



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Paliperidone palmitate

Proprietary Product Names: Invega Trinza and  
Trevicta

Sponsor: Janssen-Cilag Pty Ltd

**October 2017**

**TGA** Health Safety  
Regulation

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- AusPARs are prepared and published by the TGA.
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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

Abbreviation	Meaning
ACPM	Advisory committee for prescription medicines
ACSOM	Advisory committee for the safety of medicines
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
AUC	area under the curve
AUC <sub>0-∞</sub>	area under the curve from time zero to infinity
BMI	Body Mass Index
C <sub>max</sub>	Maximum plasma concentration
CGI-S	clinical global impression -severity
CSR	clinical study report
CV	covariance
EPS	extrapyramidal symptom(s)
ER	Extended release
EU	European Union
IDMC	Independent Data Monitoring Committee
ITT	intent-to-treat
LAI	long-acting injectable
MedDRA	Medical Dictionary for Regulatory Activities
mg eq.	milligram equivalents
MRHD	Maximum recommended human dose
NMS	neuroleptic malignant syndrome
PANSS	positive and negative syndrome scale
PK	pharmacokinetic(s)
PP1M	paliperidone palmitate 1 month formulation (tradename Invega Sustenna)

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Abbreviation	Meaning
PP3M	paliperidone palmitate 3 month formulation (tradenname Invega Trinza or Trevicta)
PQC	product quality complaint
SD	standard deviation
TEAE	treatment-emergent adverse event
US	United States

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	Major variation (extension of indications, new dose form and strength)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	20 September 2017
<i>Date of entry onto ARTG</i>	23 September 2017
<i>Active ingredient:</i>	Paliperidone palmitate
<i>Product names:</i>	Invega Trinza and Trevicta
<i>Sponsor's name and address:</i>	Janssen-Cilag Pty Ltd Locked bag 2070 North Ryde NSW 1670
<i>Dose form:</i>	Suspension for injection
<i>Strengths:</i>	175 mg, 263 mg, 350 mg and 525 mg
<i>Container:</i>	Prefilled syringe
<i>Pack size:</i>	1
<i>Approved therapeutic use:</i>	<i>Indicated for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with the 1 month paliperidone palmitate injectable product for at least four months</i>
<i>Route of administration:</i>	Intramuscular
<i>Dosage:</i>	Following the initial dose, Invega Trinza / Trevicta should be administered every three months. For the full details regarding dosage and administration please see the Product Information.
<i>ARTG numbers:</i>	261332, 261406, 261407, 261408, 261409, 261410, 261411, 261412

### Product background

This AusPAR describes the application by Janssen-Cilag Pty Ltd (the sponsor) to register Invega Trinza paliperidone palmitate 175 mg, 263 mg, 350 mg and 525 mg suspension for injection, and the additional tradename Trevicta for the following indication:

*for the treatment of schizophrenia in adult patients who have been adequately treated with the 1 month paliperidone palmitate injectable product for at least four months.*

Paliperidone is an atypical antipsychotic, acting as a centrally active antagonist of dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors, as well as an antagonist of  $\alpha_1$  and  $\alpha_2$

adrenergic receptors and H<sub>1</sub> histaminergic receptors. Paliperidone is the major active metabolite of risperidone.

An oral formulation of paliperidone (tradenname Invega) was registered in Australia in 2007 for the treatment of schizophrenia and schizoaffective disorder. A once-monthly injectable formulation (referred to in this document as PP1M (tradenname Invega Sustenna)) was registered in 2010 for the treatment of schizophrenia. The current application is for a three-monthly injection (referred to in this document as PP3M tradenames Invega Trinza and Trevicta). This product is intended to be administered only to patients with schizophrenia who have been adequately treated with a 1 month paliperidone (as palmitate) injection product for at least 4 months.

Non-adherence to antipsychotic medication is a major problem in treating schizophrenia, and long-acting injections are commonly used to improve adherence and clinical outcomes such as relapse and readmission. At present, depot antipsychotics are typically administered on a two-weekly or four-weekly basis. No other depot antipsychotic agents currently available in Australia provide 3 months of treatment in each injection.

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 September 2016. This product received marketing authorisation in the USA on 18 May 2015 and submissions for marketing authorisation have been made to regulatory authorities in the European Union (EU), Canada, Switzerland and New Zealand. The approved indication in the USA is similar to that which is currently proposed for registration, the US indication omits the term 'maintenance' and refers only to treatment of schizophrenia.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>> .

## II. Quality findings

### Introduction

The application is to register new strengths of the solution for suspension for intramuscular injection containing paliperidone 75 mg, 263 mg, 350 mg, 525 mg as paliperidone palmitate 273 mg, 410 mg, 546 mg and 819 mg, respectively, to supplement the 'Invega Sustenna' solution for suspension for intramuscular injection products containing paliperidone 25 mg, 50 mg, 75 mg, 100 mg and 150 mg (as the palmitate) currently registered in Australia by Janssen-Cilag Pty Ltd under the trade name 'Invega Sustenna' (AUST R 160858, 160856, 160859, 160860, 160857, respectively)

### Drug substance (active ingredient)

Current evidence of acceptable GMP for the sites nominated for the manufacture of the API was provided to the TGA.



## Drug product

The following details relate to this submission:

Current evidence of acceptable GMP for the sites nominated for the manufacture, quality control and packaging and labelling and release for supply of the finished products was provided to the TGA.

The finished products are packaged in 3 alternative sized syringes constructed from cyclic-olefin-copolymer, fitted with a plunger stopper and tip cap (bromobutyl rubber coated with FluroTec), a backstop, and 2 types of commercially available needles: a thin walled 22G, 1½-inch safety needle and a thin walled 22G, 1-inch safety needle (see table below for details).

**Table 1: The three alternative syringe sizes**

Package	Syringe Size	Plunger Stopper Size	Plunger Rod Size	Backstop Size
1	1-mL Long syringe	1-mL Long	1-mL Long	Small
2	2.25-mL syringe	1-3-mL	2.25-mL	Large
3	2.8-mL syringe	1-3-mL	3-mL	Large

A shelf life of 24 months when stored below 25°C has been assigned to the solution for suspension for intramuscular injection packaged in the transparent COC (Cyclic Olefin Copolymer) plastic syringe described in the dossier. An acceptable (amended) composite release and expiry specification has been submitted for the finished products.

## Biopharmaceutics

The submission included 3 clinical studies, of which Study PSY-1005 was considered the pivotal study.

### Study PSY-1005

The primary objectives of this study were:

1. To evaluate the pharmacokinetics (PK), safety, and tolerability of a 3 month injection interval formulation of paliperidone palmitate (F015), [information redacted], at a single dose of 300 milligram equivalents (mg eq.) administered in the gluteal muscle in subjects with schizophrenia (Panel A)
2. To evaluate the PK, safety, and tolerability of single escalating doses of the 3 month injection interval formulation of paliperidone palmitate administered in the gluteal and deltoid muscle in subjects with schizophrenia (Panels B and D).

Panel C subjects received 150 mg eq. of the 3 month formulation (company code: F016) [information redacted].

The following outcomes were obtained:

Panels A and C

The results from Panels A and C were compromised due to some subjects receiving incomplete injections of the study agent as a result of inadequate shaking prior to injection. However, the investigators were able to draw the following conclusions:

- A quantifiable paliperidone palmitate plasma concentration was obtained in only 3 samples (0.7%) confirming the consistency of the release of paliperidone palmitate from the 150 mg eq. and 350 mg eq. formulations.
- In general, the data supported the administration of the F015 formulation of paliperidone palmitate in the gluteal or deltoid muscle every 3 months.

- [information redacted]The pharmacokinetics of the F015 wet formulation is similar to the F015 dry formulation.

#### Panels B and D

The following conclusions were drawn from Panels B and D:

- After IM injection of 75 to 525 mg eq. in the gluteal or deltoid muscle, paliperidone palmitate is slowly absorbed, as seen by a  $T_{max}$  of approximately equivalent 23 to 34 days and an apparent half-life ( $t_{1/2}$ ) of approximately 2 to 4 months.
- The half-life was similar in the gluteal and deltoid dose groups, except for the 75 mg eq. gluteal dose group where  $t_{1/2}$  was relatively slightly smaller.
- These data support the dosing of paliperidone palmitate every 3 months.
- There were no significant differences observed for area under the curve  $AUC_{0-\infty}$  and maximum plasma concentration ( $C_{max}$ ) between the deltoid and gluteal dose groups.
- After a single IM injection of paliperidone palmitate in the gluteal or deltoid muscle, the paliperidone  $AUC_{0-\infty}$  and  $C_{max}$  increased dose-proportionally in the 75 to 525 mg eq. range.
- The LS means of  $C_{max}$  of paliperidone was higher by 27% over all dose levels after injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle, whereas there was no difference between both injection sites for  $AUC_{0-\infty}$ .
- After injection of paliperidone palmitate, the paliperidone  $AUC_{0-\infty}$  and  $C_{max}$  and the relative bioavailability were independent of Body Mass Index (BMI), or race. Exposure (median  $C_{max}$ ) was slightly higher in males after single dose administration.
- The relative bioavailability was determined to be 100%, independent of dose, injection site, BMI, race or gender.
- Paliperidone is a racemic mixture. The plasma concentrations of the R078543(+) enantiomer were consistently higher than those for the R078544(-) enantiomer. From this study, the R078543(+)/R078544(-) PK parameter ratios after IM injections of paliperidone palmitate are approximately 1.8 and 1.9 for AUC and  $C_{max}$  respectively, similar to the 1 month formulation.
- After IM administration of the 3 month formulation of paliperidone palmitate, only a small number of low paliperidone palmitate concentrations were observed which was consistent with the 1 month formulation.

### Quality summary and conclusions

There are no objections to registration from a quality or biopharmaceutics perspective.

## III. Nonclinical findings

### Introduction

Janssen-Cilag Pty Ltd has applied to register paliperidone palmitate as a suspension for injection with a dosing schedule of 4 times a year, for the treatment of schizophrenia in adults who have been adequately treated with the 1 month paliperidone palmitate injectable product for at least 4 months. Proposed strengths of the new product are 175, 263, 350 and 525 mg paliperidone, present as 273, 410, 546 and 819 mg paliperidone palmitate, respectively.

The 1 month paliperidone palmitate injectable product (25, 50, 75, 100, 150 mg; Invega Sustenna) is registered in Australia for the acute and maintenance treatment of schizophrenia in adults. In order to establish a consistent maintenance dose, the last 2 doses of the 1 month injection should be the same strength prior to commencing the 4 month injection. Dose conversion is tabulated below.

**Table 2: Dose conversion for commencement of Invega Trinza 4 monthly injection**

If the last 1 month injection paliperidone palmitate injection is:	Initiate Invega Trinza at the following dose:
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

Conversion from the 25 mg 1 month paliperidone palmitate injectable product was not studied.

The sponsor has submitted a comprehensive dossier of nonclinical studies to support the submission; nearly all of these studies have been previously submitted and evaluated in support of the registration of the 1 month paliperidone palmitate injection (Invega Sustenna; submission number PM-2009-00926-3-1). The only new nonclinical studies include 9 analytical methods and validation reports, and one local tolerance study in minipigs. Only the local tolerance study has been evaluated in this report.

The new formulation contains the same API and excipients as the Invega Sustenna formulation, apart from particle size [information redacted] and a higher concentration of the drug substance (Invega Trinza 312 mg/mL; Invega Sustenna 156 mg/mL) and of some excipients. The maximum injection volume is also increased, from 1.5 mL (150 mg paliperidone) for the Invega Sustenna product to 2.625 mL (525 mg paliperidone) for the Invega Trinza product.

## Toxicology

The nonclinical dossier comprised new data on local tolerance.

**Table 3: Local tolerance; Minipig**

Study details	Major findings (both formulations)
Study TOX10172 Preclinical Development and Safety, Janssen Research and Development, 13 October 2014. GLP  Minipig, male; n = 3/group Treatment with two formulations, IM: F013 <sup>^</sup> : 0 (saline), 0 (vehicle), 5, 20 mg eq/kg/month x 3 months;	Mortalities: nil  Body weight gain: slight ↑BW/BWG (HD), ↓food intake (Week 2).  Clinical signs: slight ↓activity (mod at HD) and tremors (except F013 LD); ↑salivation, compulsive behaviour, biting (HD).  Haematology, clinical chemistry: unremarkable.  Gross pathology: dose-related local reaction (no difference between formulations at HD).  Histopathology: dose-related inflammatory reaction with occasional granuloma; cellular reaction pattern and size

Study details	Major findings (both formulations)
F015 <sup>^</sup> : 0 (saline), 0 (vehicle), 17.5, 70 mg eq/kg single dose.  Doses were divided equally between 2 sites.	of crystalline material differed with formulation (as in TOX8249) (see text).

<sup>^</sup>F013: 4 week depot formulation; 100 mg eq/mL; 1.5, 1.5, 0.38, 1.5 mL/injection site (2 sites)

<sup>^</sup>F015: 12 week depot formulation; 200 mg eq/mL; 2.63, 2.63, 0.66, 2.63 mL/injection site (2 sites)

Formulation details included in Study TOX8249 (see SN PM-2009-00926-3-1). Doses refer to paliperidone base.

This study was an extension of Study TOX8249 in minipigs (submitted and evaluated with SN PM-2009-00926-3-1) in which three consecutive monthly IM injections of the 4 week depot formulation (F013; 5 and 20 mg eq/kg) were compared to one injection of the 12 week depot formulation (F015; 15 and 60 mg eq/kg) of paliperidone palmitate, using the same 2 formulations as in TOX8249 (F013, F015). In the present study, higher doses of the 12 week depot formulation (F015) were used. Two additional groups received F013 or F015 placebo, and two control groups received saline. For dose selection, the low doses (LD) equalled the maximum recommended human dose (MRHD) on a total mg basis and the high doses (HD) equalled the MRHD on an injection volume basis.

Although there were no clear differences in the multifocal inflammatory response between the 2 formulations, the cellular reaction pattern differed. With F015, tissue macrophages and multinucleated giant cells with cholesterol-like clefts were prominent. Although the overall inflammation was similar, it was more granulomatous in 2 LD animals while macrophages and giant cells with cholesterol-like clefts were more prominent in the HD group. With F013, histiocytosis was prominent, but no cholesterol-like clefts were seen. Also, the size of the crystalline material observed in the inflammatory cells differed: smaller than nucleus with F013 and larger than nucleus with F015. These findings are consistent with those of Study TOX8249.

Plasma exposures were generally similar across the 2 depot formulation treatments (tabulated below), with maximum plasma concentrations reached 7 to 16 days after dosing of both formulations. For both formulations, the exposure increased somewhat more than dose proportional.

**Table 4: Plasma exposures comparison for the 12 week and 4 week formulations**

Dose (mg eq/kg)	12 week depot formulation (F015)		4 week depot formulation (F013)	
	17.5	70	5	20
$C_{max}$ (ng/mL)	17.6	68.3	9.77	68.1
$AUC_{0-28d}$ (ng.d/mL)	278	1067	111	682
$AUC_{0-84d}$ (ng.d/mL)	378	1888	314	1740
$C_{av,\tau}$	4.5	23	4.0	24
$C_{max} / C_{\tau}$	25	8.6	5.1	7.0

## Nonclinical summary and conclusions

The newly submitted toxicological (local tolerance) study in minipigs is an extension of an earlier (2007) study in this species (TOX8249), which was evaluated for the registration application for Invega Sustenna (PM-2009-00926-3-1). The earlier study had compared the local tolerance of paliperidone palmitate administered IM as a single dose of the 12 week depot formulation (F015; 15 and 60 mg eq/kg) with those of 3 consecutive monthly injections of the 4 week depot formulation (F013; 5 and 20 mg eq/kg). The more recent study repeated this protocol, using higher doses of the 12 week depot formulation (17.5 and 70 mg eq/kg) but the same doses of the 4 week depot formulation (5, 20 mg eq/kg). Essentially comparable results were obtained in the old and new studies, with the qualitative histopathological differences between the 4 week and the 12 week formulations apparent in both studies. Thus, the severity of the inflammation was similar between the 2 formulations but the cellular reaction pattern differed, a consistent finding across both studies. Thus, there is no new nonclinical information in the more recent, higher dose study which would impact on the risk assessment of the 3 month injection product.

As discussed in the nonclinical evaluation report for the earlier submission, these findings have uncertain relevance to clinical local reactions to IM injection of the product, which will be assessed by the clinical evaluator.

## 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 2.

### Introduction

#### Clinical rationale

Adherence to antipsychotic therapy is essential for the continuous effective drug exposure needed for optimizing therapeutic benefit with respect to preventing or delaying relapse and/or re-hospitalization; however, patients with schizophrenia exhibit various levels of medication compliance behaviour.

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## Contents of the clinical dossier

The submission contained the following clinical information:

- Evidence proposed to support the Efficacy, Safety and Tolerability of 3 monthly injections of the formulation:
  - a. Clinical pharmacology study R092670-PSY-1005; A Single dose, open label, randomized, parallel group study to assess the pharmacokinetics, safety, and tolerability of Invega Trinza in subjects with schizophrenia.
  - b. PK reports for studies R092670-PSY-3011 and 3012.
  - c. Efficacy/Safety studies:
    - i. R092670-PSY-3011; A randomized, multicentre, double blind, non-inferiority study of paliperidone palmitate 3 month and 1 month formulations for the treatment of subjects with schizophrenia.
    - ii. R092670-PSY-3012; A randomized, multicentre, double blind, relapse prevention study of Invega Trinza for the treatment of subjects with schizophrenia.
- Evidence proposed to support the use of 3 monthly injections of the formulation outside the dosage (frequency) used in the clinical trials (3 population analyses):
  - d. A population PK report REP-1-JAN-PAL-PMX-1.
  - e. Population pharmacokinetic / pharmacodynamic modelling of two intramuscular formulations of paliperidone palmitate in Study R092670-PSY-3011.
  - f. Pharmacokinetic-pharmacodynamic modelling of two intramuscular formulations of paliperidone palmitate in Study R092670-PSY-3012.
- Invega Trinza patient and physician preference surveys summary report.
- Literature summaries 01 January 2014 to 16 February 2015.
- Clinical overview, summary of clinical pharmacology studies, summary of clinical efficacy, summary of clinical safety and literature references.

## Guidance

The following guidelines were included in those used in consideration of this submission:

- CPMP/EWP/482/99 Points to consider on switching between superiority and non-inferiority
- EMEA/CPMP/EWP/2158/99 Guideline on the choice of the non-inferiority margin

## Paediatric data

The submission did not include paediatric data.

## Good clinical practice

All studies included in this application were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

## Pharmacokinetics

### Studies providing pharmacokinetic data

- Clinical pharmacology study R092670-PSY-1005; A Single dose, open label, randomized, parallel group study to assess the pharmacokinetics, safety, and tolerability of Invega Trinza in subjects with schizophrenia.
- PK reports for studies R092670-PSY-3011 and 3012.

## Population pharmacokinetics

### Studies providing population pharmacokinetic data

- Evidence proposed to support the use of 3 monthly injections of the formulation outside the dosage (frequency) used in the clinical trials (3 population analyses):
  - a. A population PK report REP-1-JAN-PAL-PMX-1.
  - b. Population pharmacokinetic / pharmacodynamic modelling of two intramuscular formulations of paliperidone palmitate in Study R092670-PSY-3011.
  - c. Pharmacokinetic-pharmacodynamic modelling of two intramuscular formulations of paliperidone palmitate in Study R092670-PSY-3012.

### Population PK Studies

The original IM paliperidone palmitate population pharmacokinetic model was a one compartment model with 1<sup>st</sup> order elimination. The covariates effects resulted in the following conclusions: repeated injections into the deltoid muscle (compared with gluteal) resulted in a faster increase in plasma concentrations and enhanced time to achieve steady-state but did not influence overall exposure; higher doses associated with larger injection volumes increased the apparent half-life which increased time to steady-state.<sup>1</sup> Other important variables were needle length and BMI: a slower rise in plasma concentrations was found for obese subjects which can be mitigated by use of a longer needle in heavier subjects. Renal function was also important indicating that renal impairment required a reduced dose.

For the complete details of the evaluation of the PK and population PK data please see Attachment 2.

### Evaluator's conclusions on pharmacokinetics

It is of concern that the PK model used for simulations to justify dosing regimens does not include data from the long term Study 3011 being based on the single dose Study 1005 and Study 3012 where 160 received 2 injections of Invega Trinza only 18 received 3 injections.

Inter-subject variability was high. Some subjects were excluded from the PopPK analysis.

The combined plasma concentration-time profiles of paliperidone show this.

Of concern is the possibility of extended periods of low plasma paliperidone concentrations. The infrequency of the sampling in the 2 clinical studies does not show this.

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<sup>1</sup> Comment: Invega Trinza is both a greater volume and a higher concentration than Invega Sustenna

Study 1005, while showing some individuals had low plasma paliperidone concentrations for periods prior to 90 days after injection, this does not necessarily equate to the steady state situation.

It does however have clinical relevance as this is what would happen clinically after the first 3 month injection.<sup>2</sup>

The sponsor argues that clustering of relapses was not seen at a time when plasma levels would expect to be low. An alternative exploration is to compare the incidence in the first 3 month treatment period with those at steady state.

The possibility of dose dumping is reviewed clinical safety section. In Study 1005, this evaluator believes there is a clear example.

The sponsor it appears has concentrated on the physical characteristics of the new formulation as the sole determinant of absorption from the IM site.

*By slowly releasing paliperidone from the injection site, the paliperidone palmitate formulation enables a dosing interval that achieves potentially therapeutic plasma concentrations of paliperidone for 1 month (PP1M) or 3 months (PP3M), depending on [information redacted].*

And

*[information redacted]*

While this may be true in vitro there are other physical factor differences that vary and might affect in vivo uptake from the intramuscular dose; [information redacted].

The minimum volume is also greater 0.875 mL Invega Trinza versus 0.25 mL for Invega Sustenna.

These characteristics might contribute to the greater inter-subject variability seen.

Approximate dose proportionality was shown.

The PopPK study was based on data from Study PSY-1005 and Study PSY-3012. None of the subjects with  $C_{max} > 125$  ng/mL appear to have been excluded,<sup>3</sup> that is the model appears to include one patient (605113) who suffered dose dumping and 2 patients with unexplained reduced clearance (60625, 603435). The existing model failed to adequately describe the Invega Sustenna PK data from Study 3012 so a new model<sup>4</sup> was developed using both the previous and the Study 3012 Invega Sustenna data. This model then failed to adequately describe the Invega Trinza PK absorption data from Study 1005 so a model with one rapid and one slow, saturable absorption process was then adopted.

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<sup>2</sup> Clarification PSY-1005, is a single dose study in which patients had not been treated with PP1M prior to the PP3M injection. This is different than the clinical situation since all patients will be at or near steady state with PP1M before PP3M is initiated. This allows PP3M to achieve near steady state levels. If PP3M is started without this initial PP1M treatment, it would take several cycles to achieve steady state.

<sup>3</sup> except the results of subject [information redacted] which showed a dramatic rise at the end of the study.

<sup>4</sup> the model was refitted with no more than 10% uncertainty in the model parameters.



## Pharmacodynamics

### Studies providing pharmacodynamic data

#### *Study 3012 PK/PD analysis*

The PopPK model in this submission was used to develop separate models for positive and negative syndrome scale (PANSS)<sup>5</sup>, dropout and relapse. While PANSS score was treated as a continuous variable, dropout and relapse were subject to survival analysis as two separate single time-to-event (TTE) models.

The overall aim of the present PK/PD analysis was to describe the relationship between paliperidone plasma concentrations and time to relapse of symptoms of schizophrenia and/or positive and negative syndrome scale for schizophrenia (PANSS) total scores, while accounting for dropout.

#### *Study 3011 PK/PD analysis*

In Study 3011, subjects were individually titrated with Invega Sustenna in the open label phase, to ensure a balance between efficacy and tolerability. Only those subjects meeting clinical stability criteria were subsequently randomised to Invega Sustenna or Invega Trinza treatment, in the double blind phase.

The overall aim of the current population PK/PD analysis was to describe the relationship between the time course of paliperidone plasma concentrations, relapse of symptoms of schizophrenia and dropout (that is withdrawal from study for other causes than relapse of symptoms of schizophrenia), following administration of Invega Sustenna and Invega Trinza in Study R092670-PSY-3011, as well as to identify relevant covariates.

For the full details of the evaluation of the PD aspects please see Attachment 2.

### Evaluator's conclusions on pharmacodynamics

If one accepts the PopPK results above, then:

The PopPK/PD analysis of Study 3012 could really only produce a model for the time to relapse which was the primary endpoint of study 3012. The primary endpoint in Study 3012 showed statistical significance only. The  $C_{\text{trough}}$  at the double blind start and number of hospitalisations affected the model.

Study 3011 showed non-inferiority of Invega Trinza to Invega Sustenna in the primary efficacy endpoint of the percentage of subjects (per protocol) who had not relapsed at the end of the 48 week double blind phase. The PopPK/PD analysis of study 3011 did not look at this, rather the model is studied the obverse of what Study 3011 was designed to show with only a (possible) exploratory Objective 4 possibly related. Two risk factors were included in the final model for the baseline hazard of relapse: Patients on concomitant benzodiazepine medication (since last visit) had higher hazard as compared to when not on this concomitant medication; Patients at Japanese centres had higher hazard as compared to patients at non-Japanese centres.

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<sup>5</sup> PANSS was used to assess neuropsychiatric symptoms of schizophrenia. It has a 30-item scale that provides a total score (sum of the scores of all 30 items; 30-210) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items). Each scale was rated 1 (absent) to 7 (extreme). This gives a range of 180 points (30 to 210).

## Dosage selection for the pivotal studies

The 350 mg equivalent dose was the expected equivalent of the commonly prescribed 100 mg equivalent of the 1 month formulation. The 525 mg equivalent dose was chosen based on the PK and safety results from the preliminary Panel B data and was the planned highest dose to be marketed. The 175 mg equivalent F015 dose was planned to be the lowest dose to be marketed, and a similar dose (150 mg equivalent) was previously tested with gluteal injections (Panel B).

## Efficacy

### Studies providing efficacy data

Pivotal efficacy studies for 3 monthly dosage following initial once a month dosage:

- Study 3012
- Study 3011

### Evaluator's conclusions on efficacy

Statistical significance was shown in the superiority of Invega Trinza over placebo for primary endpoint for Study 3012.

The Independent Data Monitoring Committee (IDMC) charter has under 7.2.1.1 Interim Efficacy Analysis:

*If the p value from the log-rank test on time to relapse at the planned interim analysis was less than 0.0101, the null hypothesis of no treatment difference in time to relapse was to be rejected and the IDMC was to recommend that the study be terminated for significant efficacy. Otherwise, the study was to continue until 70 relapse events were observed. No stopping rules for futility were to be incorporated.*

The minutes of the Independent Data Monitoring Committee show:

*IDMC members agreed that the difference between treatment groups in relapse rates was highly statistically significant and met criteria for early study termination.*

*Based on the review of the interim analysis of the primary efficacy data, the IDMC members voted unanimously, including also Rene Kahn's vote, to discontinue the study due to established efficacy within the pre-specified significance level.*

The minutes do not show that clinical relevance of the difference was discussed.

The sponsor has claimed a clinically significant difference without giving reasons for so claiming.

After receiving for the Maintenance Phase the initial dose of Invega Trinza, only 9/ (305 + 9) or 2.9% withdrew from lack of efficacy. In the Double Blind Phase of those whose treatment with Invega Trinza continued 14/ (134 + 14) or 9.5% withdrew from relapse. While there was a longer exposure (mean 175.1 days versus 80.9 days) in the Double Blind phase<sup>6</sup> the relapse rate is still greater which is especially of concern when the PKs results show that exposure tends to increase ( $C_{min}$  increases Table 5.) from the initial dose until steady state is reached that is one would expect more relapses to occur earlier.<sup>7</sup>

<sup>6</sup> 18 or 11% received a second PP3M injection in that phase

<sup>7</sup> Clarification; some of the difference might be accounted for by the less rigid investigator's opinion criteria used in the Maintenance Phase.

**Table 5: Predose plasma concentrations of paliperidone after administration of PP1M/PP3M during the transition, maintenance and double blind phase**

Predose Plasma Concentrations Paliperidone (N, mean ± SD)	PP1M, 50mg eq. / PP3M, 175 mg eq.			PP1M, 75 mg eq. / PP3M, 263 mg eq.			PP1M, 100 mg eq. / PP3M, 350 mg eq.			PP1M, 150 mg eq. / PP3M, 525 mg eq.		
	n	mean	± SD	n	mean	± SD	n	mean	± SD	n	mean	± SD
<b>Transition Phase (PP1M)</b>												
C <sub>Day 1</sub> , ng/mL	-	-	± -	-	-	± -	-	-	± -	327	7.79	± 11.5
C <sub>Day 64, Week 9</sub> , ng/mL	9	17.4	± 10.5	27	21.5	± 9.06	155	21.6	± 11.9	145	23.0	± 14.0
C <sub>Day 92, Week 13</sub> , ng/mL	6	13.9	± 5.61	28	20.7	± 8.24	148	21.7	± 11.0	135	24.6	± 13.0
<b>Maintenance Phase (PP3M)</b>												
C <sub>Day 120, Week 17</sub> , ng/mL	6	15.1	± 5.75	22	21.0	± 6.94	142	24.1	± 12.5	119	31.7	± 18.1
<b>Double Blind Phase (PP3M)</b>												
C <sub>Day 204, Week 29</sub> , ng/mL	5	10.3	± 4.29	14	18.8	± 9.65	62	22.4	± 11.4	49	27.4	± 14.0
C <sub>Day 268, Week 41</sub> , ng/mL	4	9.44	± 2.12	9	20.2	± 9.33	56	21.5	± 10.4	39	30.1	± 15.0
C <sub>Day 372, Week 53</sub> , ng/mL	3	8.23	± 4.82	6	25.8	± 11.0	34	24.5	± 12.8	27	29.7	± 14.6
C <sub>Day 456, Week 65</sub> , ng/mL	-	-	± -	1	-	± -	8	26.7	± 18.4	16	30.7	± 14.7
C <sub>Day 540, Week 77</sub> , ng/mL	-	-	± -	-	-	± -	1	-	± -	6	36.7	± 8.74
C <sub>Day 624, Week 89</sub> , ng/mL	-	-	± -	-	-	± -	-	-	± -	2	-	± -

Note: The PK report is internally inconsistent with some of these results (for example Table 2) being labelled as after injection. The Study protocol was consulted and it states in its synopsis (Time and events schedule page 22) Venous samples of 4 mL should be obtained prior to dose administration on each PK day.

Of the 42 subjects who experienced a relapse event, 31 subjects (23.0%) were in the Placebo group and 11 subjects (7.4%) were in Invega Trinza group, the difference being statistically significant ( $p < 0.001$  based on the log-rank test).

The instantaneous risk of relapse of schizophrenia symptoms was 3.45 (95% CI: 1.73, 6.88) times higher for a subject switching to placebo than for a subject continuing to receive Invega Trinza in the interim analysis.

The sample size was based on 0.44 as a Hazard Ratio (hazard rate of Invega Trinza/hazard rate of Placebo that is, the inverse of this ratio is used to describe the efficacy result). Inverting 0.44 gives 2.27 that is, greater than the 1.73 lower bound of the 95%CI of the ratio used to describe the efficacy result.

The secondary endpoints in Study 3012 were:

PANSS (total) at End point (double blind) mean (standard deviation (SD)) change from Baseline was placebo 6.7 (14.40), Invega Trinza -0.5 (8.36). That is a difference of 7.2 (4%) from placebo in a 180 point scale.

Clinical global impression –severity (CGI-S) Score at End point (double blind) mean (SD) change from Baseline was placebo 0.4 (0.87), Invega Trinza 0.1 (0.60). That is a difference of 0.3 (4%) from placebo in a 7.0 point scale.

PSP (total) at End point (double blind) mean (SD) change from Baseline was placebo -4.2 (9.70), Invega Trinza -0.5 (6.63). That is a difference of 3.7(4%) from placebo in a 100 point scale.

No multiplicity adjustments were to be made.

Based on 95% CIs non inferiority was shown for the primary endpoint of Invega Trinza compared to Invega Sustenna in Study 3011. However the percentage of relapses for Invega Sustenna at Week 48 was the similar to that seen at interim (primary) analysis in

Study 3001 when only 37% of subjects in the Invega Sustenna group had received at least 5 injections (4 months of injections).

**Comment:** In the absence of a placebo control, equivalence and non-inferiority trials rely on certain assumptions:

- Superior efficacy of the standard treatment over placebo has been convincingly proven for a given indication in previous trials.
- Efficacy of the standard treatment will be preserved under the conditions of the equivalence or non-inferiority trial.
- If the new treatment is shown to have equivalent or non-inferior efficacy, then it too would exhibit superior efficacy to placebo if a placebo controlled trial were to be performed.

These assumptions, and the rationale for equivalence or non-inferiority margins, cannot be validated explicitly. Although new and standard treatments may be shown to be equivalent, they could both be ineffective.<sup>8</sup>

## Safety

### Studies providing safety data

Safety data from these 3 studies were not pooled due to differences in study design and objectives.

The design of these Phase III studies was not intended to support a formal evaluation of the dose response of PP3M for specific safety findings (for example extrapyramidal symptom(s)(EPS)-related adverse events (AEs), weight gain) or tolerability. Subjects were not randomly assigned to distinct dose levels of PP3M upon entering the Double blind Phase.

Any conclusion about a differential effect of PP3M dose on the incidence of adverse events in the Double blind Phase is confounded by the clinical response and tolerability of PP1M for individual subjects in the Open label Phase.

### Patient exposure

The combined exposure to Invega Trinza in the 3 studies included in this submission was 567.6 patient-years, based on 1,191 subjects (308 from PSY-1005, 379 from PSY-3012 and 504 from PSY-3011) who received at least 1 dose of Invega Trinza with 319 subjects (291 from PSY-3011 and 28 from PSY-3012) having at least 48 weeks of Invega Trinza.

For the full clinical evaluation of the safety aspects please see Attachment 2.

### Evaluator's conclusions on safety

The possibility of dose dumping is of concern. Of the 48 patients receiving 525 mg, the 24 receiving it in the deltoid showed a  $C_{max}$  mean of 12.0 ng/mL (median 11.6 ng/mL). Patient 605113 on Days 1 (6 hours post dose), 2, 4, 6, and 10 of Period 2, had measured paliperidone concentrations of 153, 416, 243, 195, and 125 ng/mL, respectively.

Based the appearance of the concentration curves for the 160 subjects receiving Invega Trinza in Study 3012 3 subjects (63801202, 60017109 and 60400605) with high

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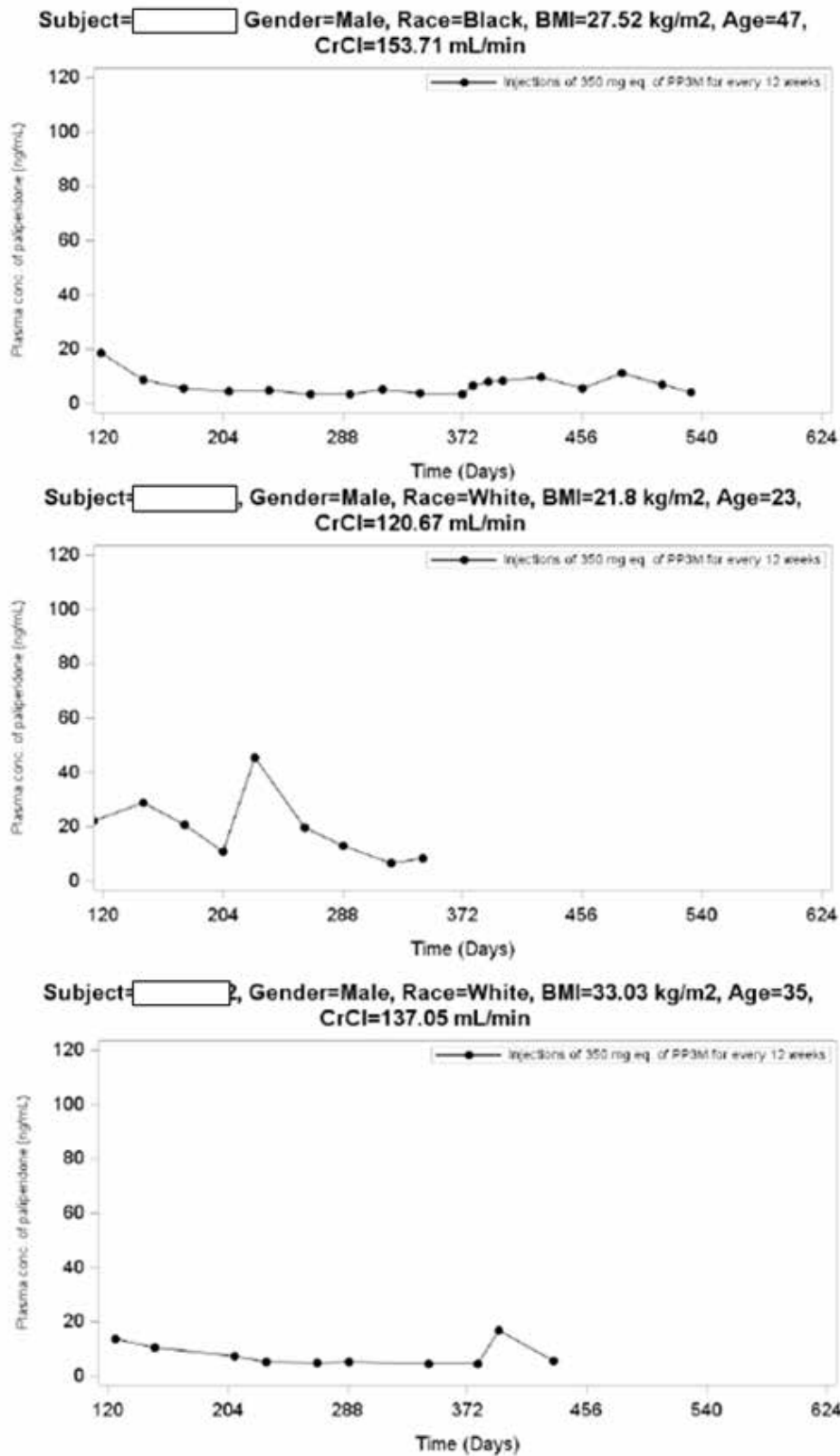
<sup>8</sup>Non-inferiority trials: determining whether alternative treatments are good enough Ian A Scott *Med J Aust* 2009; 190: 326-330.

concentrations suggested the possibility of rapid initial absorption after an injection in that the other injections in the same subjects were not associated with similar high rises. Similar events were seen in 19 of the 446 subjects receiving Invega Trinza in Study 3011.

Also of concern is the possibility of extended periods of low plasma paliperidone concentrations. The sponsor argues that clustering of relapses was not seen at a time when plasma levels would expect to be low. An alternative exploration is to compare the incidence in the first 3 month treatment period with those at steady state (see also Figure 1).

Any conclusion about a differential effect of PP3M dose on the incidence of adverse events in the Double blind Phase is confounded by the clinical response and tolerability of PP1M for individual subjects in the open label phase.

**Figure 1: Paliperidone Concentration-Time Profiles for subjects with < 7.5ng/mL**



## First Round Benefit-Risk Assessment

### First round assessment of benefits

Efficacy of the currently registered one monthly formulation was based on conventional efficacy studies, with subsequent amendments to the Dosage based on PopPK studies.

This submission included a PopPK study of the plasma paliperidone levels resulting from Invega Sustenna treatment which found that the model used previously (to support amended dosage) only fitted the current data if 10% uncertainties were assigned to the parameters.

The existing model did not fit the Invega Trinza absorption data and a two compartment model rather than a one compartment model was necessary.

That is based on the PopPK analyses the new formulation behaves differently from the existing Invega Sustenna formulation.

Evidence for efficacy rests on 2 studies:

- 3012 was a placebo controlled study that was stopped at the interim analysis because it showed statistical significance of Invega Trinza over placebo.
- 3011 was a non-inferiority study of the new formulation against the currently registered active Invega Sustenna formulation. The study did not have a placebo control. It showed non-inferiority in the primary variable. But, based on the sample size, was not powered for the secondary variables and their p values were not given.

Clinical significance was claimed compared to placebo in Study 3012. However it was not discussed. The Lower bound of the 95% CI for the primary variable was less than the Hazard Ratio used to determine the sample size. The secondary variables all showed a 4% difference from placebo.

The benefits the sponsor claims in the proposed usage are:

- The PP3M formulation is expected to have advantages in terms of medication adherence and ease of use.
- These benefits are likely to be particularly valuable for patients who prefer less frequent injections, those with limited access to healthcare, those who live in an underserved rural or inner city setting, and those who cannot coordinate bi-weekly or once monthly transportation for injection visits.
- PP3M reduces the time needed for monitoring and follow-up of patients for medication adherence, potentially providing health care providers with additional time for implementing or monitoring psychosocial programs.
- PP3M is supplied in prefilled syringes that do not require reconstitution or refrigeration, further enhancing the ease of use of this long-acting injectable (LAI) antipsychotic, especially in remote areas with limited healthcare provisions.

### First round assessment of risks

It is of concern that the PK model used for simulations to justify dosing regimens does not include data from the long term Study 3011 being based on the single dose Study 1005 and Study 3012 where 160 received 2 injections of Invega Trinza only 18 received 3 injections.

The possibility of dose dumping is also of concern. In study 1005 one of the 48 patients receiving 525 mg equivalent had this occur. In study 3012 in the 160 subjects receiving Invega Trinza a further 3 possible events were seen and in Study 3011 similar events were

seen in 19 of the 446 subjects receiving Invega Trinza; the infrequency of paliperidone measurement precluded clearer evaluation.

The PopPK studies did show the possibility of below therapeutic levels occurring in some patients with some dosage regimens, and some subjects did show this.

The sponsor argues that clustering of relapses was not seen at a time when plasma levels would expect to be low.

*'Any conclusion about a differential effect of PP3M dose on the incidence of adverse events in the double blind phase is confounded by the clinical response and tolerability of PP1M for individual subjects in the open label phase.'*

The sponsor proposes:

*'PP3M shares the same active moiety as well as the same route of administration and formulation characteristics with the commercially-available PP1M product, the Company believes that the overall extent of exposure (total number of subjects exposed) and the well documented safety profile of PP1M are particularly relevant for PP3M.'*

However the PopPK models submitted differ between the existing registered Invega Sustenna and this proposed good (Invega Trinza) that is they show an *in vivo* difference in absorption and covariates between the two.

Most of the comparisons for Safety the sponsor makes are between Invega Sustenna and Invega Trinza rather than with placebo.

In study 3012 (Placebo 145 subjects, Invega Trinza 160), while the overall number of subjects having an adverse event (AE) were similar, URTI and nasopharyngitis were 9.4% for Invega Trinza versus 3.5% for placebo in the double blind phase, weight increase was 8.8% versus 3.4%, headache was 8.8% versus 4.1% and akathisia 4.4% versus 0.7%. The psychiatric events relevant to schizophrenia were higher in the placebo group.

## **First round assessment of benefit-risk balance**

### **From CPMP/EWP/49/01**

Long-acting parenteral antipsychotic medications have several advantages over short-acting oral or intra-muscular agents when administered for the treatment of chronic schizophrenia. The major advantage is the assurance of compliance leading to fewer relapses and re-hospitalisations.

As the efficacy and safety of the immediate formulation is accepted, in line with the modified release guideline, a bridging program should be performed to support the indication.

The purpose of the development is:

- to establish the full pharmacokinetics of the novel formulation including the relevant release properties and thus to show that the formulation is a depot
- to compare bioavailability of the active ingredient from the depot versus the oral formulation, to assess the duration of an acceptable level of the active ingredient
- to compare the efficacy versus the oral formulation in stabilised patients
- to address switching from oral to the depot formulation
- to assess safety issues specific to the depot formulation.



It has been discussed whether these points could be addressed by pharmacokinetic studies and safety data alone. For this the relation between PK and effect should be known.

Most of these dot points have been fulfilled.

1. To compare the efficacy versus the oral (in this case 1month versus 3month) formulation in stabilised patients. This was conducted in Study 3011. To quote the guideline 'Placebo, as an additional arm would ensure assay sensitivity.' 37 subjects (8.1%) in the Invega Trinza group and 45 subjects (9.2%) subjects in Invega Sustenna group had a relapse event during the Double blind Phase. In interpreting the non-inferiority result the population size calculations to show with 90% power that PP3M was no worse than PP1M were based on an expected survival (percentage of subjects remaining relapse-free) rate in PP1M of 70%. Whereas Study 3001 showed a 10% relapse rate (90% survival) on Invega Sustenna at the time of the Interim (primary) Analysis when only 37% of subjects in the Invega Sustenna group had received at least 5 injections (4 months of injections).
2. To assess safety issues specific to the depot formulation. The sponsor undertook adequate length of exposure showing there exists an approximate 2% risk of dose dumping (high initial levels of paliperidone). The sponsor has generally reviewed the risk of increased AEs against those of the existing approved formulation.

Against these deficiencies the sponsor has the results of a physicians' survey that showed a willingness by physicians to accept a decrease in efficacy for patients with a history of poor adherence to dosing.

This evaluator finds the benefit-risk balance of Invega Trinza, given the proposed usage, and based on the guideline is favourable but with some reservations in relation to the approximately 2% incidence of dose dumping.

## **First Round Recommendation Regarding Authorisation**

It is recommended that authorisation of registration occur, but with the proviso that the PI carry a warning on dose dumping.

## **Clinical Questions and Second Round Evaluation of clinical data submitted in response to questions**

For details of the clinical questions and the sponsor's responses and the evaluation of these responses please see Attachment 2.

## **Second Round Benefit-Risk Assessment**

### **Second round assessment of benefits**

No new clinical information was submitted in response to questions. Accordingly, the risks are unchanged from those identified in the first round assessment of benefits.

### **Second round assessment of risks**

No new clinical information was submitted in response to questions. Accordingly, the risks are unchanged from those identified in the first round assessment of risks.

## Second round assessment of benefit-risk balance

The benefit-risk balance is thus considered unchanged.

## Second round recommendation regarding authorisation

In commenting on this evaluator's recommendations concerning the proposed PI the sponsor objected to the use of the term 'dose dumping. The recommendation regarding authorisation is recommended accordingly.

# V. Pharmacovigilance findings

## Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 7.0 (dated 9 March 2015) and Australian Specific Annex Version 1.0 (dated 22 September 2015) which was reviewed by the RMP evaluator.

## Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 6.

**Table 6: Ongoing safety concerns**

Ongoing safety concerns	
<b>Important identified risks</b>	<p>Hyperprolactinaemia and potentially prolactin-related adverse events</p> <p>QT prolongation</p> <p>Orthostatic hypotension</p> <p>Extrapyramidal symptoms/tardive dyskinesia</p> <p>Neuroleptic malignant syndrome</p> <p>Diabetes mellitus and hyperglycaemia-related adverse events</p> <p>Weight gain</p> <p>Seizures</p> <p>Somnolence</p> <p>Priapism</p> <p>Cerebrovascular accident</p> <p>Venous thromboembolism</p> <p>Leukopenia</p> <p>Agranulocytosis</p> <p>Thrombocytopenia</p> <p>Rhabdomyolysis</p> <p>Elevated plasma concentrations in patients with renal disease</p> <p>Injection site reactions (injectable formulations only)</p>

Ongoing safety concerns	
	Hypersensitivity reactions (injectable formulations only)
<b>Important potential risks</b>	<p>Carcinogenicity (pituitary adenomas, endocrine pancreas tumours, breast cancer)</p> <p>Overall increased mortality in elderly patients with dementia</p> <p>Cerebrovascular adverse events in elderly patients with dementia</p> <p>Cognitive and motor impairment</p> <p>Body temperature dysregulation</p> <p>Suicidality</p> <p>Depression in patients with affective disorders (INVEGA only)</p> <p>Increased sensitivity to antipsychotics in patients with Parkinson's disease or</p> <p>Dementia with Lewy bodies</p> <p>Gastrointestinal obstruction (in patients with pre-existing severe gastrointestinal narrowing [pathologic or iatrogenic] or in patients with dysphagia or significant difficulty in swallowing tablets) (INVEGA only)</p> <p>Decreased bone mineral density/osteoporosis</p>
<b>Missing information</b>	<p>Use in haemodialysis patients</p> <p>Exposure during pregnancy</p> <p>Exposure via breastfeeding</p>

### Pharmacovigilance plan

The sponsor is proposing routine pharmacovigilance activities for all specified safety concerns.

Although specified in the EU RMP a specific adverse event follow-up questionnaire for the important identified risk 'injection site reactions' is not proposed for Australia and has been discontinued in the EU.

The following ongoing activity is proposed as additional pharmacovigilance in the EU RMP (Table 7)

**Table 7: Additional proposed pharmacovigilance in the EU RMP**

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Post-Authorisation Safety Study (PASS) of cardiovascular and cerebrovascular adverse events in elderly patients treated with paliperidone PR, paliperidone palmitate and other antipsychotics.  (Category 2 for Xeplion) (Category 3 for Invega)	Important identified risk: cerebrovascular accident  Important potential risks: Overall increased mortality in elderly patients with dementia and Cerebrovascular adverse events in elderly patients with dementia.	To estimate the incidence of cardiovascular and cerebrovascular events among elderly patients treated with XEPLION, INVEGA, and other oral and parenteral antipsychotics.  To compare the incidence of cardiovascular and cerebrovascular events among elderly patients treated with paliperidone (stratified according to INVEGA users and XEPLION users) to the incidence among elderly patients treated with other oral and parenteral antipsychotics.  To describe the demographic characteristics, comorbidities, and concomitant medications among elderly (age ≥ 65 years) patients treated with INVEGA, XEPLION, and other oral and parenteral antipsychotics.	End of 2015

### Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities only are sufficient to mitigate the risks associated with the product.

Advice will be sought from the ACSOM regarding the sufficiency of the risk minimisation plan to mitigate risks associated with Invega Trinza. Specifically, advice will be sought regarding the adequacy of routine risk minimisation activities alone to mitigate safety issues relating to the 3 month formulation in clinical practice. This advice will be considered in the round 2 RMP evaluation.

The sponsor should justify the absence of an educational program to cover topics including but not limited to appropriate patient selection, injection technique, missed doses, re-initiation and safe use of the 3 month product.

### Reconciliation of issues outlined in the RMP report

#### *TGA recommendation 1*

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the

sponsor should provide information that is relevant and necessary to address the issue in the RMP.

*Sponsor's response:*

The sponsor confirms that comments made within the Nonclinical and Clinical Evaluation reports have been considered with regard to relevance to the RMP. The sponsor does not consider there to be any updates required to the RMP based on the sponsor's responses to the evaluators' questions/comments to date.

*RMP evaluator comment:*

It is noted that the clinical evaluator raised concerns around 'dose dumping', and therefore this issue has been referred to the Delegate for consideration. This is also discussed below under TGA recommendation 5 (below) and in the ACSOM advice.

**TGA recommendation 2**

Given the implications of incorrect administration of the 3 monthly injectable product the sponsor should justify the omission of 'medication error' as an important potential risk.

*Sponsor's response:*

The sponsor does not consider there any reason to suggest that 'medication error' should be added as an important potential risk for Invega Trinza. As reported in the RMP, medication errors reported during clinical and post-marketing use of PP1M and PP3M are regularly assessed as part of routine pharmacovigilance. These assessments have not revealed any signal that medication error should be regarded as a risk for Invega Sustenna or Invega Trinza.

As discussed in the RMP, several preventive steps have been taken to mitigate the risk of medication error with PP3M (including consideration of the product name and packaging design). In addition, a training and educational program is planned to accompany the introduction of the product in Australia, similar to what has been done in the United States (US) and the EU. This will be aimed at educating healthcare providers.

The sponsor considers these measures, along with routine pharmacovigilance, are sufficient to manage and monitor any potential for medication error with Invega Trinza and help ensure safe and effective use of the product.

*RMP evaluator comment:*

The sponsor's response is noted. However, the reasoning provided indicates that the sponsor is taking additional measures to reduce the risk of medication error. In addition, ACSOM raised concerns regarding medication error as they concluded that the level of medication error in the clinical trials was relatively high, and was expected to be higher in clinical practice. Therefore, it is recommended that medication error is added as an important potential risk in the summary of safety concerns, and the associated additional risk minimisation activities of health care provider education is also included in a revised ASA.

**TGA recommendation 3**

The sponsor should provide justification for the omission of 'inability to rapidly discontinue treatment' or similar as a safety concern.

*Sponsor's response:*

The sponsor acknowledges that it takes several months for paliperidone plasma concentrations to fall following discontinuation of PP3M. This was an important consideration for the sponsor when developing the PP3M clinical trial program and the proposed therapeutic indication. For this reason, the proposed indication for PP3M has been restricted for use only in those patients who have been adequately treated with the

1 month formulation (PP1M) for at least 4 months. The dosage and administration guidance in the PI also states that: *'In order to establish a consistent maintenance dose, it is recommended that the last two doses of the 1 month injection be the same dosage strength before starting Invega Trinza.'* This guidance is to further highlight that patients should be on a stable dose of PP1M prior to converting to PP3M.

Four months is considered the minimum time in which an adequate and stable maintenance dose of PP1M can be established, and also considered a sufficient period to allow for detection of any tolerability issues with the compound. Thus, if a patient does need to withdraw from treatment due to a tolerability issue, this is most likely to happen during the PP1M treatment period rather than after the transition to PP3M. This is supported by the low discontinuation rates observed following conversion to PP3M in the Phase III PP3M clinical studies. In Study PSY-3011, 3% of subjects in the PP3M treatment arm and 3% of subjects in the PP1M treatment arm discontinued treatment due to an adverse event during the double blind Phase, with the majority of subjects completing the 48 week treatment period (84% and 82%, respectively). In Study PSY-3012, no subjects in the PP3M treatment arm discontinued from the double blind Phase due to an adverse event.

The current Invega Trinza PI includes several statements to highlight the long-acting nature of the Invega Trinza formulation to prescribers. The dosage and administration section of the Invega Trinza PI states that *'If Invega Trinza is discontinued; its prolonged release characteristics must be considered.'* Within the precautions section of the Invega Trinza PI, the following sections are supplemented with the statement *'Consideration should be given to the long-acting nature of Invega Trinza'* warning prescribers of the possible persistence of related adverse effects:

- Neuroleptic Malignant Syndrome
- Tardive dyskinesia
- Leukopenia, neutropenia and agranulocytosis

Additionally, the following sections of the Invega Trinza PI also contain warnings regarding the long-acting nature of Invega Trinza:

- Potential for other drugs to affect Invega Trinza
- Use in pregnancy
- Use in lactation
- Overdose

The sponsor therefore considers that the current statements within the PI adequately address the prolonged release nature of Invega Trinza.

Overall, the sponsor does not consider the 'inability to rapidly discontinue treatment' to be a specific safety concern for Invega Trinza. The current guidance and warnings in the Invega Sustenna PI, along with routine pharmacovigilance, are considered sufficient to minimize and monitor any issues related to inability to rapidly discontinue treatment.

*RMP evaluator comment:*

The sponsor's comments have been considered. The concern regarding the inability to rapidly discontinue treatment in the occurrence of an adverse event has been recognised by the sponsor. The RMP evaluator respectfully disagrees with the sponsor's conclusion that this does not constitute a specific safety concern. The inability to withdraw treatment when a serious adverse event emerges, impacts the risk-benefit balance of the product; which supports its classification as an important identified risk, based on the definitions in

the EMA guideline.<sup>9</sup> Therefore, the RMP evaluator recommends that the safety concern of 'inability to rapidly discontinue treatment' is captured in the safety specification as an important identified risk.

#### ***TGA recommendation 4***

Acute psychotic episodes will invariably be treated with additional antipsychotics/sedatives whilst the patient is being treated with Invega Trinza. Cumulative effects of antipsychotics can be problematic for a number of body systems. This is complicated by the inability to rapidly discontinue a 3 month product with action possibly extending past 3 months (according to the PI the release of the drug may last for as long as 18 months). The sponsor should confirm whether the safety of additional antipsychotic treatment for acute episodes whilst on Invega Trinza has been specifically studied. If not, the sponsor should specifically comment on whether such a situation is expected to raise safety issues in real world use.

#### *Sponsor's response:*

Concomitant use of PP3M with other antipsychotics has not been specifically studied. In the Phase III studies (PSY-3011 and PSY-3012), use of concomitant antipsychotics was not permitted per protocol. However, concomitant antipsychotic medication (that is, continuation of pre-existing medication) was allowed in the single dose study (PSY-1005). In this study, patients on a stable dose of oral antipsychotic medication were give a single dose of PP3M (varying by injection location and dose). Overall, tolerability of the addition of PP3M to other antipsychotic medications was good with reasonably low numbers of adverse events, considering the population and the time patients were monitored (12 to 18 months).

The Invega Trinza PI contains the following warning regarding use of PP3M with other antipsychotics:

*'Since paliperidone is the major active metabolite of risperidone, the co-administration of Invega Trinza with oral risperidone or paliperidone is likely to result in an increase in the paliperidone concentration, within the bloodstream. Caution should be exercised when Invega Trinza is co-administered with risperidone or with oral paliperidone for extended periods of time.'*

*Safety data involving concomitant use of Invega Trinza with other antipsychotics is limited.'*

While the data is limited on the use of PP3M with other antipsychotics, the sponsor is aware that polypharmacy occurs in real-world use. It would not be expected that there would be any different issues related to polypharmacy with Invega Trinza than PP1M or any other antipsychotic. Since PP3M is meant to be used predominantly as monotherapy, and it is stated in the label that experience with the concomitant use of other antipsychotics is limited, the sponsor would expect healthcare professionals to monitor for increased side effects when starting additional antipsychotic treatment, as this would be standard of care.

#### *RMP evaluator comment:*

The sponsor has reported that there is little data on Invega Trinza in combination with other antipsychotics, and that polypharmacy can be expected in the 'real world'. This was also noted by ACSOM, and the committee advised that these issues raise the possibility of unexpected drug interactions. The PI contains statements that indicate limited safety data for concomitant use with other antipsychotics, and caution for use with drugs known to

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<sup>9</sup> EMA/838713/2011 Rev 2 Guideline on good pharmacovigilance practices (GVP) Module V – risk management systems (Rev 2).

prolong QT interval. These measures are considered adequate as the drug interactions are unlikely to be different from those with oral or 1 month formulations of paliperidone.

#### ***TGA recommendation 5***

The sponsor should provide a justification as to why dose dumping is not included as a separate safety concern for the 3 month formulation.

#### *Sponsor's response:*

As previously discussed in response to the clinical evaluator, the sponsor does not consider there is evidence to suggest that dose dumping should be considered a separate safety concern for the 3 month formulation.

As noted in Section 2 above (see Question 3), only 1 case of potential partial IV administration was suspected in the PP3M clinical trial program based on the presence of paliperidone palmitate in plasma samples and a relatively high paliperidone concentration (416 ng/mL) in a subject who received a single dose of 525 mg eq. This was not recorded as a medication error adverse event. Of note, this subject did not experience any adverse events around the time of partial IV administration, and extrapyramidal symptoms (EPS) rating scales did not meaningfully change at Day 6. Therefore, this patient was able to tolerate very high levels of paliperidone without any adverse effects.

Similarly, clinical review of safety data across all PP3M clinical trials in other subjects who experienced a plasma concentration > 125 ng/mL showed no evidence to suggest plasma concentrations > 125 ng/mL were associated with increased adverse effects.

Concentrations > 125 ng/mL were predominantly observed in the PP3M 525 mg eq. or PP1M 150 mg eq. dose group, and most likely due to inter-subject variation. Overall, no clear cases of dose dumping were observed in the Phase III studies. The level of 125 ng/mL is not indicative of dose dumping, and should simply be regarded as a value above the 95th percentile for  $C_{max}$  after the fourth injection of PP3M 525 mg eq. in the deltoid and gluteal sites, based on in the population PK model. Further, there were no clear pattern of adverse events in these patients with higher levels, and no safety issue was identified due to high drug levels.

Likewise, no cases of dose dumping have been reported with PP3M based on post-marketing experience to date (including estimated exposure of 3,614 person-years based on the 14,455 syringes of PP3M distributed up to 31 December 2015).

There is no reason to suspect that the risk of inadvertent IV administration or dose dumping will be any greater for PP3M than it is for PP1M. Both products are administered by a healthcare professional, and both products are administered via IM injection using the same injection technique. Extensive clinical and post-marketing experience with PP1M indicates a low risk of IV administration with this product. Based on a cumulative review of post-marketing data with PP1M (including an estimated 767,937 person-years of exposure, based on the 7,444,590 syringes of PP1M distributed worldwide from launch to 31 December 2014) only 11 cases of IV administration were reported. Furthermore, review of the cases involving an IV administration revealed no cases indicative of increased PP1M plasma levels.

In conclusion, the sponsor does not consider dose dumping to be a safety concern for PP3M.

#### *RMP evaluator comment:*

This resolution of this issue is being undertaken by the clinical evaluation unit (see comment for TGA recommendation 1, above).



**TGA recommendation 6**

Introduction of Invega Trinza, a 3 monthly injectable antipsychotic, has the potential to substantially change the landscape of depot antipsychotic treatment in Australia. Currently available depot products are typically administered fortnightly, or at most monthly. Whilst the introduction of a longer acting product may have positive effects on medication compliance there are disadvantages to long term treatments including the inability to rapidly discontinue treatment in the setting of adverse events. This issue importantly differentiates the 3 month product from a safety perspective. The sponsor should therefore justify the absence of specific pharmacovigilance activities to monitor this safety concern.

*Sponsor's response:*

As noted in the response to RMP Question 3, the sponsor acknowledges it takes several months for paliperidone plasma concentrations to fall following discontinuation of PP3M. However, the sponsor does not consider this to be a specific safety concern.

The current Invega Trinza PI requires that patients first receive treatment with PP1M for at least 4 months prior to converting to PP3M; this is considered a sufficient period in which to identify patients with intolerable side effects who may require treatment discontinuation. Thus, treatment discontinuation is most likely to occur during treatment with the shorter-acting PP1M, rather than with PP3M. The PI also contains several statements to highlight the long-acting nature of the product to prescribers (see RMP Question 3).

Overall, the sponsor considers the current guidance and warnings in the Invega Sustenna PI, along with routine pharmacovigilance, are sufficient to minimize and monitor any risks related to inability to rapidly discontinue treatment.

*RMP evaluator comment:*

See RMP evaluator comment for TGA Recommendation 3 and outstanding issues.

**TGA recommendation 7**

In addition, the issue mentioned in section 7 regarding the cumulative effects of other antipsychotics in the setting of an acute psychiatric episode on the background of Invega Trinza treatment need consideration in terms of the pharmacovigilance plan.

*Sponsor's response:*

As noted in the response to RMP Question 4, the sponsor does not consider the effects of other antipsychotics to be a safety issue. Routine pharmacovigilance includes a detection system that is reviewed monthly to capture any increase in reporting of individual adverse events. This would be adequate to pick up an issue with cumulative effects of other antipsychotics

*RMP evaluator comment:*

See RMP evaluator comment for TGA Recommendation 4

**TGA recommendation 8**

The long-term nature of the proposed treatment also has particular implications for women of childbearing age. If pregnancy were to occur on treatment with Invega Trinza (proposed Pregnancy Category C<sup>10</sup>) the options to change/discontinue therapy could be

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<sup>10</sup> Pregnancy category C is defined as: *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

quite limited for a substantial proportion of the pregnancy. It is unclear how this risk will be monitored or minimised.

*Sponsor's response:*

As noted in the PI, Invega Trinza should only be used during pregnancy if the benefits outweigh the risks. Pregnancy is not a contraindication for the use of Invega Trinza.

The Invega Trinza PI does contain a specific statement within the pregnancy section which highlights the long acting nature of this product. The specific text is shown below (note that this text includes some revisions that were proposed by the sponsor in response to evaluator's comments within the nonclinical evaluation report:

*'Since paliperidone has been detected in plasma up to 18 months after a single dose administration of Invega Trinza, consideration should be given to the long-acting nature of Invega Trinza as maternal exposure to Invega Trinza before or during pregnancy may lead to adverse reactions in the newborn child.'*

The sponsor considers this statement to be a sufficient warning to prescribers who are considering the use PP3M in a woman of child bearing potential.

*RMP evaluator comment:*

The proposed PI statements to minimise risk in pregnancy are generally considered appropriate. The lack of teratogenicity in animal studies with paliperidone and risperidone allay some of the concerns regarding exposure in the first trimester.

**TGA recommendation 9**

Advice will be sought from the Advisory Committee on the Safety of Medicines (ACSOM) regarding the capability of the pharmacovigilance plan to monitor the safety of real world use of this product in Australia given the issues raised above.

*Sponsor's response:*

Janssen has made note of this comment

*RMP evaluator comment:*

The ACSOM advice is discussed below

**TGA recommendation 10**

Advice will be sought from the ACSOM regarding the sufficiency of the risk minimisation plan to mitigate risks associated with Invega Trinza. Specifically, advice will be sought regarding the adequacy of routine risk minimisation activities to mitigate safety issues relating to the 3 month formulation in clinical practice.

*Sponsor's response:*

Janssen has made note of this comment.

*RMP evaluator comment:*

The ACSOM advice is discussed below.

**TGA recommendation 11**

The sponsor should justify the absence of an educational program to cover topics including but not limited to appropriate patient selection, injection technique, missed doses, re-initiation and safe use of the 3 month product.

*Sponsor's response:*

Education on the above mentioned topics is considered to be part of the preparation for product introduction to market in Australia, and not as part of a formal educational program detailed in the RMP/ASA for additional risk minimisation. This is considered by

the sponsor to be adequate at this time to help ensure safe and effective use of the product.

*RMP evaluator comment:*

See evaluation of response to TGA recommendations 13 and 14, below.

**TGA recommendation 12**

One proposed trade name for this product is Invega Trinza. The registered once monthly injectable product is named Invega Sustenna. The sponsor should explain what measures, other than the name and packaging differences, are being taken in Australia to minimise the risk of inadvertently switching products as it is likely that both formulations will be stocked in mental health formularies.

*Sponsor's response:*

As discussed in the RMP and summarized below, the sponsor has taken several measures to prevent inadvertent switching between the 1 month and 3 month products.

Appropriate labelling and packaging artwork has been developed to differentiate Invega Sustenna and Invega Trinza to reduce the chance that an error confusing these products will occur during any phase of the medication use process. Different design and colours have been used for Invega Trinza versus Invega Sustenna.

The Invega Trinza dosage strength is presented in large and BOLD font on the outer carton and is also clearly stated on the syringe label. The colour coding per strength is carried through the packaging component hierarchy. Additional risk management labelling measures for Invega Trinza are as follows:

- The instructions to 'Administer once every 3 months' with pictogram and 'Shake syringe vigorously for at least 15 seconds' with pictogram have been added to the outer carton.
- The instruction 'shake vigorously' with pictogram is added to the syringe label.
- The information intended for medical or health care professionals (IFU) contains the same pictograms for 'Shake syringe vigorously for at least 15 seconds' and 'Administer once every 3 months' as depicted on the syringe label and outer carton and enhances the link with Invega Trinza.

Besides the differentiation of the packaging and syringe label, differentiation is also obtained by selection of the name. The results from a Failure Mode and Effect Analysis (FMEA) looking at mix-up risk based on inputs from 100 European healthcare professionals considered the use of a qualifier (Invega Trinza) as the clearest approach for identifying and differentiating the proposed 3 month paliperidone palmitate formulation from the 1 month formulation, such that in prescription communications practitioners will have an additional piece of information (the qualifier), in addition to the distinctive strength of 3 month paliperidone palmitate, in order to correctly identify the product and help protect against confusion with the once every month Invega Sustenna.

Both the qualifier naming strategy and the differentiated labelling as well as packaging will facilitate correct interpretation of the prescription and product selection from dispensing and administering perspectives, thereby minimizing the risk of potential confusion between PP1M and PP3M and eliminating the need for additional measures. Thus, we believe that Invega Sustenna and the proposed Invega Trinza can safely coexist in the marketplace without any confusion.

*RMP evaluator comment:*

The RMP evaluator considers the proposed packaging and labelling to be sufficient risk minimisation measures to address the concern for confusion between the one and three month dosage forms.

**TGA recommendation 13**

The PI includes advice to shake the pre-filled syringe vigorously for 15 seconds prior to administration and to repeat if 5 minutes elapse after shaking. The sponsor should advise if there are any expected safety implications if the medication is administered without properly suspending it.

*Sponsor's response:*

The instruction to vigorously shake the PP3M syringe for 15 seconds is to ensure adequate re-suspension of the product prior to injecting. Inadequate re-suspension may result in incomplete injection of the product, resulting in lower than expected paliperidone exposure. In terms of safety, this error would not result in any increased tolerability issues but may potentially compromise efficacy if paliperidone plasma concentrations fall below the patient's individual therapeutic level.

The sponsor is aware of the need to make sure that PP3M is sufficiently shaken. Education and training of clinical staff involved in the injections will be important. There will be additional training material including educational videos and training regarding adequate shaking technique (shake vigor/motion and duration) to ensure correct and proper re-suspension of the product. Also of note, compared to the investigational product, the commercial syringes have a transparent label so that it is much easier to see if the contents are in a suspension and if the entire volume has been injected.

Training on sufficient shaking of the PP3M suspension was shown to effectively reduce occurrence of incomplete injections during the PP3M clinical trial program. In Study PSY-1005, some incomplete injections were observed during Panels A and C, and increased training of investigators was implemented prior to the subsequent panels (Panels B and D). With this increased training, no further incomplete injections were observed in Panel B or D; this was confirmed by inspection of the syringes post injection by sponsor staff to check for residual content. Additionally, the relative bioavailability of PP3M compared to immediate-release paliperidone was approximately 100% for all PP3M doses tested in Panel B and Panel D, suggesting that complete PP3M doses were injected in those panels.

In the Phase III studies (PSY-3011 and PSY-3012), the importance of shaking vigorously was emphasized during investigator meetings and there was required training for all staff involved in injections, including a video. Study drug administrators were instructed to inspect the syringe after injection to make sure there was no residual fluid. Any instances of residual fluid or anomalies with the product were recorded as a product quality complaint (PQC). If there was a PQC, the sponsor also inspected the syringes. In Study PSY-3012, no incomplete injections were observed. In Study PSY-3011, 5 incomplete injections occurred in subjects assigned to PP3M (all with active product), which were identified by PQCs as described in the clinical study report (CSR). After investigation, it was determined that these were caused by incomplete shaking. Of note, none of these 5 patients had a relapse event. Thus, incomplete injections observed in the Phase III studies did not appear to impact efficacy.

*RMP evaluator comment:*

The sponsor's response has been considered in combination with the ACSOM advice. The proposed educational plan appears appropriate to address the concerns regarding incomplete dosing/ medication error. The data from clinical trials which demonstrated a decrease in medication errors following the educational material could be considered a

measure of effectiveness for these activities. As noted in the ACSOM advice, there was concern that if medication errors occurred in the controlled setting of a clinical trial, that they could be expected to occur more frequently in clinical practice. This reinforces the need for the proposed educational materials. The RMP evaluator concludes that these are additional risk minimisation activities, and therefore these programmes should be described and attached as an appendix in a revised ASA.

***TGA recommendation 14***

It appears that the sponsor is conducting what would be considered to be additional risk minimisation activities for healthcare professionals and patients in the United States<sup>11</sup>. This includes an instructional video, patient brochure and other educational resources. However routine risk minimisation only is proposed in the EU RMP and the ASA. The sponsor should confirm whether a similar program to what is being conducted in the United States will be implemented in Australia. If so, the RMP/ASA requires revision to include details of this program including draft materials, distribution strategy and proposed measures of effectiveness.

*Sponsor's response:*

A similar program as was implemented in the US is planned to accompany the introduction of the product in EU. In the EU, these activities are considered to be part of preparation for product introduction to market, and not steps that are to be included in the EU RMP as additional measures to be taken.

In Australia, a similar program will be aimed at education of healthcare providers, and (as per EU) are considered as part of preparation for product introduction to market and not as a formal educational program detailed in the RMP/ASA for additional risk minimisation. This is considered by the company to be adequate at this time to help ensure safe and effective use of the product.

*RMP Evaluator comment:*

The US patient information brochure includes important safety information regarding adverse effects, and addresses many of the important identified risks. A similar information brochure is recommended for use in Australia, and is considered to be an additional risk minimisation activity. The patient brochure intended for Australia should be submitted as an appendix to a revised ASA. If prescriber educational materials beyond those referred to in response to TGA recommendation 13 are planned, these should also be included in a revised ASA.

***TGA recommendation 15***

The evaluator is unable to locate the product insert referred to on the product box mock-up. The sponsor should submit a copy of the product insert unless it has been previously provided.

*Sponsor's response:*

As this is an injectable product, the PI will form the package insert. As the PI is still being evaluated, the sponsor provides assurance, to the RMP evaluator, that the approved PI will be the package insert.

*RMP Evaluator comment:*

The sponsor's commitment to provide the approved PI as the package insert has been noted.

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<sup>11</sup> <https://www.invegatrinzahcp.com/>

**TGA recommendation 16**

Use of a 3 month product is a complex clinical decision, including anticipation of possible adverse events and risk factors for adverse events and should not be made solely on the patient having a stable shorter acting paliperidone dose. From a risk minimisation perspective the Delegate is advised that it would be helpful if more advice recognising the complexities of a 3 month treatment was included in the PI. The clinician should carefully weigh the risks and benefits for that particular patient as well as the established stability of paliperidone prior to commencing treatment.

*Sponsor's response:*

The sponsor agrees that the clinician needs to carefully weigh the risks and benefits when considering a transition to PP3M. As with all treatment decisions, the decision to initiate PP3M should be made based on careful evaluation of the patient's medical history, concomitant medications, and medication preferences, etcetera. This is inherent for all treatment decisions.

The sponsor believes that the current guidance in the Invega Trinza PI is sufficient to inform clinicians of the complexities of 3 monthly treatment, and the need to establish patients on a stable maintenance dose of PP1M prior to conversion to PP3M.

The PI provides clear guidance with regard to the minimum requirement of at least 4 months prior treatment with PP1M prior to the switch to PP3M. Also, the dosage and administration section further highlights the need to first establish patients on a consistent maintenance dose, by recommending that the last 2 doses of PP1M be the same dosage strength before starting Invega Trinza.

If a patient is stable on PP1M prior to converting to PP3M, there should be no reason to suspect that the efficacy or tolerability of therapy will change following the conversion to PP3M. This was demonstrated in the non-inferiority study, PSY-3011, where both treatment arms (PP1M and PP3M) had similar efficacy as well as safety. As discussed above, the low rates of relapse and low discontinuation rates over 48 weeks indicate the adequacy of the initiation with PP1M and the importance of establishing an effective dose of PP1M prior to starting PP3M.

*RMP evaluator comment:*

The sponsor's response has been noted. Additional recommendations were made (see below) which are intended to provide additional support to prescribers and support the safe use of this formulation of paliperidone.

**TGA recommendation 17**

From a risk minimisation perspective the PI would benefit from further elaboration on the definition of the 'adequately treated' patient. Patients prone to relapse with background antipsychotic treatment, including those with comorbid illicit drug use, may be less suitable for Invega Trinza given the possible cumulative effects of additional antipsychotics used to treat acute episodes.

*Sponsor's response:*

As stated in the response to RMP Question 16, the decision to initiate PP3M should be made based on careful assessments of the patient's medical history, concomitant medications, and medication preferences, etcetera.; and the benefit risk balance of the drug should be carefully considered for each individual patient.

Invega Trinza is recommended for patients who have been treated with Invega Sustenna for at least 4 months and the last two doses of Invega Sustenna should be the same. This is considered 'adequately treated.' This recommendation is based on the outcome for the two Phase III trials which showed robust efficacy and no new or unexpected safety



findings were identified. The sponsor considers the PI provides appropriate guidance for the prescribers and flexibilities for them to make informed decision based on a patient's conditions.

*RMP evaluator comment:*

The sponsor's definition of 'adequately treated' has been noted. Additional recommendations to identify suitable patients were discussed below.

**TGA recommendation 18**

In general the precautions included in the approved PI for Invega Sustenna contain more comprehensive information than the precautions proposed for Invega Trinza. In the absence of a compelling justification for these differences the RMP evaluator would favour the revision of the Invega Trinza precautions to better align with those in the Invega Sustenna PI.

*Sponsor's response:*

As previously noted in response to Question 16, the sponsor has agreed to revise the text in the Invega Trinza PI to align with the Invega Sustenna PI.

*RMP evaluator comment:*

The sponsor has addressed the evaluator's concerns in the revised PI submitted to the TGA on 16 June 2016.

**TGA recommendation 19**

The Delegate is advised of the additional observed disparities between the approved Invega Sustenna PI and the proposed Invega Trinza PI:

- a. The approved PI for Invega Sustenna includes a precaution for hyperprolactinemia which does not appear in the draft PI for Invega Trinza.
- b. The approved PI for Invega Sustenna includes a precaution for suicide which does not appear in the draft PI for Invega Trinza.
- c. The approved PI for Invega Sustenna includes a precaution for potential for cognitive and motor impairment which does not appear in the draft PI for Invega Trinza.
- d. The approved PI for Invega Sustenna includes a precaution for dysphagia which does not appear in the draft PI for Invega Trinza.
- e. The approved PI for Invega Sustenna includes a precaution for thrombotic thrombocytopenic purpura which does not appear in the draft PI for Invega Trinza.
- f. The approved PI for Invega Sustenna includes a precaution for extrapyramidal symptoms which does not appear in the draft PI for Invega Trinza.
- g. The approved PI for Invega Sustenna includes a precaution for orthostatic hypertension and syncope whereas the draft PI for Invega Trinza includes a precaution for orthostatic hypertension only.

*Sponsor's response:*

Response to parts a, c, f and g: As previously noted, the sponsor has agreed to revise the text in the Invega Trinza PI to align with the Invega Sustenna PI.

Part b: The sponsor proposes to add the existing precaution for suicide in the Invega Sustenna PI to the Invega Trinza PI. The following text (from the Invega Sustenna PI) will be added:

*'Suicide*

*The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.'*

Part d: The sponsor proposes to add the precaution for dysphagia in the Invega Sustenna PI to the Invega Trinza PI. The following text (from the Invega Sustenna PI) will be added:

*'Dysphagia*

*Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Invega Trinza and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.'*

Part e: The sponsor proposes to add the precaution for thrombotic thrombocytopenic purpura in the Invega Sustenna PI to the Invega Trinza PI. The following text (from the Invega Sustenna PI) will be added:

*'Thrombotic Thrombocytopenic Purpura (TTP)*

*No cases of TTP were observed during clinical studies with oral paliperidone, the 1 month paliperidone palmitate injectable product, or Invega Trinza. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.'*

*RMP evaluator comment:*

The sponsor has addressed the RMP evaluator's concerns in the revised PI which was submitted to the TGA on 16 June 2016.

**TGA recommendation 20**

The table comparing the EU SmPC with the proposed ASA (submitted to the TGA following submission assessment) should be incorporated into the ASA whenever it is revised.

*Sponsor's response:*

The table has been included in the updated ASA as per TGA request.

*RMP evaluator comment:*

The inclusion of this table is noted. The sponsor should ensure that the statements in this table are updated to reflect the approved version of the PI once it has been finalised.

**Summary of recommendations**

The safety concerns for Invega Trinza/ Trivecta (PP3M) are similar to those for Invega Sustenna (1 month injection; PP1M) and Invega (tablet form). However, the management of any emerging adverse event is complicated by the three month formulation. The inability to rapidly discontinue PP3M forms the basis of concerns regarding risk identification and risk mitigation strategies for this formulation of paliperidone. The recommendations for this report are provided below.

**Issues in relation to the RMP****Advice from the Advisory Committee on the Safety of Medicines (ACSOM)**

The key safety concerns raised by ACSOM were:

- The long duration of effect and associated inability to withdraw treatment at the emergence of an adverse event or in the case of pregnancy.
- The risk of administration errors as indicated by variable plasma levels, dosing errors during the clinical trials, and the relatively complex administration instructions.



- The risk of 'post-injection syndrome' (also referred to as dose-dumping).
- The risk of drug interactions, particularly those which may arise from concomitant administration of medicines that may have a cumulative risk of adverse events such as QT prolongation. This concern was increased due to the patient population which may be uncooperative with a patient alert card or similar risk minimisation measure, and may not report, or accurately report, the use of the 3 month injection.

### **Recommendations**

The following recommendations are made based on consideration of the sponsor's response to the first round RMP evaluation report and the ACSOM advice.

1. The sponsor should add 'inability to rapidly discontinue treatment' as an important identified risk in the summary of safety concerns. It is recommended that the risk minimisation activities for this risk should be a strengthening of precautions to include the contraindications listed below. The basis for this is that the clinical management of these adverse events would be compromised by the long acting nature of PP3M, and their development may not be adequately predicted by the 4 month lead-in phase:
  - Neuroleptic malignant syndrome (NMS): A history of NMS should be a contraindication for PP3M, as recurrences of NMS have been reported.
  - Congenital long QT syndrome and a history of cardiac arrhythmia: as paliperidone can prolong QT interval, use of the 3 month formulation should be contraindicated in patients at increased risk of developing QT prolongation.
  - Tardive dyskinesia: a history of tardive dyskinesia should be a contraindication for PP3M as the only treatment is withdrawal of the medication, without which the syndrome may become irreversible.
  - Low white blood cell count and history of drug induced leukopenia/ neutropenia: in the PI these are identified as risk factors for the adverse event of leukopenia/ neutropenia with the management advice including discontinuation of paliperidone until WBC numbers have recovered.
2. The sponsor should add 'medication error' as an important potential risk. The sponsor has indicated that educational videos and training of health care providers will be used (see sponsor's response to TGA Recommendation 13). The sponsor also indicated that these measures demonstrated a reduction in medication errors in the clinical trial programme. These measures are considered to be additional risk minimisation activities, and therefore should also be included in a revised ASA. The educational materials should be submitted to the TGA (as an appendix to the revised ASA) for evaluation.
3. Seventeen important identified risks were removed from the revised EU-RMP on the basis of a PRAC recommendation. These risks are still considered to be important in the Australian context. Therefore, it is recommended that these risks are reinstated in a revised ASA, along with the proposed pharmacovigilance and risk minimisation activities for these safety concerns.
4. The patient information brochure referred to by the sponsor in response to Round 1 TGA recommendation 14 is considered to be an additional risk minimisation activity (patient education). Therefore, this should be included in the ASA as an additional risk minimisation activity, and the educational materials be submitted to the TGA as an appendix to a revised ASA. The US patient information brochure has been briefly considered, and a version of this document that has been adapted to the Australian context is recommended for patient education in Australia. In addition, any educational materials for healthcare providers beyond that to address medication

errors (see above) should be included in the ASA and submitted to the TGA as they are also considered to be additional risk minimisation activities.

5. The ACSOM identified numerous concerns regarding the quality of the draft Consumer Medicine Information document. Similar issues were noted with the CMI for Invega Sustenna. In general, the information from the US patient information brochure is considered to be well worded, and the statements included in this brochure could be considered by the sponsor in revising the CMI. For example the information (on pages 12 to 13) clearly communicates the serious side effects that may occur.<sup>12</sup> In addition, the following issues should be specifically addressed in both the Invega Trinzta/Trevicta and Invega Sustenna CMI documents:
  - The description of delusions is not correct; the CMI refers to 'believing that what other people say is not true' as delusions. In contrast, delusions are '*a false belief or wrong judgment, sometimes associated with hallucinations, held with conviction despite evidence to the contrary*'.<sup>13</sup> The definition of delusions should be corrected in the CMI.
  - Under the heading 'before you start to use it' the following issues should be addressed:
    - 'Low or low blood pressure'; this should be revised to 'low or high'.
    - 'Suicide'; this should be revised to suicidal thoughts or attempted suicide or a similar statement.
    - It is recommended that 'heart beat irregularities' is added to this list.
  - The list of side effects and their classification should be revised. The following issues should be specifically addressed:
    - There is some overlap between side effects that are listed as mild and those as potentially serious, and this could lead to confusion for consumers. For example, fever (a serious side effect) is also a sign of many of the infections listed as mild side effects. Similarly, excessive thirst is listed as mild but is a symptom of diabetes which may be a serious side effect.
    - There should be a subheading for the diabetes symptoms which are currently listed under 'heart or blood pressure problems' (on page 4 of the CMI).
    - Symptoms of tardive dyskinesia are currently listed under mild side effects, but would be more appropriately classified as potentially serious
    - It is recommended that similar symptoms be listed one after another in the list of 'side effects'. For example, infection, pneumonia, common cold symptoms, flu-like symptoms should follow one after the other in the list. Alternately, the sponsor may want to change this symptom to be 'infections, including cold or flu-like symptoms, pneumonia and/or urinary tract infections'.

The RMP evaluator and the ACSOM raised concerns regarding 'dose-dumping' following administration of PP3M. It is noted that similar concerns were raised by the clinical evaluator. Therefore, the resolution of these concerns is deferred to the Delegate, and there are no recommendations from the RMP evaluator regarding this issue.

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<sup>12</sup> It is noted that on page 12 of the US patient information brochure that patients are advised to contact their healthcare provider immediately if they lose consciousness. The intent of this statement is understood, but consideration should be given as to how it is worded.

<sup>13</sup> Stedman's Medical Dictionary, 28<sup>th</sup> Edition. Maryland: Lippincott Williams & Wilkins. 2006

### ***Suggested wording for conditions of registration***

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. The suggested wording is:

The European Risk Management Plan (version 7.1, 8 March 2016, DLP 30 June 2015) and Australian-specific Annex (version 1.1, 27 April 2016), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

## **VI. Overall conclusion and risk/benefit assessment**

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

### **Quality**

There were no objections to approval. The chemistry evaluator noted that paliperidone is a racemic mixture. In the pharmacokinetic study, PSY1005, plasma concentrations of the R078543(+) enantiomer were consistently higher than those for the R078544(-) enantiomer. From this study, the R078543(+)/R078544(-) PK parameter ratios after IM injections of paliperidone palmitate are approximately 1.8 and 1.9 for AUC and  $C_{max}$  respectively, similar to the 1 month formulation.

That study also showed that on comparing deltoid and gluteal IM administration the LS means of  $C_{max}$  of paliperidone was higher by 27% over all dose levels after injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle, whereas there was no difference between both injection sites for  $AUC_{0-\infty}$ .

### **Nonclinical**

There were no objections to approval. The nonclinical evaluator noted that the new formulation contains the same API and excipients as the Invega Sustenna formulation, apart from particle size [information redacted] and a higher concentration of the drug substance (Invega Trinza 312 mg/mL; Invega Sustenna 156 mg/mL) and of some excipients. The maximum injection volume is also increased, from 1.5 mL (150 mg paliperidone) for the Invega Sustenna product to 2.625 mL (525 mg paliperidone) for the Invega Trinza product.

The evaluator noted that there is no new nonclinical information in the more recent, higher dose study which would impact on the risk assessment of the 3 month injection product.

### **Clinical**

#### **Pharmacology**

The PP3M formulation (Invega Trinza) differs from the PP1M formulation (Invega Sustenna) in its suspension strength, particle size [information redacted] and higher fill volume in order to ensure a physically and chemically stable 3 month formulation that is easily re-suspendable and minimizes injection force. The PP3M formulation contains the same drug substance and excipients as the PP1M formulation with the minor exception of the removal of disodium hydrogen phosphate.

The pharmacokinetics of the proposed formulation was assessed in a single dose, open label, randomised study (PSY-1005) which was supplemented with pharmacokinetic reports from two safety and efficacy studies (PSY-3011 and PSY-3012) and population PK analyses.

Only panels B and D from Study PSY-1005 were considered in the assessment of this study because these panels compared the pharmacokinetics of the formulation proposed for marketing. The  $C_{max}$  and AUC of PP3M increase dose proportionally. The LS mean AUC and bioavailability were similar after deltoid or gluteal intramuscular injection. The % covariance (CV) for  $C_{max}$  is larger with gluteal administration (up to around 100%) but the %CV for AUC is smaller at 22.0 to 31.7% for gluteal or deltoid administration. Bioavailability approaches 100%. Median paliperidone exposure following PP3M administration is similar to exposure following oral paliperidone treatment. The PP3M formulation is not bioequivalent to the 1 month formulation, PP3M when administered as proposed has a higher  $C_{max}/C_{min}$  ratio compared to PP1M but lower compared to the oral extended release (ER) formulation as shown in Tables 8 and 9.

PopPK simulations were conducted to predict the effects of delayed or early dosing with estimates shown in Table 10. These supported the proposed allowance of early and late injections up to 2 weeks before or after the 3 month re-injection time-point. Additional simulations were performed to estimate the PK for patients who present between 1 and 6 months overdue for PP3M re-injection. Simulations were also produced for the proposed regimen for switching to oral paliperidone.

**Table 8: Summary of the key PKs of paliperidone after administration of PP1M during the double blind phase, Study 3011**

Parameter ( $t_{max}$ : median [range])	PP1M, 50 mg eq.			PP1M, 75 mg eq.			PP1M, 100 mg eq.			PP1M, 150 mg eq.		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
$C_{pooled}$ , ng/mL	11	14.4	± 4.78	33	26.7	± 10.7	144	36.0	± 18.6	143	50.0	± 24.6
$C_{max}$ , ng/mL	12	18.6	± 7.59	36	36.7	± 11.1	170	47.2	± 22.8	166	66.0	± 29.9
$t_{max}$ , days	12	6.93	(0.00-13.90)	36	7.95	(0.00-36.88)	170	6.98	(0.00-36.09)	166	7.87	(0.00-34.98)
$AUC_{0-\infty}$ , ng·h/mL	12	11172	± 4499	36	21325	± 7807	170	26637	± 11379	166	37062	± 16386
$AUC_{0-3 months}$ , ng·h/mL	12	35515	± 13497	36	63976	± 23422	170	79911	± 34138	166	111185	± 49159
$C_{avg}$ , ng/mL	12	15.7	± 5.83	36	30.7	± 10.1	170	39.4	± 16.7	166	54.7	± 23.8
Peak-to-trough ratio	11	1.30	± 0.26	33	1.48	± 0.49	140	1.50	± 1.31	135	1.39	± 0.37
DN- $C_{max}$ , ng/mL	12	37.1	± 15.2	36	48.9	± 14.8	170	47.2	± 22.8	166	44.0	± 19.9
DN- $AUC_{0-\infty}$ , ng·h/mL	12	22343	± 8998	36	28434	± 10410	170	26637	± 11379	166	24708	± 10924
DN- $AUC_{0-3 months}$ , ng·h/mL	12	67029	± 26994	36	85301	± 31229	170	79911	± 34138	166	74123	± 32772

PK parameters were obtained during one dosing interval of 20 days (1 month). DN: dose normalized to 100mg eq. Source: ModS.3.5.1/R092670-PSY-3011/TabPK1.19 and PK1.2 Table B

**Table 9: Summary of the key PKs of paliperidone after administration of PP3M during the double blind phase, Study 3011**

Parameter ( $t_{max}$ : median [range])	PP3M, 175 mg eq.			PP3M, 263 mg eq.			PP3M, 350 mg eq.			PP3M, 525 mg eq.		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
$C_{pooled}$ , ng/mL	8	10.8	± 6.62	30	19.1	± 11.2	138	26.7	± 14.3	146	38.2	± 18.5
$C_{max}$ , ng/mL	11	23.2	± 11.0	35	35.8	± 18.3	165	46.9	± 22.4	188	66.1	± 34.4
$t_{max}$ , days	11	27.95	(0.00-90.83)	35	26.90	(6.90-55.93)	165	27.94	(0.00-87.94)	188	27.85	(0.00-91.86)
$AUC_{0-\infty}$ , ng·h/mL	11	32067	± 13539	35	55919	± 26814	165	72709	± 32555	188	99782	± 40664
$C_{avg}$ , ng/mL	11	15.8	± 6.73	35	27.7	± 13.4	165	35.9	± 15.9	188	49.3	± 19.9
Peak-to-trough ratio	8	2.54	± 2.16	29	1.98	± 0.83	137	1.97	± 1.04	145	1.86	± 0.84
DN- $C_{max}$ , ng/mL	11	46.4	± 22.1	35	47.6	± 24.4	165	46.9	± 22.4	188	44.1	± 22.9
DN- $AUC_{0-\infty}$ , ng·h/mL	11	64134	± 27077	35	74416	± 35684	165	72709	± 32555	188	66521	± 27109

PK parameters were obtained during one dosing interval of 84 days (3 months). DN: dose normalized to 350mg eq. Source: ModS.3.5.1/R092670-PSY-3011/TabPK1.19 and PK1.2.1 Table 9

**Table 10: Median  $C_{min}$  and  $C_{max}$  when switching from PP1M to PP3M at Week 17,  $\pm 1$  week, and dosing windows around the regularly scheduled 12-week dosing interval,  $\pm 1$ ,  $\pm 2$  and  $\pm 3$  weeks, after subjects reached apparent steady-state on treatment with PP3M deltoid injections**

Type	Parameter	Dose	Default	$\pm 1$ week	$\pm 2$ weeks	$\pm 3$ weeks
Switching to PP3M	$C_{min}$ (ng/mL)	175 mg eq. <sup>a</sup>	11.6	10.2		
	$C_{max}$ (ng/mL)	525 mg eq. <sup>b</sup>	58.2	60.2		
Maintenance PP3M	$C_{min}$ (ng/mL)	175 mg eq. <sup>a</sup>	11.0	10.3	9.7	9.0
	$C_{max}$ (ng/mL)	525 mg eq. <sup>b</sup>	56.4	57.1	58.0	58.8

<sup>a</sup> -X week simulations were performed with the lowest PP3M dose strength of 175mg eq. to simulate a worst-case scenario (i.e. largest % drop in  $C_{min}$ ) since the lowest dose has the shortest apparent  $t_{1/2}$ .

<sup>b</sup> -X week simulations were performed with the highest PP3M dose strength of 525mg eq. to simulate a worst-case scenario (i.e. largest % increase in  $C_{max}$ ).  
Source: Table 8

## Efficacy

Two studies examined efficacy and safety of PP3M.

### PSY 3012

PSY 3012 was a randomised, double blind, parallel group, placebo controlled, multicentre study to determine the efficacy and safety of PP3M in the prevention of relapse of schizophrenia. This study had 4 phases:

- a Screening Phase (up to 3 weeks)
- a 17 week flexible dose open label Transition Phase
- a 12 week fixed dose open label Maintenance Phase
- a randomised, double blind, fixed dose, placebo controlled relapse prevention phase during which subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo.

The double blind phase was of variable duration. Subjects could remain in the study for as long as they were clinically stable. The randomised withdrawal of treatment after symptom stabilisation with PP1M and continuation with PP3M was to assess whether continuation with PP3M resulted in a longer time to relapse compared with placebo treatment.

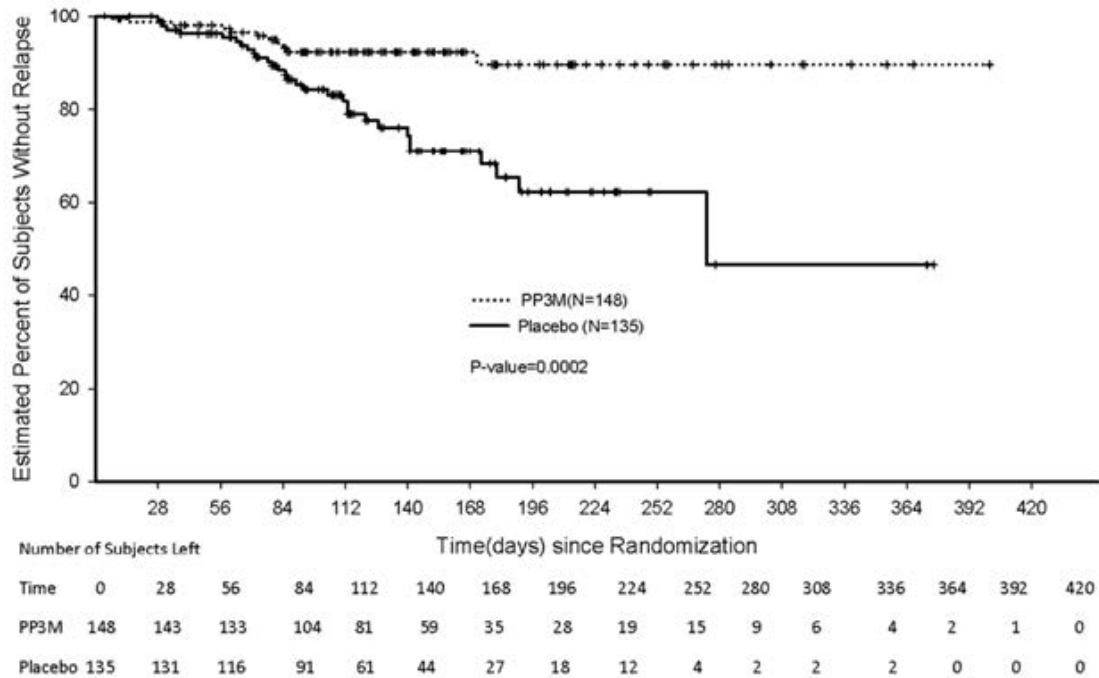
Patients were not required to have been stabilised on paliperidone prior to study entry but rather underwent a transition Phase within the study during which they commenced or continued PP1M. That Phase was followed by the maintenance Phase where all patients received PP1M prior to the randomised withdrawal for the placebo group. Clinically stable patients continued to the double blind, randomised withdrawal Phase.

A pre-planned interim analysis was conducted after the 42nd relapse event which is reported in the CER (see Attachment 2). The interim analysis showed positive results for PP3M so the study was stopped. Thus the interim analysis was the primary analysis. The final analysis included events after the interim analysis data cut-off (24 January 2014) up to study completion (09 April 2014), and is considered confirmatory.

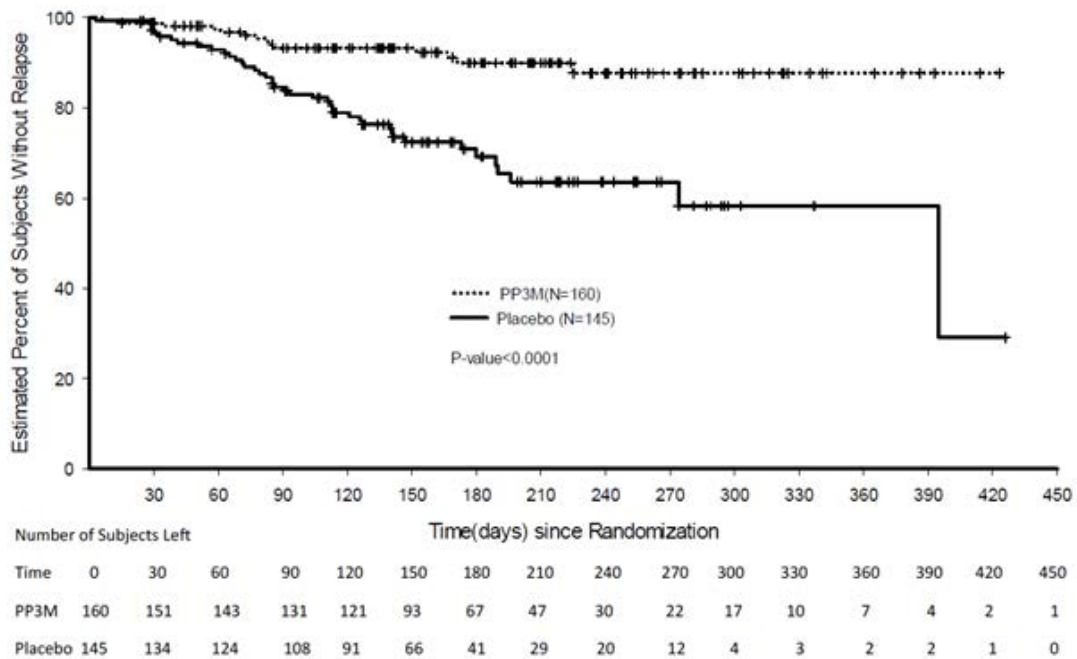
For the interim analysis, in the double blind period, 42 patients experienced a relapse event, (23.0%) received placebo and 11 (7.4%) received PP3M. The difference was statistically significant ( $p < 0.001$  based on the log-rank test). In the final analysis 42 (29.0%) patients given placebo and 14 (8.8%) given PP3M experienced a relapse event and this difference was also statistically significant ( $p < 0.001$ ). Kaplan Meier plots of time to relapse for the interim and final analyses are shown in Figures 2 and 3 respectively.



**Figure 2: Kaplan-Meier plot of time to relapse - double-blind phase - interim analysis**



**Figure 3: Kaplan-Meier plot of time to relapse - double blind phase - final (confirmatory) analysis**



**Study PSY 3011**

Study PSY 3011 was a randomised, double blind, parallel group, multicentre non-inferiority study to determine if efficacy of PP3M was non-inferior to the efficacy of PP1M for the treatment of adults with schizophrenia. The study consisted of 3 phases:

- a screening/washout/tolerability phase (up to 21 days)
- a 17 week flexible dose open label stabilisation phase

- a 48 week randomised, fixed dose, double blind controlled phase.

The primary efficacy endpoint was the percentage of subjects (per protocol) who had not relapsed at the end of the 48 week double blind treatment phase. This was determined based on the Kaplan-Meier 48 week cumulative estimate of survival (that is, percentage of subjects remaining relapse free). The predefined non-inferiority margin for difference in relapse rate between PP1M and PP3M was -15%.

Non-inferiority was demonstrated with 37 subjects (8.1%) in the PP3M group and 45 subjects (9.2%) in PP1M group experiencing a relapse event during the double blind phase. The difference (95% CI) between the treatment groups (PP3M- PP1M) in the percentages of subjects who remained relapse free was 1.2% (95%CI: -2.7%, 5.1%). Non-inferiority was confirmed by the results of the Modified Intent-to-Treat (double blind) sensitivity analysis result for the difference of 1.5% (-2.3%, 5.3%).

## Safety

The clinical evaluator was particularly concerned with the possibility of dose-dumping (rapid initial absorption of PP3M after injection) and with a possibility of increased likelihood of relapse due to low serum levels of paliperidone with the PP3M formulation compared to the PP1M formulation but that wasn't apparent in the results from studies PSY 3012 and PSY 3011.

The higher  $C_{max}$  of paliperidone after PP3M compared to PP1M did not result in a noticeable difference in the frequency or nature of AEs attributed to paliperidone in the Phase III studies. The only noticeable difference in treatment emergent adverse events (TEAEs) was for injection site reactions which were reported for 7.9% of patients given PP3M compared with 5.9% given PP1M. These differences were mostly due to higher incidences of swelling and induration associated with PP3M as shown in Table 11.

Overall the safety profile of PP3M was very similar to that of PP1M, including the frequency of extrapyramidal effects and the extent of weight gain.

**Table 11: Treatment-emergent adverse events related to injection site during the double blind phase (safety analysis set)**

Injection Site Related Group Dictionary-Derived Term	PP3M (N=504) n (%)	PP1M (N=512) n (%)
<b>Total no. subjects with adverse events</b>	40 ( 7.9)	30 ( 5.9)
<b>Injection site</b>	40 ( 7.9)	30 ( 5.9)
Injection site induration	14 ( 2.8)	6 ( 1.2)
Injection site pain	12 ( 2.4)	14 ( 2.7)
Injection site swelling	7 ( 1.4)	2 ( 0.4)
Injection site erythema	4 ( 0.8)	3 ( 0.6)
Pain in extremity	4 ( 0.8)	4 ( 0.8)
Injection site mass	2 ( 0.4)	1 ( 0.2)
Injection site pruritus	1 ( 0.2)	0
Injection related reaction	0	1 ( 0.2)
Injection site abscess	0	1 ( 0.2)
Injection site cyst	0	1 ( 0.2)
Injection site fibrosis	0	1 ( 0.2)
Injection site haematoma	0	1 ( 0.2)
Injection site inflammation	0	1 ( 0.2)
Injection site nodule	0	1 ( 0.2)
Injection site warmth	0	1 ( 0.2)

Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Source: Table 66

## Risk management plan

The RMP evaluator has noted the potential risks which were considered by the ACSOM. In summary these were:

- The long duration of effect and associated inability to withdraw treatment at the emergence of an adverse event or in the case of pregnancy.
- The risk of administration errors as indicated by variable plasma levels, dosing errors during the clinical trials, and the relatively complex administration instructions.
- The risk of 'post-injection syndrome' (also referred to as dose-dumping).
- The risk of drug interactions, particularly those which may arise from concomitant administration of medicines that may have a cumulative risk of adverse events such as QT prolongation. This concern was increased due to the patient population which may be uncooperative with a patient alert card or similar risk minimisation measure, and may not report, or accurately report, the use of the 3 month injection.

The RMP evaluator considered that these risks could be managed by amendments to the PI, including additional contraindications and by amendments to the safety specifications of the RMP. The basis for the recommendations was that the clinical management of the adverse events below would be compromised by the long acting nature of PP3M, and their development may not be adequately predicted by the 4 month lead-in phase.

The proposed contraindications to use of PP3M were:

- Neuroleptic malignant syndrome (NMS): a history of NMS should be a contraindication for PP3M, as recurrences of NMS have been reported.
- Congenital long QT syndrome and a history of cardiac arrhythmia: as paliperidone can prolong QT interval, use of the 3 month formulation should be contraindicated in patients at increased risk of developing QT prolongation.
- Tardive dyskinesia: a history of tardive dyskinesia should be a contraindication for PP3M as the only treatment is withdrawal of the medication, without which the syndrome may become irreversible.
- Low white blood cell count and history of drug-induced leukopenia/ neutropenia: in the PI these are identified as risk factors for the adverse event of leukopenia/ neutropenia with the management advice including discontinuation of paliperidone until WBC numbers have recovered.

## Risk-benefit analysis

### Delegate's considerations

Inter-subject variability for  $C_{max}$  with Invega Trinza was somewhat larger than seen with Invega Sustenna. The inter-subject variability for AUC was proportionally less than that of  $C_{max}$ . Deltoid or gluteal administration had similar pharmacokinetics and there was minimal difference in PK with increased patient weight. PK simulations supported the proposed dose adjustments for missed doses and for switching to oral treatment. The between subject variability for paliperidone pharmacokinetics following delivery from Invega Trinza is similar to the variability for paliperidone extended release tablets.

The difference in median pharmacokinetic profiles among the three paliperidone formulations may cause some variation in exposure within patients and some dose adjustment either upwards or downwards may be needed on switching between formulations however this occurs with any switching between products. This issue of



concern is the longer time period in which patients may have either a higher or lower exposure to paliperidone than would have been the case on either oral or 1 month paliperidone. However, there is a relatively broad therapeutic index for paliperidone and this potential variability in exposure for individual patients does not appear to have been associated with reduced safety or efficacy in the Phase III clinical studies.

Efficacy of the PP3M formulation and dose regimen has been well demonstrated in a randomised withdrawal study and a non-inferiority study. While there was no placebo control group in the non-inferiority study, given the high relapse rate seen in the placebo control group in study PSY3012 it is acceptable that no placebo group was included as a control in the non-inferiority study. The difference in relapse rates between Invega Sustenna and Invega Trinza was not clinically significant and supports the proposed dose recommendations for Invega Trinza. Given that many patients did not stabilise on paliperidone preparations in the clinical trials it is important that Invega Trinza only be used as proposed that is in that population who have stabilised on a 1 month depot paliperidone preparation.

There were no clinically significant differences in the safety profile of the PP3M formulation compared with the current monthly formulation. The only clinical area where safety has not been assessed is the proposed catch-up and early dose regimens. Missed doses of PP3M will require more intensive follow up and treatment to resume Invega Trinza than is required for missed doses of Invega Sustenna due to the long duration of action of Invega Trinza. Larger variations in drug concentration and AUC would be expected under these circumstances.

ACSOM have recommended additional contraindications which are intended to apply to the 3 month preparation of paliperidone but not to other paliperidone preparations. Given these contraindications have been recommended due to the prolonged exposure to an antipsychotic agent the same contraindications would need to apply to any other prolonged action depot antipsychotic agent as a precedent would have been established.

It is not clear that these additional contraindications would improve the safety of longer acting depot antipsychotic agents or the management of patients requiring antipsychotic treatment. Specifically, it is not clear how management of neuroleptic malignant syndrome (NMS) or leukopenia/ neutropenia would be more difficult with a 3 month depot preparation compared to a 1 month preparation. Additionally paliperidone is less strongly associated with prolonged QT syndrome than some other atypical antipsychotic agents (for example, ziprasidone) so contraindicating use of PP3M due to the potential for QT prolongation appears to be a disproportionate response. Likewise ACSOM's justification for recommending that PP3M be contraindicated in patients with a history of tardive dyskinesia appears more as a justification for using the minimum dose and duration of any antipsychotic agent to achieve adequate response rather than a justification for contraindicating longer acting depot antipsychotic agents for all patients with a history of tardive dyskinesia. The advice of the committee is particularly requested on these issues.

### ***Summary of issues***

The Delegate had received advice which would lead to additional contraindications applying to all depot antipsychotic preparations with duration of action longer than 1 month. It is not clear to the Delegate that these contraindications are justified.

Variability in the AUC and  $C_{max}$  of paliperidone when given as PP3M is similar to that of oral paliperidone however the duration of extremes of AUC and  $C_{max}$  is likely to be longer given the depot nature of the product. It is not clear how this should be expressed in the PI.

### Proposed action

The Delegate had no reason to say, at this time, that the application for Invega Trinza / Trevicta should not be approved for registration subject to finalisation of the PI and RMP to the satisfaction of the TGA

### Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Contraindications unique to longer acting depot antipsychotic preparations including Invega Trinza have been recommended by the ACSOM due to the difficulty reversing actions of such long acting antipsychotic products. Further advice on these contraindications, as discussed is requested.
2. There is potential for higher and lower total exposures (AUC) and maximum and minimum exposures to paliperidone on switching from a 1 month depot preparation to Invega Trinza. While no clear evidence of increased or different adverse effects or reduced efficacy was apparent in the Phase III clinical trials advice on whether this variability is adequately expressed in the draft PI is requested.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### Response from sponsor

On the 24 June 2016, the sponsor received the Delegate's request for the ACPM advice. The sponsor thanked the Delegate for the opportunity to provide comment to the ACPM on the particular issues raised below.

1. *Contraindications unique to longer acting depot antipsychotic preparations including Invega Trinza have been recommended by the ACSOM due to the difficulty reversing actions of such long acting antipsychotic products. Further advice on these contraindications, as discussed is requested.*

Sponsor's response:

As noted by the Delegate, the RMP evaluator recommended inclusion of additional contraindications for Invega Trinza (paliperidone palmitate 3 month injection [PP3M]) based on advice received from the ACSOM. The RMP evaluator's basis for the recommendations was that the clinical management of the adverse events listed below would be compromised by the long acting nature of PP3M, and their development may not be adequately predicted by the 4 month lead-in phase. The proposed contraindications to the use of PP3M were related to: NMS; congenital long QT syndrome and a history of cardiac arrhythmia; tardive dyskinesia, and low white blood cell (WBC) count and history of drug-induced leukopenia/neutropenia.

The sponsor understands the concern of the RMP evaluator and ACSOM about the long acting nature of Invega Trinza, but does not consider the contraindications for Invega Trinza should be any different from other long acting injectable (LAI) antipsychotics. We have noted the RMP evaluator and ACSOM's comments relating to the contraindications and we also note that the Delegate has made comments, in the summary of issues, that these may not be justified. The sponsor would like to take this opportunity to provide a justification for why these precautions should remain as precautions and not be moved to the contraindications section of the PI.

The sponsor understands there could be concern in initiating a 3 month medication if the medication was initiated without prior exposure to shorter acting versions of these medications. However, for a patient to start on Invega Trinza, the patient needs extensive

exposure to other forms of paliperidone or risperidone. Prior to starting the 1 month paliperidone palmitate injectable product (PP1M; Invega Sustenna), patients need to have demonstrated tolerability to risperidone (whose major metabolite is paliperidone) or oral paliperidone. Per the Invega Trinza PI, a patient then needs to be on PP1M for at least 4 months (5 injections) prior to starting Invega Trinza. This is an extensive period of time to determine tolerability to the medication. Further, it is recommended that the dose of PP1M is stable prior to starting Invega Trinza by administering the same strength for the last 2 doses. The benefit of the 4 month lead-in period was demonstrated in the Phase III studies with PP3M, as shown by the low discontinuation rates observed following conversion to PP3M. In Study PSY-3011, 3% of subjects in the PP3M treatment arm and 3% of subjects in the PP1M treatment arm discontinued treatment due to an adverse event during the double blind phase, with the majority of subjects completing the 48 week treatment period (84% and 82%, respectively) (Table 12). In Study PSY-3012, no subjects in the PP3M treatment arm discontinued from the double blind phase due to an adverse event (Table 13). As part of the consideration to initiate Invega Trinza, the clinician may also decide to maintain a patient on PP1M treatment for longer than the required 4 months to confirm tolerability if the patient had a history of significant adverse events.

**Table 12: PSY 3011 Completion/withdrawal information during the double blind phase**

	PP3M (N=504)	PP1M (N=512)	Total (N=1016)
<b>Total Entered Double Blind</b>			
<b>Reason For Withdrawal/Termination</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Completed</b>	422 ( 84)	420 ( 82)	842 ( 83)
Completed DB without a relapse	383 ( 76)	373 ( 73)	756 ( 74)
Relapse	39 ( 8)	47 ( 9)	86 ( 8)
<b>Withdrawn</b>	82 ( 16)	92 ( 18)	174 ( 17)
Adverse event	15 ( 3)	13 ( 3)	28 ( 3)
Blind broken by investigator	1 (<1)	0	1 (<1)
Death	1 (<1)	2 (<1)	3 (<1)
Lost to follow-up	7 ( 1)	12 ( 2)	19 ( 2)
Pregnancy	2 (<1)	0	2 (<1)
Withdrawal of consent	50 ( 10)	53 ( 10)	103 ( 10)
Other	6 ( 1)	12 ( 2)	18 ( 2)

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**Table 13 PSY 3012 Completion/withdrawal information during the double blind phase**

	Placebo (N=145)	PP3M (N=160)	Total (N=305)
<b>Subject Completed Trial</b>			
<b>Reason For Withdrawal/Termination</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Completed</b>	122 ( 84)	148 ( 93)	270 ( 89)
Completed DB due to study termination	80 ( 55)	134 ( 84)	214 ( 70)
Relapse during DB phase	42 ( 29)	14 ( 9)	56 ( 18)
<b>Withdrawn</b>	23 ( 16)	12 ( 8)	35 ( 11)
Adverse event	1 ( 1)	0	1 (<1)
Blind broken by investigator	1 ( 1)	0	1 (<1)
Lost to follow-up	1 ( 1)	3 ( 2)	4 ( 1)
Exposure to prohibited medications	1 ( 1)	0	1 (<1)
Pregnancy	1 ( 1)	0	1 (<1)
Withdrawal of consent	10 ( 7)	7 ( 4)	17 ( 6)
Other	8 ( 6)	2 ( 1)	10 ( 3)

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The sponsor agrees with the Delegate's comment that it is unclear whether these proposed contraindications would improve the safety of longer acting depot antipsychotic agents or the management of patients requiring antipsychotic treatment. The significant

adverse outcomes noted by the RMP evaluator above (that is, NMS, tardive dyskinesia, prolonged QT, and neutropenia) are rare events that have the potential to occur with any antipsychotic medication. It is likely that a patient will be prescribed antipsychotic medications other than PP3M if these contraindications are included in the PI. By introducing these contraindications it reduces the number of patients that can benefit from the receipt of treatment only four times a year versus monthly. Poor adherence to medication is common in patients with schizophrenia and can lead to relapse and other serious adverse outcomes (for example, hospitalization and suicide). The risk for poor adherence is much higher than for these adverse events. Particularly for people with difficulty accessing healthcare such as in rural areas, there are multiple advantages of longer coverage with LAI medication and these considerations should be balanced against these four risks which are rare and can often be mitigated. The specific events in question will be discussed further below.

### *Neuroleptic Malignant Syndrome*

The risks of developing NMS with Invega Trinza are extremely low given the gradual release of paliperidone from the injection site and the previous exposure to paliperidone prior to the initiation of PP3M. In general, NMS is related to the initiation of a new antipsychotic medication or in rarer cases with an increase in dose. Patients typically develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks and nearly all within 30 days.<sup>14</sup> NMS is also less likely to occur if a patient has been on a stable dose of their antipsychotics for a long period of time and there are no issues of nonadherence. Thus, NMS is unlikely to occur during treatment with Invega Trinza given that patients have already been established on a stable dose during treatment with PP1M for at least 4 months. Glazer and Kane<sup>15</sup> found no evidence to suggest that LAI medications increased the risk of NMS compared with the oral route. In fact the risk of NMS due to non-adherence may be reduced in patients receiving regular long-acting injectable (LAI) treatment. For example, if someone is intermittently non-adherent to oral medications, there may be a higher risk of developing NMS by restarting a higher dose after being non-adherent for multiple days. Recurrences of NMS have been reported, especially when a patient is restarted on a neuroleptic with high potency or too quickly after their initial episode. However, most patients who require continued antipsychotic treatment are able to have a neuroleptic safely reintroduced with proper precautions including very slow titration and careful monitoring. With a patient with a history of NMS, an oral medication would be initially introduced to establish tolerability and only after an extended period of time would one start a LAI like PP1M.

No cases of NMS were seen in the PP3M clinical program. In the extremely unlikely event of NMS occurring due to PP3M (and not another short acting antipsychotic added to PP3M), the management would be the same as with PP1M with supportive care until symptoms improve.

### *QT Prolongation*

For patients with a history of QT prolongation, this risk is true for all antipsychotic medications and, as the Delegate noted, the lengthening of the QT prolongation appears to be less with paliperidone than some other antipsychotic medications.<sup>16, 17</sup> Further, the QT prolongation is thought to be due to blockade of potassium channels involved in

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<sup>14</sup> Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist*. 2011; 1: 41-47

<sup>15</sup> Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry*. 1992; 53 :426- 433.

<sup>16</sup> Khasawneh FT, Shankar GS. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. *Cardiol Res Pract*. 2014; 2014: 273060.

<sup>17</sup> Li EC, et al. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy*. 2010; 30: 684-701.

repolarization of cardiac muscle. The activity of paliperidone on these channels is thought to occur quickly after oral dosing and likely would be detected during the tolerability testing of oral paliperidone or risperidone, or during the PP1M treatment for 4 months. A clinician would likely be monitoring patients with a history of QT prolongation carefully during treatment, particularly during treatment initiation. The current PI for Invega Trinza already contains a statement that 'Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.' New onset of QT prolongation during PP3M treatment would likely be due to the addition of additional medication that prolongs QT or due to electrolyte imbalance (hypokalaemia or hypo-magnesium) or to new cardiac issues. In these circumstances, the management of the patient would be to address the new cause of the prolonged QT, such as discontinuing the new medication, correcting the electrolyte imbalance, or treating the cardiac condition. The management would be no different than that of PP1M and likely the prolongation would be no longer.

In the Phase III trials with PP3M, prolongation of QT more than 60 msec occurred in only 1 subject treated with PP3M, which lessened at subsequent evaluations.

#### *Tardive Dyskinesia*

As reported for oral formulations,<sup>18</sup> the risk of tardive dyskinesia (TD) and other movement disorders appears to be lower with atypical (second-generation) LAIs (for example, risperidone LAI,<sup>19</sup> PP1M<sup>20</sup>) than for typical antipsychotic LAIs (for example, haloperidol decanoate). The sponsor performed a review of TD associated with the PP1M program which showed a low risk of TD with paliperidone, with no difference between the oral and LAI formulations, and a risk estimate of persistent TD of 0.12% for PP1M.<sup>21</sup> Although unpleasant, TD is not life threatening and in many cases resolves with discontinuation of the medication.

As the Delegate mentioned, with a patient with a history of TD, it is important that the lowest possible dose be used. This recommendation is reflected in the current precautions in the Invega Trinza PI. Further, there will be multiple months of exposure to PP1M prior to initiating PP3M to determine if the previous TD reoccurs and to determine if the risks and benefits of initiating a 3 month compound are appropriate in a particular patient. If TD develops in a patient on PP3M (either new TD or in patient with a previous history) then the treatment would be to discontinue or to lower the medication. The decision to discontinue medication should be made based on careful consideration of the risk and benefits of the treatment, which depends on the severity of the TD, the impact of the TD on the patient, and the effectiveness of the medication. If a patient can only be successfully treated with a LAI, these treatment benefits have to be weighed against the TD. Based on a recent review,<sup>22</sup> some authors have suggested there is insufficient evidence to support drug cessation or reduction as effective treatments for TD, especially when contrasted with robust evidence for the risk of psychotic relapse. There may also be some advantages to the long-acting nature of the medication (whether PP1M or PP3M) when TD develops.

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<sup>18</sup> Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: A systematic review of 1-year studies. *Am J Psychiatry*. 2004; 161: 414-425.

<sup>19</sup> Gharabawi GM, et al. An assessment of emergent tardive dyskinesia and existing dyskinesia in patients receiving long-acting, injectable risperidone: Results from a long-term study. *Schizophr Res*. 2005; 77: 129-139.

<sup>20</sup> Gopal S, et al. Number needed to treat and number needed to harm with paliperidone palmitate relative to long-acting haloperidol, bromperidol, and fluphenazine decanoate for treatment of patients with schizophrenia. *Neuropsychiatr Dis Treat*. 2011; 7:93-101.

<sup>21</sup> Gopal S, Xu H, Bossie C, Burón JA, Fu DJ, Savitz A, Nuamah I, Hough D. Incidence of tardive dyskinesia: a comparison of long-acting injectable and oral paliperidone clinical trial databases. *Int J Clin Pract*. 2014; 68: 1514-1522.

<sup>22</sup> Caroff SN, Hurford I, Lybrand J, Campbell EC. Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. *Neurol Clin*. 2011; 29: 127-148

Often dyskinesia worsens when medication is abruptly withdrawn and so a slow decrease in dose is needed. This is accomplished with discontinuation of Invega Trinza due to its slow release properties.

In the Phase III program with PP3M, one patient had an adverse event of TD while on PP3M. This subject (in Study PSY-3011) had an adverse event of TD on Day 373 (moderate severity; Abnormal Involuntary Movement Scale<sup>23</sup> (AIMS) total score = 6) that led to treatment discontinuation. The subject was next seen at the follow-up visit 3 months later, at which time the adverse event of TD was resolved (AIMS total score = 0). At the follow-up visit, the subject would still have had significant levels of paliperidone. It is unknown if the symptoms of TD resolved earlier, but these results suggest that symptoms may resolve long before the medication is eliminated from the body.

#### *Leukopenia, neutropenia, and agranulocytosis*

Leukopenia, neutropenia, and agranulocytosis are rare but serious haematological side effects associated with the use of typical and atypical antipsychotic drugs, especially clozapine. As with the other adverse events noted above, the risk of these events is a risk for all antipsychotic medications, with paliperidone not having a higher known risk than other medications. Very few instances of leukopenia and neutropenia have been reported with paliperidone.<sup>24</sup> In patients with a history of antipsychotic-induced dyscrasias, risperidone (whose major metabolite is paliperidone) has been reported as a safe alternative.<sup>25, 26</sup> In contrast, prolonged leukopenia has been observed in some patients switched from clozapine to olanzapine or quetiapine.

As with the other adverse events described in the sections above, leukopenia or neutropenia are more likely to occur earlier in treatment and therefore most likely to be seen during prior treatment with PP1M. Further, unlike with clozapine, antipsychotic induced neutropenia is not associated with frank agranulocytosis with such low WBC counts that infection is a danger. Often neutropenia is transient caused by viral infections or other medications. In these cases, the WBC count can be monitored over time. In the case where the neutropenia seems to be related to the antipsychotic medication, the management would be similar for PP1M and PP3M. The decision on continuing PP3M would be based on the extent of neutropenia, history of neutropenia with other antipsychotic medication (if a previous history then more likely that any antipsychotic will have this effect), and a discussion of the risks and benefits of continuing or discontinuing treatment. Even if the decision is to discontinue PP3M, then the WBC would be monitored over time until it improved. If needed, granulocyte colony stimulating factor can be used as has been done with full agranulocytosis with clozapine.<sup>27</sup> The sponsor considers that the benefits of the long-acting nature of product needs to be weighed on an individual basis with the risks of usually benign neutropenia and supports the continued inclusion of this as a precaution and not a contraindication.

In summary, the sponsor considers that any warnings related to use of Invega Trinza in certain subpopulations (such as those listed by the evaluator above) should remain in the precautions section and not in the contraindications section of the PI. The sponsor

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<sup>23</sup> AIMS records the occurrence of tardive dyskinesia (TD) in patients. It is a 12 item anchored scale that is clinician administered and scored. It assesses orofacial movements, extremity and truncal dyskinesia and global severity as assessed by the examiner and the patients awareness and distress associated with them.

<sup>24</sup> Kim JN, et al. Paliperidone-induced leukopenia and neutropenia: a case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35: 284-285.

<sup>25</sup> Coşar Bet al. Does switching to another antipsychotic in patients with clozapine-associated granulocytopenia solve the problem? Case series of 18 patients. *J Clin Psychopharmacol* 2011; 31: 169-173.

<sup>26</sup> Mahmood T, et al. Risperidone appears safe in patients with antipsychotic-induced blood dyscrasias. *Int Clin Psychopharmacol*. 1996; 11: 53-54.

<sup>27</sup> Hazewinkel AW, et al. Add-on filgrastim during clozapine rechallenge unsuccessful in preventing agranulocytosis. *Gen Hosp Psychiatry*. 2013; 35 :576.e11-2.

considers that the clinician, along with those patients who may have a history of these conditions (NMS, tardive dyskinesia, prolonged QT, and neutropenia), should make a risk benefit decision about the use of Invega Trinza, rather than contraindicating this medication when this may be the best option for an individual patient, particularly considering paliperidone, as noted by the Delegate, has some advantages over some other antipsychotic medications with regard to some of these events (QT prolongation, TD, possibly neutropenia). These risks are common to all antipsychotic medications and the management of them (as described above) would be similar for a 1 month LAI as well as a 3 month LAI.

The sponsor is willing to work with the Delegate to strengthen the language in these precautions, if needed, to highlight the long acting nature of Invega Trinza and the need to balance risks and benefits in treating patients with a history of these conditions. Invega Trinza is an important and, at present, a unique option for patients with schizophrenia and this option should be made available as long as the medication is used safely and the prescriber is aware of the risks when initiating the medication. Adding the proposed contraindications would, in effect, preclude the use of the product in some patients for whom benefits may outweigh the risks.

- 2. There is potential for higher and lower total exposures (AUC) and maximum and minimum exposures to paliperidone on switching from a 1-month depot preparation to Invega Trinza. While no clear evidence of increased or different adverse effects or reduced efficacy was apparent in the Phase III clinical trials advice on whether this variability is adequately expressed in the draft Product Information is requested.*

The sponsor acknowledges the Delegate's comments regarding how variability across the three paliperidone formulations is expressed in the PI. The sponsor accepts the recommendations to include a paragraph on adequately expressing the variability across the formulations; however, the sponsor proposes a minor editorial change to the text (to read as provided below).

The between subject variability for paliperidone pharmacokinetics following delivery from Invega Trinza is similar to the variability for paliperidone extended release tablets. Because of the possible within subject differences in pharmacokinetic profiles among the three paliperidone formulations, caution should be exercised when making a direct comparison of their pharmacokinetic behaviour in a given patient.

The above proposal is aimed at providing assurance that, while between subject variability in a 3 month interval at steady state is similar across the three formulations, individual differences in for example, maximum and minimum exposures across formulations (for example PP3M versus PP1M) may exist, and hence a direct comparison should be avoided. Since the above text is being added, the sponsor also agrees with the Delegate's other recommendation to delete Figure 1 from the PI.

### **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 efficacy, safety and quality, agreed with the Delegate and considered Invega Trinza and Trevicta modified release injection pre-filled syringe and 2 safety needles in a kit containing 175 mg, 263 mg, 350 mg and 525 mg of paliperidone palmitate to have an overall positive benefit-risk profile for the proposed indication;

*Invega Trinza and Trevicta, 3 month injections, are indicated for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with the 1 month paliperidone palmitate injectable product for at least four months.*

In making this recommendation the ACPM

- noted that paliperidone palmitate demonstrated reasonable efficacy for the proposed.

The committee agreed with the ACSOM in that the safety concerns for the PP3M preparation are greater than for the PP1M preparation. The committee highlighted several properties of this long acting preparation that raised particular and serious safety concerns.

- The long duration of effect means that it is impossible to withdraw the therapy if adverse events develop. The committee noted that serious adverse events from paliperidone include tardive dyskinesia, QT prolongation, serotonin syndrome, neuroleptic malignant syndrome and neutropenia/leukopenia.
- The three month interval between injections may directly lead to less contact between the patient and health practitioners and consequently less monitoring for safety and efficacy. The committee emphasised that contact between a patient and health practitioners should be based on clinical need and not be based solely on the administration interval for medicines.
- The variability of plasma levels and the high number of detected administration errors indicated that there are technical difficulties in the administration of the PP3M.
- Additional medicines may be prescribed by a prescriber who is unaware that the patient has previously been administered long acting paliperidone. The patient may have an inaccurate recollection of the length of time since the PP3M injection. Patients with schizophrenia may not cooperate in using a patient alert card. These issues raised the possibility of unexpected drug-drug interactions, including serious events such as tardive dyskinesia, neutropenia/leukopenia, neuroleptic malignant syndrome and QT prolongation.

The ACPM agreed with the ACSOM on the safety issues associated with a long acting injection of paliperidone:

- The inability to rapidly discontinue treatment in response to adverse event.
- Adverse events in the patient's history that are considered 'precautions' with respect of PP1M may more properly be considered 'contraindications' with respect of PP3M. For example, it would not be appropriate to use PP3M for a patient who experienced tardive dyskinesia, QT prolongation or neuroleptic malignant syndrome with PP1M.
- The concerns of the use of PP3M in women of childbearing age if an unplanned pregnancy were to occur and unavoidable exposure to paliperidone occurred in the first trimester.

The ACPM recommended the inclusion of statements in the contraindications section of the PI and relevant sections of the CMI to reflect the advice previously given by the ACSOM regarding previous history of the following severe adverse events: neuroleptic malignant syndrome (NMS), congenital long QT syndrome or a history of cardiac arrhythmia, tardive dyskinesia and low white blood cell count and drug-induced leukopenia/ neutropenia.

### ***Specific advice***

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Contraindications unique to longer acting depot antipsychotic preparations including Invega Trinza have been recommended by the ACSOM due to the difficulty reversing*



*actions of such long acting antipsychotic products. Further advice on these contraindications, as discussed is requested.*

The ACPM supported the inclusion of the following adverse events in the contraindications section of the PI and relevant sections of CMI, as previously recommended by the ACSOM:

- Previous history of neuroleptic malignant syndrome (NMS) in association with paliperidone.
- History of QT prolongation and cardiac arrhythmia in association with paliperidone.
- History of tardive dyskinesia in association with paliperidone.
- Low white blood cell count and history of drug-induced leukopenia/ neutropenia in association with paliperidone.

The ACPM was of the view that patients presenting histories of these adverse events are at a much greater risk since first principle of treatment for each of these severe adverse events is immediate cessation of the antipsychotic. Immediate cessation of medication is not possible due to the long duration of effects from depot preparation.

2. *There is potential for higher and lower total exposures (AUC) and maximum and minimum exposures to paliperidone on switching from a 1 month depot preparation to Invega Trinza. While no clear evidence of increased or different adverse effects or reduced efficacy was apparent in the Phase III clinical trials advice on whether this variability is adequately expressed in the draft PI is requested.*

The ACPM as of the view that the variability was adequately expressed in the 'Long-acting 3 month paliperidone palmitate injection versus other paliperidone formulations' section of the draft PI:

*'The concentration of paliperidone remaining in the circulation 18 months after dosing of 525 mg Invega Trinza is stopped is estimated to be 3% (following deltoid injection) or 7% (following gluteal injection) of the average steady-state levels.' 'The between-subject variability for paliperidone pharmacokinetics following delivery from Invega Trinza is similar to the variability for paliperidone extended-release tablets. Because of the difference in median pharmacokinetic profiles among the three paliperidone formulations caution should be exercised when making a direct comparison of their pharmacokinetic properties.'*

No further statement or information is required.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Invega Trinza and Trevicta paliperidone palmitate 175 mg, 263 mg, 350 mg and 525 mg suspension for injection prefilled syringe indicated for:

*Invega Trinza and Trevicta are 3 month injections that are indicated for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with the 1 month paliperidone palmitate injectable product for at least four months.*

### **Specific conditions of registration applying to these goods**

The European Risk Management Plan (version 7.1, 8 March 2016, DLP 30 June 2015) and Australian-specific Annex (version 1.1, 27 April 2016) submitted with application PM-2015-02788-1-1, to be revised to the satisfaction of the TGA, must be implemented in Australia.

## **Attachment 1. Product Information**

The PI for Invega Trinza approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>> . The PI for Trevicta is identical except for the product name.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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