ-3001 and the low weight subjects in the Pali (No DB)/Pali group in Study PSZ-3002 (high incidence of akathisia). No analysis of baseline bodyweight by gender or age-group was presented here, so the effect of baseline bodyweight could not be fully ascertained.

No new, unexpected serious TEAEs or death occurred in any study presented here, but the effect of study medication on lipid parameters is of particular concern as these appear more marked in adolescents than adults. The metabolic analysis was inconclusive and further study is required to quantify the magnitude of the risk of developing metabolic syndrome, and its sequelae. However, the findings in this submission support a trend towards developing metabolic syndrome (and increased cardiovascular risk). In particular:

1. Study PSZ-3001 demonstrated dose-related changes in weight, BMI and waist circumference. Such trends continued into the open-label study, when weight gain of at least 7% occurred in 41% of the Placebo/Pali group and 38% of the Pali (DB)/Pali group from double-blind baseline (compared to 33% Total from the open-label baseline). The biggest changes that occurred from the open-label baseline were in the newly exposed Placebo/Pali and Pali (No DB)/Pali groups, as expected from new exposure to study medication at higher doses than recommended. These findings are comparable to quetiapine in adolescents in an open-label 26 week study, which revealed 45% of subjects had at least a 7% weight gain (see Seroquel PI). No values of percent weight-gain at the 15% and 25% levels are presented in this submission for paliperidone in adolescents.
2. Whereas total cholesterol rose by 8.3% from baseline to endpoint in the 6 week study, PSZ-3001, with a tendency towards hypertriglyceridemia, the findings in the open-label study at endpoint revealed in excess of 20% changes from normal baseline in many lipid parameters. This is consistent with risperidone in which “*significant rises in triglycerides*” were noted (see Risperdal PI).
3. Homeostasis model assessment (HOMA) analysis revealed all groups in studies PSZ-3001 and PSZ-3002 had pre-existing glucose resistance at baseline with accompanying increased beta-cell function, but no consistent changes occurred between the groups from baseline to their respective endpoints. However, in Study PSZ-3002, all groups had a shift from baseline fasting glucose to high glucose at endpoint, suggesting the potential to develop hyperglycaemia.

Differences in incidences of TEAEs between 12-14 year olds and 15-17 year olds may be due to the small numbers of the younger age-group that participated in the Phase III studies. While both age groups showed an apparent dose-response relationship for somnolence and akathisia in Study PSZ-3001, the latter AE was especially high in 12-14 year-olds (28.6%). Indeed, younger subjects in the High dose group had 100% incidence of TEAEs. Furthermore, 12-14 year olds in Study PSZ-3002 had higher incidences of TEAEs in the new exposure to study medication, Placebo/Pali and Pali (No DB)/Pali groups, especially in regards to akathisia. No analysis of age by gender or baseline bodyweight was presented here so the effect of age could not be fully ascertained. Based on these findings, dosing in 12-14 year-olds cannot be recommended.

Females generally showed higher incidences of TEAEs (especially somnolence and akathisia) than males in Study PSZ-3001 (except the High group) and in the Placebo/Pali and Pali (No DB)/Pali groups in Study PSZ-3002. No analysis of gender by age group or baseline bodyweight was presented here so the effect of gender could not be fully ascertained.

The information provided in this submission regarding an effect of racial origin on incidence of TEAEs was inconclusive. In terms of US versus non-US subjects, the percentage of TEAEs in all treatment groups, irrespective of the study, was much higher in US subjects. Furthermore, no US subject was diagnosed with akathisia. This raises the question of whether there are inherent differences between those selected to participate in the studies from the US and those not in the US, or indeed, there are major cultural differences in the experience of and diagnosis of schizophrenia.

Study PSZ-3002 protocol amendment INT-2 in June 2008, that is, one year after study commencement, deleted the following phrase: *“As there is specific interest in the long-term tolerability of the higher doses investigators will be encouraged to titrate the dose to the maximum tolerable level”*. The mode dose (that is, the dose most frequently taken) data provided appear to reflect this approach, whereby most subjects exceeded the recommended starting dose of 3 mg. The high incidence of weight gain, prolactin levels, lipid parameters and the higher incidence of EPS-related AEs compared with paliperidone in adults in the open-label study lend further support to a trend towards supra-maximal dosing in the clinical trials cited in this application.

List of questions

Pharmacokinetics

1. What is the volume of distribution, elimination half-life and single-dose PK parameters for paliperidone in Study PSZ-1001?
2. In the population PK analysis, why was body weight used as a covariate on clearance when the adult model used for paliperidone identified lean body mass as a significant predictor of apparent oral clearance of paliperidone? The supporting reference by Reigner BG and Welker cites lean body weight not body weight *per se*.
3. In the efficacy study, PSZ-3001, secondary objectives included an exploration of the PK of paliperidone and relationships between its PK and results of efficacy parameters (PANSS scores) as well as safety parameters of interest. PK data from Study PSZ-3001 were used in the PK modelling for paliperidone use in adolescents but no PK information is provided. Where are the PK data for Study PSZ-3001 located in this submission?

Efficacy: 6 week pivotal efficacy study PSZ-3001

1. What proportion of subjects in each treatment group had a first diagnosis of schizophrenia at age less than 12 years?
2. What proportion of subjects had a family history of schizophrenia?
3. How was the initial diagnosis of schizophrenia established for subjects accepted into this study?
4. What community supports and non-pharmacological interventions did subjects receive during this study?
5. What are the mean, median and range of pre-study hospital admissions for psychosis (by treatment group) for subjects enrolled into this study?

Efficacy: 6 month open-label safety study PSZ-3002

1. Were subjects who entered the open-label study from double-blind treatment all commenced on 6 mg paliperidone, irrespective of their final dose of double-blind active treatment (and body-weight category)?

2. What proportion of subjects enrolled in the 6 month open-label study withdrew from the double-blind study (by double-blind treatment group)?
3. To evaluate study biases, were the investigators and/or subjects in this study aware of the concurrent open-label safety study, PSZ-3002, during the conduct of PSZ-3001? In particular, were investigators and/or subjects aware of the inclusion criterion of at least 21 days participation in Study PSZ-3001 prior to entry into PSZ-3002?
4. Subjects who entered the open-label study after receiving active treatment in the efficacy study were analysed as a single group. This is a protocol deviation but no further information is provided. What proportion of subjects from the Low, Medium and High groups in PSZ-3001 entered the open-label study and what are their baseline characteristics and PANSS total scores at open-label end-point?

Safety

1. A table in the overview of clinical data in the dossier does not include the incidence rates for individual AEs. What are the individual incidence rates (presented in tabulated format) for the AEs displayed in this table?

First round clinical summary and conclusions

First round benefit risk assessment

First round assessment of benefits

The following benefits for administering paliperidone in an adolescent population with schizophrenia have been identified:

- Paliperidone appears to have some benefit in terms of efficacy for the 15-17 year age-group at a dose of 3 mg for those weighing under 51 kg, and a daily dose of 6 mg for those weighing at least 51 kg.
- Currently there is no Australian approved product for 12 year-olds with schizophrenia to receive an atypical antipsychotic (Seroquel is approved for 13-17 years, inclusive).
- Approval of Invega allows medical practitioners another choice of atypical antipsychotic agent in an adolescent population with diagnosed schizophrenia.
- From the submitted studies (and adult studies in paliperidone), most TEAEs tended to occur at higher dosages (9-12 mg/day). Restricting the dosage to a maximum of 6 mg/day for the heavier subjects may help to minimise some observed AEs (especially extrapyramidal AEs).
- The sponsor has recommended in its PI that all adolescents be commenced on a dose of 3 mg/day. For the heavier patients, this dosage may be sub-optimal but it vies on the side of caution, which is to be commended.
- Dose titration of paliperidone appears less complex than dose titration with Seroquel (quetiapine).
- The effects of paliperidone on weight gain are significant but may appear more favourable than quetiapine in adolescents with schizophrenia.
- In the sponsor's *Paediatric Investigation Plan*, paliperidone 3 mg/day in adults is comparable to a 1 mg/day risperidone dose, which is not considered an effective dose in the treatment of schizophrenia. Hence, paliperidone may offer some benefit over risperidone.

- The open-label study is ongoing and hence two years' data are expected to be available in late 2013. There is a lack of long-term safety data for antipsychotics in adolescents and so this new information will assist in understanding the longer-term effects of paliperidone in relation to maturational, growth, behavioural and cognitive development, and also greater understanding of the metabolic risk this agent poses.
- The results of the on-going Phase III study, PSZ-3003, which is a comparator study of paliperidone versus aripiprazole, will be available in late 2013 too. It is hoped the study findings will help establish the role of paliperidone in the acute and maintenance phase of schizophrenia and help to further quantify the metabolic risk of paliperidone (especially as aripiprazole is claimed to have much less effect on weight gain than most other approved atypical antipsychotic agents).
- No deaths were reported in all paliperidone Phase I and Phase III studies at cut-off point.

First round assessment of risks

The risks of administering paliperidone to adolescents (12-17 years, inclusive) with schizophrenia are considerable:

- Short term efficacy (6 weeks) was only established in a small group of subjects in one treatment arm (Medium group in the pivotal efficacy study, representing 48 subjects). Most of these subjects were in the 15-17 year age-group.
- The US subjects (which more closely align with the Australian population) failed to show any significant effect in efficacy or much benefit after 6 months treatment with open-label paliperidone.
- There is no PK data in children and adolescents to support a 3 mg dosage regimen (the recommended starting dose in the Invega PI).
- The effects of toxicity on age were much more apparent than efficacy, with those younger subjects having generally higher incidences of TEAEs than their older peers. Study PSZ-3001 demonstrated dose-response relationships with akathisia and somnolence that were markedly higher in the High dose group in 12-14 year-olds. In the open-label study, 12-14 year-olds newly exposed to study medication (that is, those in groups Placebo/Pali and Pali (No DB)/Pali), had much higher incidences of TEAEs (especially akathisia in the latter group) than their older peers. On this basis, the younger age-group appear to be more sensitive to developing TEAEs (especially EPS related adverse events) than the 15-17 year age-group.
- Dosage reductions are recommended in all forms of renal dysfunction in adults but there are no comparative data in children or adolescents taking paliperidone. It is expected that dosage reduction will be required in any patient with a creatinine clearance below 80 mL/min.
- The long term safety data is limited in regards to the effects of paliperidone upon growth, maturational, behavioural and cognitive development. Such effects cannot be ruled out without further study.
- The findings for reduced IGF and IGFBP-3 levels in these studies suggest a possible effect on growth hormone and its sequelae. Further study is required. Similarly, the effect of paliperidone on endocrine function, testosterone levels in males in particular, has not yet been established.
- In Study PSZ-3002, 7.4% of subjects demonstrated markedly raised serum prolactin levels (females much greater than males). While the effect of paliperidone is predicted from its pharmacological effects on dopamine D2 receptors, such raised levels in an

adolescent population are of concern at a time of major maturational, behavioural and cognitive development.

- The raised cholesterol fractions and triglycerides in the Phase III studies are a concern in relation to the risk of developing metabolic syndrome. The lipid results found in adolescents taking paliperidone appear worse than in adults.
- The effects on weight gain and metabolism in adolescents, including the risk of developing metabolic syndrome have not been studied over a prolonged period. However, the findings in this submission are of concern. Weight gain of at least 7% from study baseline to endpoint in the open-label study of 33% is of particular concern, especially when this level rises to 39% if the results of the double-blind baseline are taken into consideration. These findings are similar to those found in quetiapine. The sponsor does not think the findings in relation to weight gain are clinically significant. The sponsor argues the changes relate to normal changes in growth and development by using standardised normative data derived from a US population. Given the findings in terms of efficacy and toxicity in the US subjects and the diverse range of subjects from other countries (particularly Asia), the use of US normative data seems an inappropriate measure and downplays the real effect/risk of paliperidone on weight gain.
- In terms of hyperglycaemia, all groups in Study PSZ-3002 had a shift from baseline fasting glucose to high glucose at endpoint, suggesting the potential to develop hyperglycaemia. Given epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related AEs in patients treated with atypical antipsychotics, monitoring is recommended.
- The Phase III studies demonstrated a treatment-emergent effect on raised pulse rate (supine and standing). This was particularly seen in the 15-17 year age group (with a dose-response relationship) and is consistent with this finding in adults taking paliperidone and adolescents taking olanzapine. The significance of this effect has not been determined.
- Females tended to have higher incidences of TEAEs than their male counterparts, especially somnolence, headache, akathisia and prolactin levels. From the Invega PI, adult females are reported to have a 19% reduction in apparent clearance compared to males. The higher incidences in some observed TEAEs in the Phase III studies lend support to lower dosage regimens in females and hence greater risk to females should dose modification not ensue.
- Study PSZ-3002 dosed according to clinical response and tolerability of study medication rather than a weight-based dosing schedule (as used in Study PSZ-3001). The sponsor asserts that as most TEAEs were found in heavier subjects, no weight-based dosage schedule is required. While most TEAEs were experienced in heavier subjects (which accounted for a majority of participants in the Phase III studies) there were exceptions. In particular, those weighing <51kg in the High group in Study PSZ-3001 had a markedly higher incident rate than the other groups. Furthermore, higher incidence rates of akathisia were found in the low-weight subjects in the Pali (No DB)/Pali and Pali (DB)/Pali groups in Study PSZ-3002. Therefore, low-weight subjects may be more at risk should no weight-based dosing schedule be employed.
- The Phase III studies did not demonstrate appreciable changes of study drug on QT indices but such an effect cannot be discounted in the use of antipsychotics, especially in subjects with a history of cardiac arrhythmias, congenital long QT syndrome or those subjects taking concomitant medications that prolong the QT interval.
- Six subjects in Study PSZ-3002 were categorised under “suicidal behaviour”, which included two suicide attempts. All of these cases came from the treatment group Pali

(No DB)/Pali. Five additional indeterminate cases were also recorded from this group. This treatment group was recruited independently from the pivotal efficacy (double-blind) study and formed a more severely unwell population than those entering from the double-blind study (based on PANSS total score and CGI-S score). Both Phase III studies had similar entry criteria (including a Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children Present and Lifetime version (K-SADS-PL)⁷ diagnostic interview to assess suicidality and a requirement to have a score of ≤ 2 for each item). This finding highlights the need for vigilance for suicidal and self-harming behaviours in an adolescent population.

- Paliperidone has been demonstrated in the acute phase treatment of schizophrenia in adolescents only in one treatment arm and not in first episode presentations. Furthermore, maintenance of efficacy has not been demonstrated in the open-label study, or relapse prevention. Administering paliperidone beyond established acute episodes of schizophrenia potentially places subjects, many of whom are vulnerable, at risk of unwanted and unnecessary side-effects.
- Adolescents with schizophrenia taking paliperidone have higher rates of some AEs than adults. This was particularly evident in relation to EPS-related AEs (especially akathisia and Parkinsonism). No adolescent subject taking paliperidone had established tardive dyskinesia but, given a weak association between the development of Parkinsonism and developing tardive dyskinesia, as well as the propensity of antipsychotic agents to develop this condition, the risk of administering paliperidone (especially at doses exceeding 6 mg/day) need to be carefully weighed.
- Although effects on reduced thyroid function, blood dyscrasias (leukopenia, thrombocytopenia and agranulocytosis in particular), seizures, neuroleptic malignant syndrome, body temperature dysregulation, and gastro-intestinal obstruction have not been identified with paliperidone in adolescents, the risk remains in place for all antipsychotic agents and need to be factored into a risk-benefit assessment process.
- Unlike adult data that suggests no dose-response relationship in TEAEs below 6 mg/day, PSZ-3001 has demonstrated this does occur in adolescents, suggesting a higher likelihood of toxicity in this population (particularly the younger, lighter subjects).
- A comparison of pre- and post-market AEs for paediatric paliperidone ER as of two years ago, suggests higher rates of EPS-related TEAEs, weight gain and dyslipidaemia in the Phase III clinical trials for the target population. Caution needs to be exercised in comparing post-marketing data to controlled trials.

First round assessment of benefit-risk balance

The benefit-risk balance of paliperidone ER, given the proposed extension of indication, is not favourable. Only one treatment arm (the Medium group), representing 48 subjects, demonstrated clinical efficacy over the 6 week study period. Only 16 of these subjects were in the 12-14 year age-group, with no demonstrated efficacy in this sub-population. Considering the net mean reduction in PANSS total score was only 9.4 points, this result translates into a modest clinical benefit.

Efficacy findings in the open-label study, PSZ-3002, have limited usefulness, given the study limitations. The findings did not provide convincing evidence of efficacy over the 6 months' study duration and therefore maintenance treatment with paliperidone ER cannot be recommended (this was not a study objective).

⁷ The K-SADS-PL is designed to obtain severity ratings of symptomatology, and assess current and lifetime history of several psychiatric disorders.

In contrast to efficacy, significant dose-related toxicity has been demonstrated particularly in relation to extrapyramidal-related TEAEs. The 12-14 year old age-group is at particular risk of developing akathisia. The incidence of many TEAEs appeared higher during the open-label study, even allowing for higher dosing than in the pivotal study. In the absence of TEAE-specific prevalence data, it is difficult to determine the risk of developing a particular AE. However, most of the observed TEAEs were expected as a class effect of neuroleptic agents.

The risk of developing metabolic syndrome and cardiovascular disease (as evidenced by significant weight gain and adverse lipid fractions in studies PSZ-3001 and PSZ-3002) by giving paliperidone to adolescents is too great when balanced against a possible short-term reduction in symptoms.

When the results are available for the entire 2 year safety study, PSZ-3002, as well as the ongoing Phase III safety and efficacy comparative study, PSZ-3003, the risk to the patient will become much clearer. As the application currently stands, given the lack of demonstrable efficacy beyond 6 mg/day and the higher AE profile for doses exceeding 6 mg/day (especially EPS-related and metabolic-related AEs), the evaluator cannot recommend this product for the proposed indication. Invega currently poses too great a risk to adolescents with schizophrenia for the expected benefit.

The evaluator would recommend rejection of the proposed extension of indications for paliperidone use in adolescents with schizophrenia, if such indication relied solely on the submitted PK data. Even though the sponsor failed to provide a dose-ranging study in adolescents or demonstrate similar PK to adults at doses below 6 mg/day, the risk to the adolescent subject, provided they do not have renal impairment, is not regarded as high by this evaluator. Adult data clearly demonstrates consistency in PK parameters from 3-12 mg/day. Furthermore, based on PK data from risperidone in children and adolescents, the evaluator is confident the risk of administering paliperidone ER to the 15-17 year age group (representing 80% of the study population) is acceptable, especially given the lower expected toxicity for a 3mg/day dosing regimen in this age-group.

The benefit-risk balance of paliperidone ER is unfavourable given the proposed usage, but would become favourable if the changes recommended below are adopted.

First round recommendation regarding authorisation

The evaluator believes the clinical data provided in this submission does not support the safe and effective use of paliperidone in an adolescent population. On this basis, rejection of the proposed extension of indication of paliperidone to adolescents (12-17 years, inclusive) in schizophrenia is recommended.

Furthermore, should the application for extension of indications not continue to the next Milestone, this evaluator recommends the submitted safety-related data in relation to children and adolescents is still included in the PI.

The benefit-risk balance of paliperidone ER is unfavourable given the proposed usage, but would become favourable if the following recommended changes are adopted:

1. Approval is restricted to acute treatment only (in established schizophrenia);
2. Approval is restricted to the 15-17 year age group (as currently licensed for risperidone, of which paliperidone is the major metabolite);
3. The dosage range is restricted to 3-6 mg once daily, that is, a maximum daily dose of 6 mg. If higher doses are approved, then the evaluator recommends a dosing-based schedule based on bodyweight as per the pivotal study; that is, those weighing less than 51 kg should be given a lower dose than those weighing at least 51 kg.

Sponsor's response to the list of questions

The TGA clinical evaluator's summary of the sponsor's responses to the questions raised above are included under *Second Round Clinical Evaluation Report*, below.

Second round clinical evaluation report

Evaluation of responses to clinical questions

Questions on pharmacokinetics

Question 1

Sponsor's response

The sponsor confirmed that a sparse sampling approach was used in Study PSZ-1001, and so single-dose PK parameters were not estimated through non-compartmental analysis. The basis of this approach was to minimise blood sampling of participating subjects. Furthermore, because of the limited sample size and sparse sampling approach, the PSZ-1001 PK data alone were not considered sufficient to precisely estimate the volume of distribution (V) as a proportion of bioavailability (F) (V/F) and elimination half-life. Instead, the sponsor applied pop-PK modelling and simulation techniques to the combined sparse paliperidone plasma concentration data from PSZ-1001 and the pivotal efficacy Study PSZ-3001. Using this approach, the sponsor showed that the primary PK parameters (apparent clearance as a proportion of bioavailability (Cl/F) and V/F), which are independent of the dosing regimen (single versus multiple dose), in adolescents were comparable to adults.

Detailed information was presented in the pop-PK report. A total apparent V/F of 442 L was estimated (that is, the sum of central and peripheral volumes of distribution [V₂+V₃, 198 L+244 L]) and was found to be similar to the estimate reported for adults (487 L). Because the adolescent pop-PK model was based on adolescent and adult data, individual estimates for V₂ and V₃ confirm they are similar for the presented subgroups. Similarly, the Cl/F was estimated for adolescents as 12.5 L/h, similar to that reported for adults (13.8 L/h). Given that Cl/F and V/F are similar in adolescents and adults, the terminal half-life is also similar, i.e. approximately one day (that is, 24 hours).

Clinical comment on response

The sponsor's response to this question is satisfactory. Given one of the study objectives of PSZ-1001 was to characterise the PK of paliperidone after single dose administration in adolescents and, in particular, determine the volume of distribution and elimination half-life, this study failed to achieve these outcomes in a stand-alone Phase I PK study. It would appear the study design, particularly employing a sparse sampling method, was unlikely to achieve the study objectives. The PK results in adolescents appear more reliant on the pop-PK analysis than a specific PK study and are therefore only an approximation to the adolescent population.

The PK findings between adolescents and adults appear comparable using the pop-PK analysis, and when the multiple-dose data in PSZ-1001 was normalised to 6 mg/day. Given 80% of PSZ-1001 subjects were over 15 years of age and over 51 kg in baseline bodyweight, that is, approximating an adult population, the comparative PK data between adolescents and adults is not unexpected. However, in the context of the PI recommendation of a 3 mg once daily paliperidone dose, the submitted data do not support such a dosage regimen. There is no comparison of the PK of the proposed 3 mg daily dose in adolescents with the 6 mg dose in adults. While extrapolation of the PK data to the proposed dosage regimen, based on adult paliperidone dose-proportionality studies and adolescent studies in risperidone, has some merit, this needs to be weighed up against

the potential risk in dosing subjects. For instance, it appears 6 mg daily paliperidone leads to higher exposure, and 3 mg daily to lower exposure, in children and adolescents compared with adults.

Question 2

Sponsor's response

The sponsor provided an explanation why the pop-PK model developed for adolescents used bodyweight as a covariate instead of lean body mass, as used in the adult pop-PK model. The sponsor used bodyweight as subjects' dose adjustments were made on bodyweight recommendations. Furthermore, the sponsor substantiated its claim that lean body mass and bodyweight were well correlated and therefore equally useful as covariates.

Clinical comment on response

The sponsor's response is satisfactory.

Question 3

Sponsor's response

The sponsor confirmed the PK data for the pivotal efficacy Study PSZ-3001 were not submitted in its application. Similar to Study PSZ-1001, the efficacy study used a sparse sampling approach to PK analysis. The study design did not allow performance of a non-compartmental analysis. The sponsor provided individual data as part of this response for evaluation, and made reference to the pop-PK analysis report included in the dossier for the results (discussed above in question 1).

Clinical comment on response

The sponsor's response is satisfactory and confirms the absence of non-compartmental PK data analysis in this submission.

Questions on efficacy Study PSZ-3001

Question 1

Sponsor's response

The proportion of subjects with a first diagnosis of schizophrenia before the age of 12 years in the pivotal efficacy Study PSZ-3001 was provided. Overall, 22% (n=44) of subjects had a first diagnosis before the age of 12 years, ranging from 14% in the placebo group to 28% in the High group.

The distribution by age of first diagnosis of schizophrenia was also provided. The youngest age of first diagnosis was three years old (one subject in the High treatment group).

Clinical comment on response

The sponsor's data is satisfactory. Given the difficulty in establishing a diagnosis of schizophrenia in children, especially under 12 years of age, this evaluator has concerns over the appropriate diagnosis of (and recruitment of) children given a definitive diagnosis of schizophrenia from as young as three years of age. No data on recruitment by age and country was submitted in this application (or requested by the TGA) so no comment can be made as to where younger subjects were recruited.

While accepting the sponsor recruited subjects who satisfied the DSM-IV criteria and had confirmed the diagnosis using the K-SADS-PL, these measures are not without limitations. Diagnosis is made on the basis of a set of subjective behaviours and perceptions rather than rigorous scientific objective measures.

Question 2

Sponsor's response

The sponsor confirmed data on family history of schizophrenia was not collected on its participating subjects in the pivotal efficacy study and is therefore not available for evaluation. The sponsor stated *"While early-onset patients are more likely to have a family history of the disease [schizophrenia], there is no clear evidence that family history affects response to medication"*.

Clinical comment on response

While accepting the explanation the sponsor provided, family history of schizophrenia (and mental illness per se) in first degree relatives, may have provided more confidence in the correct diagnosis of this very young population.

Question 3

Sponsor's response

The sponsor referred to the study's inclusion criteria. The treating psychiatrist established a diagnosis of schizophrenia based on DSM-IV criteria over one year prior to study entry, based on medical histories obtained from the subject and family. Diagnosis was confirmed using the K-SADS-PL.

Clinical comment on response

The sponsor did not specifically address the question *"How was the initial diagnosis of schizophrenia established for subjects accepted into this study?"* This question may appear ambiguous. Given over 40% of participants (see Question 5, below) with an established first diagnosis of schizophrenia had never been hospitalised, this evaluator wanted to establish how participants had been diagnosed in the community and by whom. A large proportion of subjects diagnosed in an outpatient setting may be unreasonably high, at least compared to the Australian environment, which again challenges the accuracy of diagnosis of study participants, and generalisability.

Given the sponsor's information, the diagnosis of schizophrenia based on histories taken from family and subjects over the preceding year again challenges the accuracy of diagnosis of study participants. One would have more confidence if a subject's case manager and other psychiatric reports were used in the establishment of a diagnosis. Of course, this information may have been known to the treating psychiatrist but it is unclear from the answer provided.

Question 4

Sponsor's response

The sponsor confirmed the subject could not receive insight-oriented psychotherapy or cognitive behavioural therapy during the course of the pivotal efficacy study. However, subjects could receive other non-pharmacological treatment (inpatient or outpatient) or community support during the course of the study. The preference was that any treatment of this kind continued unchanged from prior to study entry through the screening and treatment period of the study.

Clinical comment on response

The sponsor's response is satisfactory.

Question 5

Sponsor's response

The sponsor provided tabulated data on the number of prior hospitalisations for psychosis for subjects in each treatment group. Forty-one percent of all subjects had never had a previous admission for psychosis and 28% had only had one admission.

The sponsor also provided tabulated data for the duration of the most recent hospitalisation prior to the double-blind treatment phase and the time since last acute psychotic symptom.

Clinical comment on response

The sponsor's response is satisfactory. All treatment groups in the pivotal efficacy study appeared well balanced in terms of prior hospitalisations, duration of the most recent hospitalisation prior to the double-blind treatment phase and the time since last acute psychotic symptom. Of note, 67% of subjects had had one or no previous admissions for psychosis.

Questions on efficacy Study PSZ-3002

Question 1

Sponsor's response

The sponsor confirmed all subjects who entered Study PSZ-3002 after PSZ-3001 initially received paliperidone ER 6 mg once daily, irrespective of their final dose in PSZ-3001. The treatment blind was continued until PSZ-3001 was completed, even after subjects entered the open-label study. In PSZ-3002, the starting paliperidone ER dose of 6 mg could be changed after five days, depending on clinical symptoms or side effects.

Clinical comment on response

The sponsor's response is satisfactory. It was unclear from the submission whether every subject entering PSZ-3002 from PSZ-3001 was dosed at 6 mg once daily. The sponsor has clarified this to the evaluator's satisfaction. There is no information in this submission on when the study blind/analysis for PSZ-3002 was undertaken, and when the results of the least effective dose (that is, 3 mg/day) were disseminated to the participating centres. None of the latter was addressed in the questions. This has safety implications, as the mode dose data indicates supra-maximal dosing of subjects as evidenced by the few numbers of subjects who received 3 mg/day, as well as some AE high rates.

Question 2

Sponsor's response

The sponsor provided tabulated data of the study completion/withdrawal information of subjects who enrolled in the 6 month open-label Study PSZ-3002 from PSZ-3001. Subjects could enrol after participating in at least 21 days of PSZ-3001. The only reason subjects who withdrew early from PSZ-3001 could enter PSZ-3002 was lack of efficacy in the double-blind study.

The 34 subjects who withdrew from PSZ-3001 from lack of efficacy represent 85% of the total number of subjects who withdrew from lack of efficacy in this study. Hence, a majority of subjects withdrawing from lack of efficacy in PSZ-3001 entered the open-label study. The Placebo and Low treatment groups accounted for 85% of total withdrawals from lack of efficacy who entered the open-label study.

Clinical comment on response

The sponsor's response is satisfactory. It is evident that a high proportion of subjects who withdrew from PSZ-3001 entered the open-label study from lack of efficacy. It is also evident these withdrawals occurred after 21 days of double-blind treatment. No specific

details are provided by number of subject withdrawals from lack of efficacy per treatment week and by country (not requested as part of the TGA questions). The body of this report indicated most withdrawals from PSZ-3001 occurred in Ukrainian and Russian centres. The large proportion of study withdrawals in Week 4 (Days 22-29) and the high proportion of uptake of withdrawals into PSZ-3002 suggests investigator/selection bias has occurred (see Question 3, below).

Question 3

Sponsor's response

Investigators were aware of the need for at least 21 days treatment in PSZ-3001 before entry into PSZ-3002. The informed consent form for parents and guardians stated that there was an option of another study at the end of PSZ-3001. The wording of the consent form was as follows: "There is an extension (follow-up) study for you to continue to receive treatment with this study drug after your participation has ended." The consent form for parents and guardians did not mention the 21 day time period. The assent form for minor subjects did not mention the follow-up study.

Clinical comment on response

The sponsor's response is satisfactory. Although the effect cannot be quantified here, the role of investigator bias in selecting patients out of the pivotal efficacy study may have had a major influence on the final outcomes, in particular the lack of efficacy in the Low and High treatment arms. This is based on the fact investigators were fully aware of the open-label study running concurrently to the pivotal efficacy study, the criterion for at least 21 days completion of the pivotal study before recruitment into the open-label study and such a high proportion of study withdrawals (from lack of efficacy) in the pivotal study from Placebo and Low treatment groups into the open-label study. Subjects' parents and guardians were aware of the extension study and this too may have played a part in subjects possibly selecting themselves out of the pivotal study. For such a high proportion of subjects to withdraw from PSZ-3001 for lack of efficacy, and agree to paliperidone treatment seems unreasonably high to the evaluator.

Question 4

Sponsor's response

The sponsor provided tabulated data of the proportion of subjects in PSZ-3001 who entered the open-label study by double-blind treatment group. Overall, 78% (n = 156) of the double-blind subjects entered the open-label study and study treatment groups ranged from 76% to 80%.

Tabulated data on demographic and baseline characteristics of each treatment, as well as diagnosis and psychiatric history of those entering the open-label study were provided. Generally, the groups were well balanced and similar in all parameters compared to the entire PSZ-3001 study population.

Tabulated data were provided for PANSS total scores at open-label baseline and open-label end-point by double-blind treatment group. The Medium group had a much lower mean baseline PANSS total score compared to the Low and High groups (consistent with the greater efficacy demonstrated in the Medium group in the pivotal efficacy study). At open-label endpoint, the Medium group achieved far less reduction in mean PANSS total scores than those from the Low and High groups, reportedly due to the lower score at baseline in the Medium group.

Clinical comment on response

The sponsor's data is satisfactory. The sponsor did not clarify why the three active treatment arms in the double-blind pivotal efficacy study, PSZ-3001, were combined and analysed as a single group in the open-label study. Examination of the data and the 4.3

points mean reduction in PANSS total score at 6 months in the Medium group may explain this approach. While the baseline score for the Medium group was in the order of 10 points less than the other treatment arms and therefore represented less ill subjects, it was the only group in the pivotal efficacy study that demonstrated statistical separation compared to placebo. Taken at face value, this reduction of 4.3 points does not demonstrate continued efficacy of paliperidone. For reasons cited above under *Other efficacy study: PSZ-3002*, the evaluator does not consider study PSZ-3002 as pivotal and therefore these findings have limited usefulness in efficacy assessments.

Question on safety

Sponsor's response

The sponsor provided tabulated data for the incidence of adverse drug reactions reported by paliperidone ER-treated subjects in studies PSZ-3001 and PSZ-3002. This data relates to 314 subjects exposed to paliperidone. This data does not include data from PSZ-1001, the adolescent PK study.

Clinical comment on response

The sponsor's response is unsatisfactory. This question requested the sponsor provide data on the incidence of all AEs, irrespective of relationship to study treatment. The question may appear ambiguous. The basis of this request was to assist in the comparison of paliperidone in adolescents against paliperidone in adults, as well as competitor products. Such comparison has been partially made.

Second round benefit-risk assessment

Second round assessment of benefit

The clinical information submitted in the sponsor's response to TGA questions does not change the original assessment of benefits (see above under *First round clinical summary and conclusions*).

Second round assessment of risks

The clinical information submitted in the sponsor's response to TGA questions does not change the original assessment of risks (see above under *First round clinical summary and conclusions*).

Second round assessment of benefit-risk balance

The benefit-risk balance for paliperidone ER, given the proposed usage, is unfavourable. The clinical information submitted in the sponsor's response to TGA questions does not change the original unfavourable assessment of the benefit-risk balance (see above under *First round clinical summary and conclusions*).

Final recommendation regarding authorisation

It is recommended that the submission not be approved. The clinical information submitted in the sponsor's response to TGA questions does not change the original recommendation that the submission be rejected unless certain conditions are met, as outlined under *First round recommendation regarding authorisation*, above.⁸

The evaluator recommended several revisions be made to the draft PI and Consumer Medicine Information (CMI) documents, in the event this application is approved. Details of these recommendations are beyond the scope of this AusPAR.

⁸ A summary of the sponsor's response to the CER and recommendations is included in the Delegate's overview under *Overall Conclusion and Risk/Benefit Assessment - Risk-Benefit Analysis*, below.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) EU-RMP Invega and Xeplion version 1.0 issue date 23 August 2011 (plus addendum to EU-RMP Invega and Xeplion version 1.0 issue date 15 September 2011) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (please note for the purposes of this evaluation, safety concerns identified by the sponsor as specific to Xeplion have not been included):

Table 7. Ongoing safety concerns.

<p>Important identified risks</p>	<ul style="list-style-type: none"> • Hyperprolactinaemia and potentially prolactin related events • QT prolongation • Orthostatic hypotension • Extrapyrimal symptoms/tardive dyskinesia • Neuroleptic malignant syndrome • Diabetes mellitus and hyperglycaemia-related adverse events • Weight gain • Seizures • Somnolence • Priapism • Cerebrovascular accident • Venous thromboembolism • Leukopenia • Agranulocytosis • Thrombocytopenia • Rhabdomyolysis • Neonatal drug withdrawal syndrome • Elevated plasma concentrations in patients with renal disease
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<p>Important potential risks</p> <ul style="list-style-type: none"> • Safety concerns from non-clinical • Safety concerns from clinical trials and post-marketing 	<ul style="list-style-type: none"> • Carcinogenicity (pituitary adenomas; endocrine pancreas tumours; breast cancer) • Overall increased mortality in elderly patients with dementia • Cerebrovascular adverse events in elderly patients with dementia • Cognitive and motor impairment • Antiemetic effect • Body temperature dysregulation • Suicidality • Depression in patients with affective disorders • Increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy bodies • Gastrointestinal obstruction
<p>Important missing information</p>	<ul style="list-style-type: none"> • Use in haemodialysis patients • Use during pregnancy • Use in nursing mothers • Long-term safety in patients with schizoaffective disorder. • Long-term safety in paediatric patients with schizophrenia*

* 'Long-term safety in paediatric patients with schizophrenia' is specific to Australia and is dealt with separately in the addendum to the EU-RMP.

OPR reviewer comment:

Long-term paediatric safety associated with paliperidone has not been adequately studied and therefore it has been included as missing information in the RMP addendum. Schizophrenia is a chronic illness and it is likely that adolescents who demonstrate clinical improvement with paliperidone would be continued on it long-term. The absence of long-term paediatric safety data is considered a significant limitation of the RMP.

Additionally, the clinical evaluator noted that paliperidone has not been assessed in children or adolescents with impaired renal or hepatic function. If approved, it is recommended that '*Safety in children or adolescents with impaired renal or hepatic function*' should be added as important missing information. If added, the sponsor should address this safety concern with an appropriate pharmacovigilance and risk minimisation plan.

Otherwise the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns except for the following:

- Important potential risks 'Cerebrovascular accident/overall increased mortality in elderly patients with dementia' and 'cerebrovascular adverse events in elderly patients with dementia' will be evaluated in a post-authorisation safety trial.
- Important missing information 'Long-term safety in patients with schizoaffective disorder' is being evaluated with ongoing long term trials.

The above additional pharmacovigilance activities are not discussed in detail in this report as they do not relate to the proposed adolescent indication.

Of importance to this application, important missing information 'long-term safety in paediatric patients with schizophrenia' is subject to additional pharmacovigilance by two ongoing studies.

Routine pharmacovigilance activities are proposed for all ongoing safety concerns. The routine pharmacovigilance activities described are consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*. This is acceptable.

Risk minimisation activities

It is proposed that routine risk minimisation activities are sufficient for all ongoing safety concerns. The sponsor's rationale for routine risk minimisation is acceptable and product labelling is considered sufficient to mitigate the identified safety concerns associated with paliperidone.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP (and addendum) is applicable without modification in Australia unless so qualified:

Ongoing safety concerns

- If the expansion of the patient population is approved, 'Safety in children or adolescents with impaired renal or hepatic function' should be added as important missing information. It would be expected that the sponsor should address this safety concern with an appropriate pharmacovigilance and risk minimisation plan.

Pharmacovigilance plan

- The findings of both ongoing paediatric studies should be expeditiously reported to the TGA when available.
- Additional pharmacovigilance should be considered for the important identified risk 'hyperprolactinaemia and potentially prolactin related events'.

Risk minimisation plan

The evaluator recommended several revisions be made to the draft PI and CMI documents, in the event this application is approved. Details of these recommendations are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No data were submitted.

Nonclinical

Based on the submitted nonclinical data, and in view of the approved use of risperidone (the active, prodrug of paliperidone) in adolescents (and children > 5 years of age), there were no nonclinical objections to extending the population for paliperidone treatment to include adolescents of ages 12–17 years.

Supporting nonclinical data included a new oral repeat-dose toxicity study in juvenile rats, and previously evaluated oral repeat-dose toxicity studies with risperidone in juvenile rats and dogs.

The findings in the new (GLP) study with paliperidone were consistent with those previously observed with this compound in adult animals and with those of its active prodrug risperidone in juvenile and adult animals. These included anticipated CNS class effects such as sedation and ptosis, as well as elevations in prolactin levels; the consequences of these effects prevented determination of a NOAEL. In a subset of rats allocated to a recovery/reproductive phase, no overall effects on mating, conception or the fertility index were observed.

The findings in the new juvenile rat repeat dose toxicity study occurred at systemic exposures (plasma AUC) similar to or less than the exposure anticipated in adolescent patients receiving the maximal recommended dose (12 mg/day). The exposure margins would be greater at the clinical dose of 3 mg/day.

The nonclinical evaluator noted that the exposure to paliperidone achieved in a previous juvenile dog study with risperidone was up to 11 fold the maximal anticipated paliperidone exposure in adolescents receiving 12 mg/day.

Clinical

Pharmacology

A PK study and a pop-PK analysis were submitted. The PK study was a multicentre, multinational, open-label, multiple-dose, Phase I study in children and adolescents with schizophrenia, schizoaffective disorder or schizophreniform disorder. Twenty-five subjects (18 males, 7 females) were enrolled from 13 centres in 6 countries (Argentina, 2; Belgium, 2; Finland, 2; Korea, 5; US, 8). Their mean (standard deviation; SD) age was 14.6 years (\pm 2.18) with range 10-17 years. Median bodyweight was 64.5kg with range from 31 to 89 kg.

The study included 3 dosage groups each given approximately 0.086, 0.129, and 0.171 mg/kg/day paliperidone ER, corresponding to daily doses of 6, 9 and 12 mg, respectively, for a 70 kg adult on a mg/kg basis. The dose was determined based on the dosage group and the subject's body weight and was rounded to the nearest whole mg. Only dose normalised data to 6 mg were presented.

The pop-PK data set for model development comprised 162 subjects from the above Phase I study (n = 25; 18 males and 7 females) and PK data from a single Phase III efficacy study (PSZ-3001; n = 137; 87 males, 50 females) in which PK samples were taken on Days 15 and 36 of the 6 week study. No separate PK data from Study PSZ-3001 were presented in the submission. The adolescent PK data were compared with data from 153 adult subjects (110 males and 43 females) enrolled in 3 studies (PALIOROS-SCH-1011, R076477-PO1-1010 and R076477-RE1-1001). These adult studies were specifically chosen to facilitate the evaluation of dose, age and renal function.

Modelling was based on limited data with few low body weight adolescents included in the dataset. No adolescent subjects included in this analysis received the proposed initial dose of 3 mg daily. The analysis extrapolated results and assumed linear PK of paliperidone for

adolescents. Linearity has been demonstrated in adults. Although the predicted PK results for adolescents from this model were similar to those in adults, adolescents had reduced apparent clearance as well as higher plasma exposure in low weight subjects. A subset of the adult population (58 of 947 subjects) included in the simulations weighed less than 51 kg. Within the exposure range, the exposure values for adolescents and adults weighing less than 51 kg were more likely to be at the higher end of the distribution. The analysis predicted that a reduction of the dose from 6 mg to 3 mg in adolescents would result in a mean average plasma concentration that was approximately 50% and 38% lower in adolescents weighing at least 51 kg and less than 51 kg, respectively, than that obtained following a 6 mg dose in adults.

Efficacy

One pivotal efficacy and safety study was submitted. This was a double-blind, randomised, placebo-controlled, multicentre study conducted in an outpatient setting at 35 centres in Russia, India, Ukraine, Romania and the USA. Thirty subjects (15% of total) were enrolled in 9 centres in the USA. The study had 3 phases: a screening phase with a possible overlapping washout period, a 6 week double-blind treatment phase, and a 1 week follow-up visit for subjects who did not enter an optional, long-term, open-label safety study (R076477-PSZ-3002).

Subjects were randomised to 1 of 4 treatment groups: Placebo; paliperidone ER Low; paliperidone ER Medium; and paliperidone ER High corresponding to non-overlapping milligram per kilogram groups. The dose regimens for each group are shown in Table 5 of this AusPAR.

The major inclusion criteria were: age from 12-17 years inclusive; weight at least 29 kg; and diagnosis of schizophrenia according to the DSM-IV criteria at least one year before screening. The diagnosis was established using the K-SADS-PL, including all supplements. Subjects should have had at least one adequate treatment with an antipsychotic before participation in this study, must have had a PANSS total score between 60 and 120 inclusive at screening and baseline, must not have been a danger to themselves or others, and must have had family support available to be maintained as outpatients.

The primary efficacy variable was the change in the PANSS total score from baseline to the last post-randomisation assessment in the double-blind period of the study. Secondary efficacy variables included the change from baseline to end point in the CGI-S score, the CGAS score, the sleep VAS score, and the responder rate. Responders were defined as those subjects who showed a 20% or more reduction from baseline to end point in the PANSS total score.

Some 200 subjects were eligible for assessment of efficacy. Mean age of study subjects was 15.4 years, 59% were male, 61% were White and 24% were Asian. Mean baseline weight was 59.8 kg and 18% of subjects were aged from 12 to 14 years. Mean (range) age at diagnosis of schizophrenia was 12.9 years (3-16 years). Some 90% of subjects had previously received psychotropic medication. The most common antipsychotic medication previously taken was risperidone (36% ITT population). Data were provided on the percentage of subjects having taken specific psychotropic medications prior to the double-blind phase of the study. Baseline PANSS scores and efficacy results are shown in Table 8, below:

Table 8. Baseline PANSS scores and efficacy results: Study PSZ-3001.

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)
Baseline				
N	51	54	48	47
Mean (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Median (Range)	88.0 (65;118)	89.5 (70;118)	88.0 (69;119)	90.0 (63;119)
End Point				
N	51	54	48	47
Mean (SD)	82.7 (21.45)	81.9 (19.54)	73.3 (21.99)	77.7 (18.24)
Median (Range)	81.0 (36;129)	80.0 (45;121)	70.0 (33;126)	75.0 (49;135)
Change From Baseline				
N	51	54	48	47
Mean (SD)	-7.9 (20.15)	-9.8 (16.31)	-17.3 (14.33)	-13.8 (15.74)
Median (Range)	-5.0 (-59;28)	-5.5 (-52;23)	-16.0 (-53;19)	-12.0 (-62;30)
p value (minus Placebo) ^a		0.508	0.006	0.086
Diff. of LS Means (SE)		-2.1 (3.17)	-10.1 (3.27)	-6.6 (3.29)
95% CI ^b		(-8.36;4.16)	(-16.58;-3.67)	(-13.07;-0.09)

^a Based on ANCOVA model with treatment (Placebo, Paliperidone ER Low, Paliperidone ER Medium, Paliperidone ER High) and country as factors, and baseline value as a covariate. P values associated with closed testing procedure using Dunnett's test.

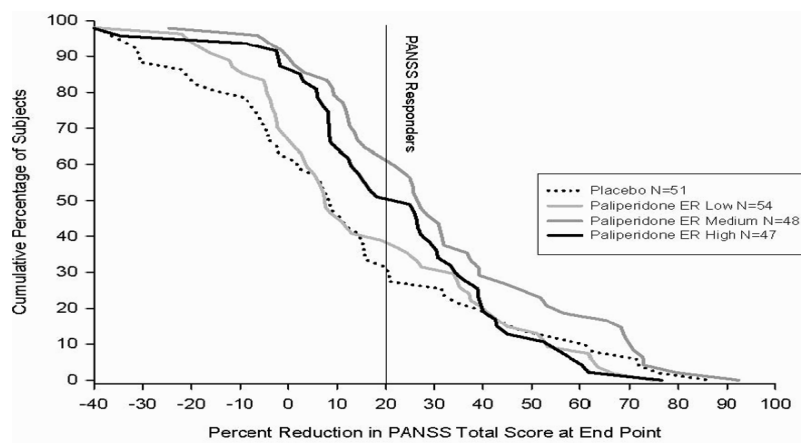
^b The 95% confidence intervals are unadjusted for multiplicity.

Differences in change from baseline in PANSS total score were not statistically significant for the Low or High dose paliperidone groups but were for the Medium dose group. It should be noted that only the low body weight, Medium dose group received the proposed dose regimen. The 20% responder rate analysis is summarised in Table 9 and Figure 2, below.

Table 9. PANSS Total Score; ≥ 20% and ≥ 30% Improvement from Baseline to End-Point (last observation carried forward; LOCF) for the ITT analysis set for Study PSZ-3001.

	Placebo (N=51)		Paliperidone ER Low (N=54)		Paliperidone ER Medium (N=48)		Paliperidone ER High (N=47)	
	n	%	n	%	n	%	n	%
CHANGE IN PANSS TOTAL ≥ 30% OR < 30%								
END POINT								
≥ 30% Improvement	14	27.5	17	31.5	22	45.8	18	38.3
< 30% Improvement	37	72.5	37	68.5	26	54.2	29	61.7
Total	51		54		48		47	
P-value(minus Placebo) (a)				0.601		0.031		0.124
CHANGE IN PANSS TOTAL ≥ 20% OR < 20%								
END POINT								
≥ 20% Improvement	17	33.3	21	38.9	31	64.6	24	51.1
< 20% Improvement	34	66.7	33	61.1	17	35.4	23	48.9
Total	51		54		48		47	
P-value(minus Placebo) (a)				0.479		0.001		0.043

Figure 2. The Cumulative Response Rate for Percent Change from Baseline to End Point (LOCF) in PANSS Total Score in Study PSZ-3001.*



*This Figure represents those subjects who responded to study treatment as well as those who did not (or their condition worsened), at the end of the 6 week study period. The vertical axis represents the number of subjects in each study arm (see boxed text), with cumulative percentage of subjects at “100”

representing the total treatment arm population. The horizontal axis represents the degree of change in baseline PANSS total scores. Negative figures (that is, those based to the left of zero) signify a worsening in mental state whereas those numerically positive (that is, those based to the right of zero) signify an improvement in mental state. In the Placebo group for example, point zero on the x-axis i.e. no change from baseline in PANSS total score at study end-point bisects the curve at 60% on the y-axis. The latter means 60% of the Placebo group (31 subjects, n = 51) achieved a positive effect to treatment whereas 40% failed to respond to treatment (n = 20) or their condition worsened. Thus approximately, 33% of the Low group (n = 18) failed to respond to treatment or their condition worsened, 10% of the Medium group (n = 5) and 15% of the High group (n = 7) likewise.

A reduction of at least 20% in the PANSS total score occurred in a significantly higher percentage of subjects in the Medium and the High groups compared with placebo (64.6%, p = 0.001 versus 51.1%, p = 0.043 versus 33.3%, respectively). At the 30% responder level, only the Medium group achieved statistical separation compared with placebo (45.8% versus 27.5%, p = 0.031).

Various subgroup analyses were performed, though the study was not powered to determine statistically significant differences among these subgroups. Of particular note, the effect of paliperidone on age (12-14 years and 15-17 years) was examined. No treatment arm in the 12-14 year age-group showed statistical separation compared to placebo, unlike the 15-17 year age-group. In an actual dose analysis of PANSS total scores by age-group, only the 3 mg dose in the 12-14 year age-group had a larger reduction than placebo (-16.1 versus -11.6, respectively). The submission did not include responder rates or onset of therapeutic effect for the 12-14 year age group by treatment arm.

Some information on longer term efficacy is available from an open-label, multicenter study of flexibly-dosed paliperidone in adolescents aged 12 to 17 years with a DSM-IV diagnosis of schizophrenia. This was initially a 6 month study but was extended to 2 years to obtain additional safety data. A total of 148 subjects had at least 6 months (180 days) of exposure to open-label paliperidone ER at mode doses of ≥ 3 mg daily. Subjects who completed Study PSZ-3001 or who had discontinued that study due to lack of efficacy, but who had completed a minimum of 21 days of the study could enrol in this open-label study. Subjects who had not participated in Study PSZ-3001 could be enrolled directly. This was not necessarily a follow-on or extension study because it commenced prior to study PSZ-3001.

The study consisted of a screening and washout phase of up to 21 days, an open-label treatment phase of up to 2 years, and a post-treatment (follow-up) visit, 1 week after the subject's final dose of study drug.

The planned dose range was 1.5 mg to 12 mg paliperidone ER daily. Treatment started with a dose of 6 mg daily. The dosing distribution on study is shown in Table 6 of this AusPAR.

Total PANSS scores reduced from a mean of 82.5 at study commencement to 68.9 (LOCF, ITT) during the first 6 months of study.

Safety

No new safety issues were identified from this submission however the following are of concern:

- There was a general increase in the incidence of TEAEs with increasing dose.
- The effect of paliperidone on lipid parameters appears more marked in adolescents than in adults given the same dose.
- The metabolic analysis was inconclusive and further study is required to quantify the magnitude of the risk of developing metabolic syndrome, and its sequelae however

paliperidone was associated with increased serum cholesterol and triglycerides, increased body weight and increased fasting glucose levels. These results support a trend towards an increased risk of developing metabolic syndrome.

- The incidence of extrapyramidal AEs appears to be higher in adolescents than in adults given the same dose. Higher incidences of dystonia, hyperkinesia, tremor and Parkinsonism were found in adolescents compared to adults receiving paliperidone with the incidence of EPS-related AEs increasing with duration of exposure. In PSZ-1001, subjects were exposed for up to 9 days and 20% experienced an EPS (comparable to the rate found in adult populations receiving paliperidone in longer-term studies). In the 6 week efficacy study, this rate rose to 31% (46/150) and in the 6 month safety study the rate rose to 40% (114/282). However, these rates are based on the number of subjects experiencing at least one AE not the number of events per se so a direct comparison is not possible.
- Weight gain appears to be of similar magnitude to that seen in adolescents given quetiapine. In the open-label extension study weight gain of at least 7% occurred in 41% of the Placebo/Pali group and 38% of the Pali (DB)/Pali group from DB baseline (compared to 33% total from the OL baseline). The biggest changes that occurred from the OL baseline were in the newly exposed Placebo/Pali and Pali (No DB)/Pali groups.
- Sedation appears more likely in adolescents compared with adults given the same dose.

Clinical evaluator's recommendation

The clinical evaluator considered the benefit-risk balance of paliperidone ER was unfavourable given the proposed usage, but would become favourable if the following recommended changes were adopted:

1. Approval restricted to acute treatment only (in established schizophrenia);
2. Approval restricted to the 15-17 year age-group (as currently licensed for risperidone, of which paliperidone is the major metabolite);
3. The dosage range was restricted to 3 to 6mg once daily i.e. a maximum daily dose of 6 mg. If higher doses were approved then the evaluator recommended a dosing-based schedule based on bodyweight as per the pivotal study i.e. those weighing less than 51 kg should be given a lower dose than those weighing at least 51 kg.

Risk management plan

The RMP includes all indications and age groups for whom paliperidone has an indication. The sponsor proposes routine pharmacovigilance for all safety concerns except for the following:

- Important potential risks 'Cerebrovascular accident/overall increased mortality in elderly patients with dementia' and 'cerebrovascular adverse events in elderly patients with dementia' will be evaluated in a post-authorisation safety trial.
- Important missing information 'Long-term safety in patients with schizoaffective disorder' is being evaluated with ongoing long term trials.

In regard to long term safety in paediatric patients with schizophrenia, an addendum to the RMP stated that "*long term safety in the paediatric population as an additional item of important missing information...is considered adequately managed via labelling and the surveillance activities proposed in the pharmacovigilance plan*". The RMP evaluator considered the above statement and recommended that the PI clearly communicate that long term safety in adolescent patients with schizophrenia has not been studied. Other

amendments to the PI, not specifically pertaining to use in adolescents were also proposed (details of these are beyond the scope of this AusPAR).

Risk-benefit analysis

Delegate considerations

The sponsor provided a response to the CER and recommendations therein. Notable information from that document is that the sponsor regards maintenance of effect as having been adequately demonstrated and considers that ethical issues with adolescents have limited use of extended placebo-controlled studies for the demonstration of maintenance effect. The sponsor has also noted that almost all subjects with schizophrenia require treatment with antipsychotic medication for their entire lives and therefore it would be unrealistic to restrict treatment of paliperidone ER only in the acute setting.

The sponsor was willing to accept the age restriction recommended by the clinical evaluator, that is, 15-17 years. The sponsor has not accepted the clinical evaluator's recommended dose restriction to a maximum of 6 mg daily or higher doses based on body weight as per the pivotal study because the sponsor considered there are inadequate data to support such a recommendation. Data from the subgroup analyses of efficacy in the pivotal study for the 15-17 year age group and the ≥ 51 kg group were provided the sponsor's response to the CER. The frequency of mode dose of paliperidone for subjects aged 15-17 years in the open extension study was presented to support the full current dose range for that age group. Some 88% of subjects aged 15-17 years had a mode dose of ≥ 6 mg/day.

The Delegate does not consider that a dose regimen of paliperidone for adolescents with schizophrenia has been adequately established. The sponsor's proposed initial dose of 3 mg daily for adolescents across a wide range of body weights is a different approach from that taken with risperidone where paediatric dosing is based on body weight. The sponsor's proposed dose regimen is likely to result in higher exposures for younger individuals and those of low body weight compared with older and heavier adolescents and adults given the same dose. It is not clear whether overall exposure in adolescents would be higher or lower than for adults in clinical practice as only the starting dose for adolescents is proposed to be lower than for adults. The same dose range for adults is proposed for adolescents.

The sponsor has proposed that adjustments be made to the dose according to the assessed clinical response, however in the pivotal clinical study no dose response was demonstrated. The high dose group did not show a statistically significant difference from placebo for the primary efficacy endpoint or for the 30% response rate, though it did for the 20% response rate. In the open-label follow-on study very few adolescents continued to receive 3 mg daily with most receiving from 6 to 12 mg daily while on study. The proposed dose regimen allows for an adolescent who initially receives paliperidone 3 mg daily and who does not respond adequately to have their dose escalated up to 12 mg daily, a dose for which there is no evidence of efficacy in that age group.

The CER includes extensive consideration of the risks and benefits of treatment of adolescents with paliperidone. The Delegate considers the following issues are of major concern:

- Subjects were enrolled primarily from countries with cultures that are substantially different from Australian culture. Cultural factors are known to vary the presentation of schizophrenia. This is of particular concern for schizophrenia in adolescents which is considered to be difficult to diagnose accurately, particularly in younger adolescents.

- Initial diagnosis of some of the study subjects with schizophrenia from age 3 years suggests that DSM IV diagnostic criteria were not consistently applied prior to study entry and this may have affected subject selection.
- The proposed initial dose for adolescents of 3 mg daily was used only in the low body weight, Medium dose group in the pivotal study. This group comprised 16 adolescents with weight \leq 51 kg.
- Dose response was not demonstrated, there was no statistically significant difference from placebo for the High dose group versus placebo for the primary efficacy endpoint. This was particularly apparent in adolescents aged 12-14 years, where those given 6 mg or 12 mg paliperidone daily had similar reductions in total PANSS to those given placebo. The larger difference from placebo for the 3 mg dose appears as an anomaly for this group. However all that can reasonably be stated regarding dose response from the pivotal study is that no dose response to paliperidone was demonstrated.
- It is proposed to give 3 mg daily initially to adolescents up to age 17, though this dose was only given to those with body weight \leq 51 kg in the pivotal clinical study.
- The open-label, long term extension study provided open flexible dosing to 6 months. Few subjects received the proposed 3 mg starting dose, with the majority receiving from 6-12 mg as their most frequent daily dose. Efficacy of this dose regimen was not demonstrated in the 6 week pivotal study. In regard to efficacy, that study has shown that with paliperidone doses mostly between 6 and 12 mg daily, adolescents remaining on study generally did not have increases from baseline in their PANSS total scores. The Delegate regards this evidence as insufficient to demonstrate efficacy in either maintenance treatment or prevention of relapse of schizophrenia.
- Long term safety of the proposed dose regimen in adolescents has not been adequately examined. It appears likely that adolescents given the same doses as adults will have higher incidences of AEs including metabolic syndrome and extrapyramidal effects.

Proposed action

A clinically significant benefit in reduction of signs and symptoms of schizophrenia for the proposed dose regime of paliperidone in adolescents aged from 12-17 years or in adolescents aged 15-17 years has not been adequately demonstrated. In addition, it is likely that adolescents are more likely to experience AEs from exposure to paliperidone than are adults given the same dose. The Delegate therefore finds the risk/benefit ratio is unfavourable and proposes to reject this submission.

Advice requested from ACPM

The Delegate sought general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and in particular requested the ACPM address the following:

- Should concern about studies in schizophrenia being conducted in countries that are culturally dissimilar to Australia influence consideration of the applicability of those studies' results to the Australian population? It is noted that the Guidelines do not provide advice on this issue.
- Whether the evidence of efficacy for the 6 mg/day dose in acute treatment of schizophrenia in adolescents weighing $>$ 51 kg could be considered sufficient to support use of paliperidone for that subgroup.

- Whether the evidence of efficacy for the 6 mg/day dose in acute treatment of schizophrenia in adolescents aged 15-17 years could be considered sufficient to support use of paliperidone for that subgroup.
- If either of the above is considered acceptable, is it then acceptable to extrapolate the evidence for maintenance of efficacy obtained in studies of adults to adolescents. This extrapolation is necessary if long term treatment is to be supported, given the lack of acceptable data on prevention of recurrence or relapse in adolescents.

Response from sponsor

Background

This is in response to the Delegate's Overview and request for ACPM advice.

As outlined in the response to the CER, the sponsor has accepted the TGA's recommendation to restrict the age range to adolescents aged 15-17 years. The focus of this response will therefore be on the risk/benefit profile of paliperidone ER in this group of older adolescents. Particular concerns and comments raised by the Delegate regarding the risk/benefit profile of paliperidone ER will be addressed throughout. The sponsor is also proposing some revisions to the dosing recommendations in response to the TGA's concerns about the use of paliperidone ER in adolescents with lower body weights (that is, < 51 kg). Finally, the comments made by the Delegate regarding the applicability of the studied population are discussed.

Risk/Benefit in adolescents aged 15 to 17 years old

The Delegate raised concerns that the proposed dose regimen of paliperidone ER has not demonstrated a clinically significant reduction in the symptoms of schizophrenia in adolescent subjects (in either ages 12-17 years or ages 15-17 years). Further, the Delegate is concerned that adolescents are more likely to experience AEs associated with paliperidone ER than adults, leading to an unfavourable risk/benefit profile. As discussed below, the sponsor maintains the risk/benefit profile of paliperidone ER is favourable, particularly when considering the 15-17 year old age range.

The use of paliperidone ER in adolescents with schizophrenia is supported by the positive outcome of the double-blind, placebo-controlled Study R076477-PSZ-3001 (referred to as PSZ-3001) and the results of the open-label maintenance study R076477-PSZ-3002 (referred to as PSZ-3002). The majority of subjects enrolled in these studies were aged 15-17 years old (74% of subjects in PSZ-3001 and 73% of subjects in PSZ-3002).

Demographic and baseline disease characteristics in adolescents aged 15-17 years in PSZ 3001 are provided in the submission. Compared with younger adolescents, these subjects are generally more similar to adults in terms of maturation (mostly post-pubertal), onset of illness (during or after puberty), and body weight. Most subjects (76%) aged 15-17 years in PSZ-3001 were in the heavier weight group (that is, ≥ 51 kg), and the PK of paliperidone ER in adolescents ≥ 51 kg are similar to those in adults.

Efficacy

The efficacy of paliperidone ER was established in Study PSZ-3001, which achieved its primary outcome of at least one dose group (Medium dose) achieving a statistically significant separation from placebo for the primary endpoint (the change from baseline to end point in PANSS total score). When the primary efficacy analysis was performed for the older adolescent group (15-17 year-olds), both the Medium and High dose groups were significantly superior to placebo. In addition, the by-dose analysis in older adolescents showed that the 3, 6, and 12 mg doses all significantly separated from placebo, although

the number of subjects exposed to the 3 mg dose was limited. All secondary efficacy measures were significantly superior to placebo for the Medium and High dose groups in subjects aged 15-17 years old (Table 10, below). These results show a robust response in this group of older adolescents, similar to the efficacy results in acute studies of paliperidone ER in adult schizophrenia.

Table 10. Overview of Key Secondary and Other Efficacy Results for Study R076477-PSZ-3001 - Subjects 15-17 Years of Age (Intent-to-Treat Analysis Set).

	Placebo (N=42)	Low (N=38)	Paliperidone ER	
			Medium (N=33)	High (N=34)
Secondary Efficacy Variables				
CGI-S Score, n	42	38	33	34
Median (range) baseline	4.0 (3;6)	4.0 (3;6)	5.0 (3;6)	4.0 (4;6)
Median (range) change at end point (LOCF)	0.0 (-3;1)	0.0 (-3;1)	-1.0 (-3;0)	-1.0 (-3;0)
p value (vs placebo) ^a		0.674	<0.001	0.003
CGAS Score, n	42	38	33	34
Mean (SD) baseline	49.0 (10.97)	45.6 (10.32)	47.1 (11.17)	46.0 (10.10)
Mean (SD) change at end point (LOCF)	3.9 (14.19)	5.1 (11.58)	14.2 (12.01)	10.4 (9.16)
p value (vs placebo) ^b		0.689	<0.001	0.011
Other Efficacy Variables				
Responder Rate ^c				
n (%)	14 (33.3%)	16 (42.1%)	23 (69.7%)	19 (55.9%)
p value (vs placebo) ^d		0.276	0.002	0.041

^a p values for between-treatment group comparisons are from an analysis of covariance model on ranks with treatment and country as factors, and baseline value as a covariate; no adjustment for multiplicity.

^b p values for between-treatment group comparisons are from an analysis of covariance model with treatment and country as factors, and baseline value as a covariate; no adjustment for multiplicity.

^c Responder defined as those who achieved a 20% or higher reduction from baseline in the PANSS total score at end point.

^d p values for pairwise comparisons with placebo using a generalized Cochran-Mantel-Haenszel test for row mean score differences controlling for country.

CGAS=Children's Global Assessment Scale, CGI-S=Clinical Global Impressions-Severity, LOCF=last observation carried forward; SD=standard deviation.

The Delegate specifically queried the efficacy of the 6 mg dose in both older (15-17 years) and heavier (≥ 51 kg) adolescents. A sizable proportion of subjects aged 15-17 years ($n = 34$) and subjects ≥ 51 kg ($n = 32$) received a 6 mg dose in PSZ-3001. Analysis of the primary endpoint showed a statistically significant separation from placebo for the 6 mg dose in both these subgroups: in subjects aged 15-17 years, the mean change in PANSS total score in the 6 mg dose group (-15.2) was statistically significantly superior ($p = 0.029$) to that in the placebo group; in subjects ≥ 51 kg, the mean change in the Medium dose group (all of whom received 6 mg) was -16.5, which was also statistically superior ($p = 0.004$) to placebo. These changes in the 6 mg group in the older and heavier adolescents are similar to the change in PANSS scores observed in the acute treatment of adult schizophrenia with paliperidone ER (-16.9). The Medium dose group for the ≥ 51 kg group also showed statistically significant improvements compared with placebo on the CGI-S as well as other secondary measures. Overall, the 6 mg dose showed clinically meaningful and statistically significant changes compared with placebo in primary and secondary efficacy measures in the acute treatment of adolescent schizophrenia. The 6 mg dose was also the most common dose in PSZ-3002 (43% of subjects aged 15 to 17 years), which supports the efficacy of this dose as a maintenance therapy in adolescent subjects.

The Delegate also commented that no dose response was demonstrated in PSZ-3001 because of the lack of statistical separation from placebo for the High dose group. However, the efficacy analysis conducted in subjects aged 15-17 years of age did show statistical separation from placebo for both the Medium and High dose groups for the primary efficacy variable. In addition, an analysis similar to that reported in the original submission showed that in 15-17 year-olds, there is a significant dose-response ($p = 0.0045$ by a linear trend test and $p = 0.0002$ by the Jonckheere-Terpstra test) among the actual doses for the primary efficacy variable (change from baseline to end point in PANSS total score).

The maintenance of efficacy is supported by the long term, open-label study, PSZ-3002. The results of the interim 6 month analysis of PSZ-3002 were submitted and a summary has been provided. The results of PSZ-3002 showed a similar change in PANSS score

regardless of entry group. After initial response, the PANSS and other measures maintained this improvement without any evidence of reduced efficacy or the development of tolerance to the benefits of paliperidone ER. The change in PANSS score is supported by improvements in secondary outcome measurements such as CGI-S, CGAS, and PANSS subscales. There was also a high rate of completion in PSZ-3002: only 23% of subjects had withdrawn from the study at the time of the 6 month interim analysis, with only 9% due to lack of efficacy and 4% due to AEs. Completion rates are often used as end points in effectiveness trials as a measure of overall effectiveness and tolerability.

Safety

The sponsor considers the safety and tolerability of paliperidone ER in adolescents, particularly older adolescents (15-17 years), similar to that of adults with schizophrenia. Summary data on TEAEs in subjects aged 15-17 years and subjects weighing ≥ 51 kg are provided. For comparison, AEs in pooled adult schizophrenia studies listed in the US prescribing information for Invega are also provided. Overall, the pattern and frequency of TEAEs in older and heavier adolescents were similar to those observed in the overall study population (12-17 years). The most common ($\geq 5\%$ in the Total paliperidone ER treatment group) dose-related TEAEs in adolescents aged 15-17 years were somnolence, headache, akathisia, and tremor (reported in 12.4%, 11.4%, 8.6%, and 6.7% of subjects in the Total paliperidone ER treatment group, respectively). These events occurred at a comparable incidence in adults across doses of 3 to 12 mg. Somnolence may occur more often in adolescents than adults at the higher dose levels, but this can likely be compensated by dose adjustment.

Extrapyramidal symptoms are a concern with most antipsychotic medications and are a known risk of paliperidone ER. Data were provided on the incidence of EPS-related events for subjects aged 15-17 years in PSZ-3001 and for adults in the US prescribing information for Invega. Overall, the incidence of EPS-related adverse events in PSZ-3001 appears lower in subjects aged 15-17 years compared with the overall study population (12-17 years), particularly in the High paliperidone ER treatment group. The incidence rates of all EPS-related AEs in older adolescents in the Medium (21.2%) and High (26.5%) treatment groups were comparable to the rates observed in adults at doses of 3 to 12 mg (13% to 26%). The incidence rates of hyperkinesia, parkinsonism, and dystonia in older adolescents are also comparable to those in adults; the incidence of dyskinesia is lower while rates of tremor are mildly higher. Overall, these results suggest that the risk of EPS-related adverse events is similar between adults and adolescents aged 15-17 years old.

The Delegate expressed concerns about body weight and other changes in metabolic parameters. The metabolic effects of paliperidone ER in adolescents are discussed below. These results are only available for the total population (12-17 years), rather than 15-17 year age range, but overall, these data suggest a comparable metabolic safety profile for adolescents and adults.

The assessment of weight gain is difficult in adolescents since it is expected that most adolescents, even in the 15-17 year range, will gain weight as part of normal growth and maturation. In PSZ-3002, the changes in height, weight, and BMI were assessed in the total population (12-17 year olds) based on expected growth curves. The 'z score' is the change in the growth curve, with 1 being one SD and 0.5 considered a significant change in the growth curve. When taking into consideration the median duration of exposure to paliperidone ER in PSZ-3002 (182 days) along with expected normal growth in this population, the mean change from open-label baseline to endpoint in standardised score for weight was 0.1 (4% above the median of normative data). Based on comparison to the normative data, these changes are not considered to be clinically significant. The sponsor has included this information about weight gain with adolescents in the body weight section of the proposed Australian PI. The requested presentation of weight gain data as

an adjusted percentage change in body weight has not been added to the PI, as that data is not available. In PSZ-3001, weight gain as an AE was more common in the younger (12-14 years) adolescent group (8.9%) than older adolescents (2.9%). Weight gain in older adolescents does not seem to be higher than in adult studies when normal growth is accounted for, although the overall weight gain is higher in adolescents. As with adults, the sponsor recommends regularly monitoring of weight.

As requested by the TGA, the sponsor has added some additional text in the Australian PI regarding changes in lipid parameters. Mean lipid parameters (cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides) showed small changes during the treatment period in PSZ-3001 and PSZ-3002. However, the sponsor does not consider these changes to be more pronounced than those observed in adults. Changes in lipid parameters in acute schizophrenia studies are summarised for adults and adolescents (12-17 years) in the US prescribing information for Invega. Although the percentage of adolescent subjects with an abnormal change appears relatively high for some parameters at various dose levels, the actual number of adolescents experiencing a shift at each dose level is small (1-2 subjects, except for HDL), and the data are generally comparable to adults. With PSZ-3002 and its longer duration of treatment, the mean changes from open-label baseline to end point were small in the paliperidone ER total group: 1.4 mg/dL for cholesterol, -0.3 mg/dL for HDL, 0.2 mg/dL for LDL, and 4.4 mg/dL for triglycerides. The mean changes were 0.7, -0.1, -0.9, and 6.0 mg/dL for those with at least 24 weeks of exposure, indicating there was no worsening of lipids overtime. Changes in fasting glucose levels also appear comparable between adolescents and adults. In PSZ-3001, shifts from normal fasting baseline glucose levels to high at any time were observed at similar low rates in subjects treated with placebo (2.4%) and paliperidone ER (2.6%), with only 3 subjects in the High paliperidone ER dose group experiencing an abnormal shift. These findings are comparable to those in adults in 6 week studies (3.2%-4.8% across the dose range of 3-12 mg). In PSZ-3002, there was no evidence of a trend toward increasing fasting glucose values over time and the percentage of subjects experiencing a shift in fasting glucose from normal to high from open-label baseline was low (2.3%). In summary, although metabolic changes are a risk, this risk does not appear any greater in adolescents than in adults when normal growth is considered.

Dosing recommendations

In response to the Delegate's concern regarding lower weight adolescents being exposed to excessive doses of paliperidone ER and a subsequent increase in side effects, the sponsor is proposing the weight-based dosing schedule shown in Table 11, which is consistent with the US prescribing information for Invega. The text in the *Dosage and Administration* section of the proposed Australian PI has been updated accordingly.

Table 11. Proposed weight-based dosing schedule.

Weight Category	Initial Dose	Recommended Dose	Maximum Dose
<51 kg	3 mg	3-6 mg	6 mg
≥51 kg	3 mg	3-12 mg	12 mg

This dosing schedule limits the exposure in lower weight adolescents to 6 mg, while allowing heavier adolescents to be treated with the full range of doses. As detailed above, the efficacy of the 3, 6 and 12 mg doses have been demonstrated in heavier (≥ 51 kg) adolescents. The AEs for heavier adolescents and older adolescents (15-17 years) are similar to those experienced by adults across this dose range.

As the Delegate points out, only a small number of subjects were exposed to the 3 mg dose in PSZ-3001 and in the open-label study PSZ-3002. Despite the small numbers, the 3 mg dose was shown to be statistically superior to placebo for the primary efficacy variable in

both the overall population as well as the older adolescents in PSZ-3001. The 3 mg dose also produced statistically superior improvements in CGI-S and CGAS compared with placebo in the overall population, and median/mean changes in these parameters were similar for the 3, 6, and 12 mg dose groups. Overall, the data support the efficacy of the 3 mg dose level. It is clear from PSZ-3001 that the 1.5 mg dose is an ineffective dose.

The sponsor is proposing a lower starting dose in adolescents (3 mg) compared with adults (6 mg). Taking into consideration the dose-response pattern that was observed for some of the safety parameters in PSZ-3001, paliperidone ER 3 mg/day, the lowest efficacious dose, is expected to provide the optimal benefit-risk balance. While this dose may be associated with lower paliperidone exposure for some individuals, it can be adjusted within the recommended dose range (3-12 mg/day in subjects \geq 51 kg, and 3-6 mg/day in subjects $<$ 51 kg) to attain the balance between efficacy and tolerability and to tailor the treatment to the needs of each individual patient.

Population studied

The Delegate expressed concern that the population of adolescents studied may not match that of Australia. For PSZ-3001, 19.5% of the enrolment was from the US and EU. For PSZ-3002 (which also enrolled subjects from PSZ-3001), 34.9% of the subjects were from the EU and US. These populations and treatments are likely similar to those in Australia.

Unlike other psychiatric illnesses, the prevalence of schizophrenia is similar across cultures. This has been shown by multiple World Health Organization (WHO) studies utilising standardised measures to determine the diagnosis. The older studies have been confirmed by the more recent Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO) studies looking at outpatient care of schizophrenia care across many regions. The broad concepts across cultures are similar (delusions, hallucinations, negative symptoms, disorganizations), but the details (such as the content of the delusions) may vary from culture to culture. In examining the demographic characteristics of the subjects enrolled in PSZ-3001 and PSZ-3002 (mostly White, around age 16, pubertal or post-pubertal onset, previous treatment with antipsychotics [mostly atypical]), the sponsor considers them to be representative of the adolescent schizophrenia population in Australia.

In PSZ-3001, for the primary efficacy variable (PANSS), a possible interaction between treatment and country was explored using the same analysis of covariance (ANCOVA) model as for the primary outcome. An interaction was to be considered statistically significant if the 2-sided p value was $<$ 0.10. Based on this evaluation, no 'treatment by country' interaction was observed ($p = 0.439$). The effect of region was also assessed in PSZ-3002. The mean decrease in PANSS total score from open-label baseline to end point for the Total group was comparable for the non-US subjects (-14.0, $N = 232$) and the US subjects (-13.7; $N = 46$), and slightly greater for the EU subjects (-16.9, $N = 53$) than the non-EU subjects (-13.2, $N = 225$).

The Delegate also queried the consistency of the use of the DSM-IV diagnosis, specifically regarding 1 subject that was apparently diagnosed at age 3. To determine the length of illness, it is unclear if investigators consistently applied the same questions. Some may have queried when the patient started to show signs of illness as opposed to when the patient was first diagnosed. However, a few outlying ages should not necessarily suggest that the overall diagnosis is suspect. Diagnosis in adolescents can be difficult, and subjects often have multiple diagnoses before schizophrenia is considered. Because of this difficulty, all diagnoses were confirmed with a structured interview, the K-SADS, the gold standard for determining diagnosis in children and adolescents. The K-SADS has been validated in multiple cultures. Further, symptoms were assessed by the PANSS throughout the study. This instrument has been used in many international studies of adolescent and

adult schizophrenia across many cultures, having been validated in adolescents and multiple languages.

Conclusion

The data presented support the efficacy and long-term safety (up to 6 months) of paliperidone ER in adolescents aged 15-17 years. The long-term study provides support for paliperidone ER in adolescents aged 15-17 years. The long-term study provides support for maintenance of effect and the placebo controlled acute study supports the dose-response relationship in adolescents aged 15-17 years. Overall, the presented data show a favourable risk/benefit profile, similar to that seen in adults.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of quality, safety and efficacy agreed with the Delegate that these products have an overall negative benefit-risk profile for the proposed indication.

In making this recommendation the ACPM expressed significant concern about the design, duration, patient selection, screening and analysis of the pivotal clinical study and considered the study inadequate to support the proposed extension of indication. The studies were not designed for the proposed population and did not reliably investigate proposed dosing regimens.

In addition, the ACPM advised that the benefit-risk profile for these products in the proposed population group is not comparable to that of risperidone. The different metabolic adverse event profile, is highly relevant and of potentially greater long term impact for this group.

Outcome

This application was withdrawn by the sponsor on 22 October 2012, prior to a decision being made by the TGA.

Attachment 1. Extract from the Clinical Evaluation Report

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