



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Paliperidone

Proprietary Product Name: Invega

Sponsor: Janssen-Cilag Pty Ltd

**December 2009**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide 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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## I. Introduction to Product Submission

### Product Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Active ingredient(s):</i>	Paliperidone
<i>Product Name(s):</i>	Invega
<i>Sponsor's Name and Address</i>	Janssen-Cilag Pty Ltd Locked Bag 2070 North Ryde, NSW 1670
<i>Dose form(s):</i>	Modified release tablet
<i>Strength(s):</i>	3 mg, 6 mg, 9 mg and 12 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	28 or 56 tablets
<i>Approved Therapeutic use:</i>	Treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers ( lithium and valproate).
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	9 mg once daily in the morning with adjustment within the recommended dose range of 3 to 12 mg daily.

### Product Background

Invega (paliperidone) modified release tablets were first registered in September 2007 for the treatment of schizophrenia, including acute treatment and recurrence prevention. Invega is currently approved for the treatment of schizophrenia, including acute treatment and recurrence prevention. The proposed new indication is *“for the treatment of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers”*.

Paliperidone is the 9-hydroxy metabolite of risperidone. Paliperidone is a centrally active dopamine D<sub>2</sub> antagonist with predominant serotonergic 5HT<sub>2A</sub> antagonistic activity. Paliperidone is also active as an antagonist at alpha<sub>1</sub> and alpha<sub>2</sub>-adrenergic receptors and H<sub>1</sub> histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or beta<sub>1</sub> and beta<sub>2</sub>-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

Schizoaffective disorder is a psychotic illness with prominent mood symptoms in addition to the core symptoms of schizophrenia. Patients may have episodes of elevated mood, and/or episodes of depression. Management usually involves the combination of antipsychotic with antidepressants (when depressed) and/or mood stabilisers (when manic, or for prophylaxis). The more recent approvals for antipsychotic medications for the treatment of schizophrenia have not included schizoaffective disorder as a sub-group of schizophrenia. This approach is consistent with the current European Union (EU) guideline *CPMP/EWP/559/95 Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia*.

## Regulatory Status at the Time of Submission

The product received initial ARTG Registration in September 2007 (3 mg (AUSTR 130502), 6 mg (AUSTR 130714), 9 mg (AUSTR 130717) and 12 mg (AUSTR 130732).

An identical application for this extension of indication was submitted in the USA in February 2009. Approval was given on 31 July, 2009. Applications have also been made in the EU August 2009 in and New Zealand in February 2009, both of which are currently under evaluation.

## Product Information

The approved product information current at the time this AusPAR was developed is contained at Attachment 1.

## II. Quality Findings

### Drug Substance (active ingredient)

The active ingredient of Invega is paliperidone (USAN/INN/AAN) and is referred to as R076477 by the company. The chemical name is: ( $\pm$ )-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4Hpyrido[1,2-a]pyrimidin-4-one. It contains one chiral centre and has a MW of 426.49 (Fig. 1.).

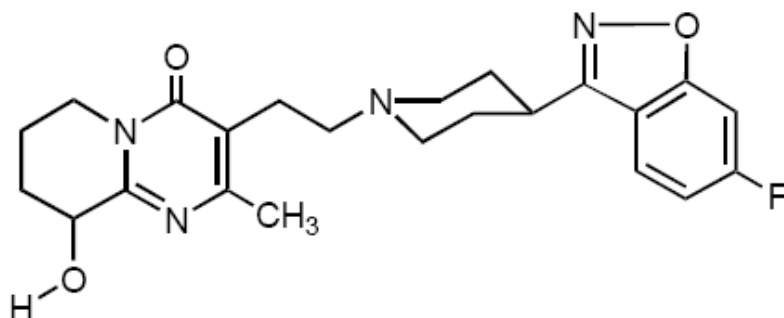


Figure 1. Structure of paliperidone.

### Drug Product

The excipients of Invega are carnauba wax, cellulose acetate, hydroxyethylcellulose, macrogol, polyethylene oxide, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

### Quality Summary and Conclusions

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

## III. Non-Clinical Findings

### Introduction

To support the use of Invega (paliperidone) in combination with antidepressants and/or a mood stabilizer, one analytical report has been included in this module to study the influence of valproate on solubility and dissolution rate of paliperidone at different pH levels, < 2.0, 6.8 and 7.4, simulating the standard pH conditions in the GI tract. The analytical methods used are simple and straightforward. No other new nonclinical data were provided to support the proposed new indication.

## Pharmacokinetics

Valproate co-administration has been shown to affect the pharmacokinetics of several commonly prescribed medicines. To investigate the effects of valproate on the pharmacokinetics of paliperidone, the dissolution rate and solubility of paliperidone in the presence of valproate under the standard pH conditions of the GI tract have been studied *in vitro*.

The presence of valproate had no effects on the intrinsic dissolution rate of paliperidone, expressed as mg% dissolved *vs* time, at different pH levels. The dissolution rate was mainly determined by the pH of the solvents, that is, paliperidone had the highest dissolution rate at acidic pH and the lowest at pH 7.4, *ca* a 240-fold difference.

Similarly, the solubility of paliperidone was also mainly determined by pH of the solvents, showing > 100-fold decrease from pH < 2 to pH of 7.4. The presence of valproate did not affect the solubility of paliperidone at pH < 2 and pH 7.4, but (unlike the case of dissolution) resulted in a 46% decline of solubility at pH 6.8.

On the currently submitted data alone, no clear conclusion can be drawn whether or to what extent the observed decreased solubility of paliperidone at pH 6.8 might impact the overall release rate or absorption of paliperidone in the presence of valproate.

Other supporting data were found in the Clinical Summary of the submission:

(1) An *in vitro* study investigated the required water volume to dissolve a 12 mg paliperidone tablet during the first 6 h postdose, when the tablet remained in the upper part of the GI tract (which has a pH of 6.8). The results showed that it required about twice the water volume to dissolve the released paliperidone as a result of the decreased solubility in the presence of valproate (0.1-0.4 mL and 0.2-0.7 mL in the absence and presence of valproate, respectively). This required volume is considerably smaller than the water volume typically available in the upper part of the GI tract (375 mL/6 h). Therefore, it can be inferred that the decrease of paliperidone solubility (from 1.0 mg/mL to 0.54 mg/mL at pH 6.8) by the influence of valproate is unlikely to affect the fraction of paliperidone that can be dissolved.

(2) Exposure to paliperidone in people who were co-administered valproate (15.7 ng/mL) was similar to the exposure in people who were co-administered lithium (16.7 ng/mL), based on the median paliperidone plasma concentrations. Since lithium has not been demonstrated to affect the pharmacokinetics of other drugs, the potential for lithium to cause pharmacokinetic interactions with paliperidone is considered to be low. The comparable median paliperidone plasma concentrations after co-administration with lithium or valproate suggested that the latter is not expected to affect the pharmacokinetics of paliperidone in a clinically relevant manner.

(3) Published drug-drug interaction studies between valproate and risperidone (of which paliperidone is the active metabolite) have demonstrated that adding valproate to the existing risperidone tablet did not alter the resultant plasma concentrations of risperidone and paliperidone (Spina *et al.* 2000, Yoshimura *et al.* 2007).

## Non-Clinical Summary and Conclusions

Based on the above findings, the potential for an adverse effect of valproate on the overall dissolved fraction and absorption of paliperidone under clinical conditions is low and unlikely to be clinically relevant at standard pH conditions of the GI tract.

The information provided in the current submission has no impact on the nonclinical sections of the proposed PI document.

There are no nonclinical objections to the extension of indications of Invega as proposed by the sponsor.

## **IV. Clinical Findings**

### **Introduction**

Invega is currently approved for the treatment of schizophrenia, including acute treatment and recurrence prevention. The proposed new indication is “*for the treatment of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers*”.

Two evaluable studies were submitted.

### **Pharmacokinetics**

There was no requirement for a reassessment of pharmacokinetics in a submission of this type.

### **Pharmacodynamics**

There was no requirement for a reassessment of pharmacodynamics in a submission of this type.

### **Efficacy**

**Study R076477-SCA-3001:** Multicentre, double-blind, randomised, placebo controlled parallel-group study.

Three hundred and sixteen patients were enrolled at study sites in four countries (USA: 37%, India: 32%, Ukraine: 20%, Russia: 11%). The inclusion criteria were ability to provide informed consent, male or female gender, 18 to 65 years age range, non-pregnant for women, lifetime and current diagnosis of schizoaffective disorder (DSM-IV 295.70), confirmed by the structured clinical interview for DSM-IV disorders (SCID) at screening, experience of an acute exacerbation (with a PANSS<sup>1</sup> total score  $\geq 60$  at the time of study enrolment and at time of randomisation), onset of current episode (exacerbation of psychotic symptoms) not less than 4 days and no more than 4 weeks prior to screening, score of  $\geq 4$  at screening and at randomisation on at least 2 of the following PANSS items: Hostility (P7), Excitement (P4), Tension (G4), Uncooperativeness (G8) and Poor Impulse Control (G14), score of  $\geq 16$  on the Young Mania Rating Scale (YMRS)<sup>2</sup> and/or a score of  $\geq 16$  on the Hamilton Rating Scale for

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#### **<sup>1</sup> Positive and Negative Syndrome Scale (PANSS)**

The PANSS is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention and poor impulse control. The 30 symptoms are rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms, and gauge their relationship to one another and to global psychopathology. The PANSS interview process typically takes between 30 and 40 minutes to complete. The PANSS served as the primary efficacy measure and was administered at baseline, on Day 4, and at all subsequent visits.

#### **<sup>2</sup> Young Mania Rating Scale (YMRS)**

The YMRS was designed to measure the severity of manic symptoms and to gauge the effect of treatment on mania severity. The YMRS is a checklist of 11 items that are ranked on a scale of 0 to 4 or 0 to 8. Seven of the items are ranked 0 to 4 and have descriptors associated with each severity level (that is, 0, 1, 2, 3 and 4). Four of the items (irritability, speech, content and disruptive-aggressive behaviour) are scored 0

Depression (HAM-D-21)<sup>3</sup>, general medical healthiness, compliance, hospitalisation or willingness to be hospitalised at the screening time. The 316 patients entered a washout period of at least 2 days and no longer than 5 days, during which their current psychotropic medications were discontinued while in hospital. On this note, (a) subjects receiving depot antipsychotics, including long-acting injectable risperidone and paliperidone palmitate, within 2 treatment cycles of screening visit, (b) subjects receiving therapy with clozapine within 3 months prior to randomisation and (c) subjects with a previous history of lack of response to antipsychotic medication were excluded.

Of the 316 enrolled patients (mean age = 37.3 years, range 18 to 61 years, male 64.8%), randomisation was n = 100 for paliperidone ER high dose, n = 109 for paliperidone ER low dose and n = 107 for placebo. Of the 100 patients randomised to paliperidone ER high dose, two (2) did not receive study medication. Of the 109 patients randomised to paliperidone ER low dose, one (1) did not receive study medication. Therefore a total of n = 313 received at least one dose of study medication. Of the 313 patients, 212 (67.7%) completed double-blind treatment. The highest completion rate was observed in the paliperidone ER high dose group (78.6%), and the lowest completion rate was observed in the placebo group (58.9%).

Efficacy was evaluated using the following assessment parameters at baseline (Day 0) and on day 4, weeks 1, (Day 8), 2 (Day 15), 3 (Day 22), 4 (Day 29) and 6 (Day 43):

- PANSS
- CGI-S-SCA<sup>4</sup>
- CGI-C-SCA<sup>5</sup>

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to 8 and have descriptors for every other increment (that is, 0, 2, 4, 6 and 8) to allow for the poor cooperation seen in severely ill subjects. The YMRS was administered at baseline on Day 4, and at all subsequent visits.

### **<sup>3</sup> Hamilton Rating Scale for Depression (HAM-D-21)**

The HAM-D-21 is a 21-item, clinician-rated scale that evaluates depressed mood as well as the vegetative and cognitive symptoms of depression. The items are rated on either a 5-point (0 to 4) or a 3-point (0 to 2) scale. The 5-point scale uses a rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe) and 4 (very severe). A rating of 4 is usually reserved for extreme symptoms. The 3-point scale uses a rating of 0 (absent), 1 (probable), and 2 (definite). The HAM-D-21 was administered at baseline, on Day 4, and at all subsequent visits.

### **<sup>4</sup> Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA)**

Similar to the original Clinical Global Impression Severity scale, the CGI-S-SCA is a 7-point scale that measures the clinician's impression of the severity of illness exhibited by a patient. The CGI-S-SCA is a syndrome-specific scale that includes an overall severity score as well as scores for the positive, negative, manic, and depressive domains of the illness. With the CGI-S-SCA, the clinician assesses the level of overall impairment, as well as that related to each domain, at the time of the visit and during the week prior to the visit. A rating of 1 is equivalent to "normal, not ill at all", and a rating of 7 is equivalent to "among the most extremely ill patients". The rating of 2, 3, 4, 5 and 6 represent "minimally," "mildly," "moderately," "markedly," and "severely" ill categories. The CGI-S-SCA was performed at baseline on Day 4, and at all subsequent visits.

### **<sup>5</sup> Clinical Global Impression of Change for Schizoaffective Disorder (CGI-C-SCA)**



- HAM-D-21
- YMRS

The **primary** efficacy endpoint was the change in the PANSS total score from baseline to Week 6 last observation carried forward (LOCF) end point.

**Secondary** efficacy endpoints included:

- Actual and change from baseline to Week 6 LOCF end point for the PANSS subscales and factor scores;
- Actual and change from baseline to Week 6 LOCF end point in the CGI-S-SCA score;
- The CGI-C-SCA score at Week 6 LOCF end point.
- Responder rates, defined as the percentage of patients experiencing a  $\geq 30\%$  improvement from baseline in PANSS total score and having a CGI-C-SCA of 1 or 2 at Week 6 LOCF end point.
- Time to first response to treatment.

**Other** efficacy endpoints included:

- Actual and change from baseline to Week 6 LOCF in the HAM-D-21 score.
- Actual and change from baseline to Week 6 LOCF in the YMRS score.

**Primary endpoint analyses:**

- From baseline to end point (LOCF), median and mean changes showed a decrease in PANSS total scores in all treatment groups, indicating improvement in the severity of neuropsychiatric symptoms. The mean (SD) change from baseline to Week 6 LOCF end point was -21.7 (21.4) in the placebo group, -27.4 (22.1) in the paliperidone ER low dose group, and -30.6 (19.1) in the paliperidone ER high dose group.
- There was a statistically significant improvement from baseline to Week 6 LOCF end point in PANSS total score for subjects in the paliperidone ER high dose group compared with the placebo group ( $p=0.003$ ), while the paliperidone ER low dose group did not separate from placebo at the Week 6 LOCF end point. In assessing change in PANSS total score the ANCOVA model used adjusted for baseline PANSS values as well as concomitant medication stratum and country.
- The decrease from baseline in PANSS total scores for the paliperidone ER high dose group was significantly greater than that of the placebo group at Week 2 LOCF

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Like the original Clinical Global Impression Change scale, the CGI-C-SCA is a 7-point scale measuring the clinician's impression of the change occurring in the illness over a course of treatment, relative to baseline. The CGI-C-SCA measures overall change, as well as change in the positive, negative, manic and depressive domains, relative to baseline. The baseline reference for this parameter consists of notes from the baseline consensus and patient interviews. A rating of 4 is equivalent to "no change". Ratings  $< 4$  are equivalent to "improvement" (1-very much improved, 2-much improved, 3-minimally improved) and ratings  $> 4$  are equivalent to "worsening" (5-minimally worse, 6-much worse, 7-very much worse). The CGI-C-SCA was to be completed by the same clinician for every assessment. If this was not possible, the rating clinician reviewed the subject's presentation (along with review of clinical notes) with the rater who completed the initial evaluation. The CGI-C-SCA was performed on Day 4 and at all subsequent visits.

( $p=0.004$ ), Week 3 LOCF ( $p=0.001$ ), Week 4 LOCF ( $p=0.008$ ) and Week 6 LOCF ( $p=0.003$ ).

- The effect on PANSS total score of the interaction between treatment and the other fixed-effect factors (country, concomitant medication stratum, and country classified as U.S. or non-U.S) and between treatment and baseline PANSS total score at Week 6 LOCF end point revealed no significant at the 10% significance level.
- The post-hoc analysis of the effect of outlier data points on the primary efficacy endpoint showed that the results were robust, and that potential outliers did not contribute to the distance of any other observations. Following the exclusion of the 8 outlier observations, the analysis of the primary efficacy endpoint demonstrated that both paliperidone ER low dose and paliperidone ER high dose were statistically significantly different from placebo ( $p=0.044$  and  $p<0.001$ , respectively)
- When given as monotherapy, the mean (SD) change from baseline to Week 6 LOCF end point was -20.6 (20.8) in the placebo group, -28.9 (20.8) in the paliperidone ER low dose group, and -31.0 (19.9) in the paliperidone ER high dose group.
- When administered in combination with antidepressants and/or mood stabilizers, the mean (SD) change from baseline to Week 6 LOCF end point was -23.5 (22.5) in the placebo group, -24.7 (24.2) in the paliperidone ER low dose group, and -30.0 (17.9) in the paliperidone ER high dose group.
- Consistent with the lack of a significant interaction between treatment and concomitant medication stratum, the mean improvement in the primary efficacy variable with paliperidone ER high dose was consistently superior to placebo when administered either as monotherapy or in combination with antidepressants and/or mood stabilisers.
- Results of exploratory analysis by subgroup baseline affective symptomatology (manic symptoms baseline YMRS  $\geq 16$  [ $n = 257$ ] or  $< 16$  [ $n = 53$ ] for manic subgroup, depressive symptoms baseline HAM-D-21  $\geq 16$  [ $n = 201$ ] or  $< 16$  [ $n = 109$ ] for depressive symptoms baseline HAM-D-21  $\geq 16$  [ $n=201$ ] or  $< 16$  [ $n=109$ ] for depressive subgroup, mixed symptoms baseline YMRS  $\geq 16$  and HAM -D-21  $\geq 16$  [ $n=148$ ] or YMRS and HAM-D-21  $< 16$  [ $n=162$ ] were consistent in showing that paliperidone ER high dose treatment was more effective than placebo in improving the PANSS total score at Week 6 LOCF end point regardless of subjects' baseline affective symptomatology.

### Secondary and other endpoint analyses

- § On the PANSS subscale scores (total scores based on 24 items), there was a statistically significant difference in LS mean change from baseline to Week 6 LOCF end point between the placebo group and the paliperidone ER high dose group for the PANSS positive subscale score ( $p<0.001$ ) and the PANSS general psychopathology subscale score ( $p=0.008$ ), while the paliperidone ER low dose group did not separate from placebo on any of the subscale scores at the Week 6 LOCF end point.
- § On the PANSS factor scores, there was a statistically significant difference in LS mean change from baseline to Week 6 LOCF end point between the placebo group and the paliperidone ER high dose group for the PANSS positive factor score ( $p<0.001$ ), the PANSS disorganized thought factor score ( $p = 0.004$ ), and the PANSS uncontrolled hostility/excitement factor score ( $p = 0.001$ ), while the paliperidone ER low dose group

did not separate from the placebo on any of the factor scores at the Week 6 LOCF end point.

- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in CGI-S-SCA overall score for subjects in the paliperidone ER high dose group compared with the placebo group ( $p=0.001$ ), while the paliperidone ER low dose group did not separate from placebo at the Week 6 LOCF end point.
- § Statistically significant improvements were noted in CGI-S-SCA overall score for subjects in the paliperidone ER high dose group compared with the placebo group from baseline to Week 2 LOCF ( $p=0.002$ ), Week 3 LOCF ( $p<0.001$ ), Week 4 LOCF ( $p<0.001$ ), and Week 6 LOCF end point ( $p=0.001$ ), while the paliperidone ER low dose group separated from placebo at Week 4 LOCF ( $p=0.018$ ).
- § There was a statistically significant difference at the Week 6 LOCF end point in CGI-C-SCA overall score for subjects in both the paliperidone ER low dose ( $p=0.013$ ) and high dose ( $p<0.001$ ) groups compared with the placebo group.
- § Statistically significant CGI-C-SCA overall scores were noted for subjects in the paliperidone ER high dose group compared with the placebo group at Week 2 LOCF ( $p<0.001$ ), Week 3 LOCF ( $p<0.001$ ), Week 4 LOCF ( $p<0.001$ ), and Week 6 LOCF end point ( $p<0.001$ ), while the paliperidone ER low dose group separated from placebo at Week 3 LOCF ( $p=0.005$ ), Week 4 LOCF ( $p=0.043$ ), and Week 6 LOCF end point ( $p=0.013$ ).
- § The responder rate, as per composite response, revealed at endpoint that there was a greater proportion of composite responders in the paliperidone ER low dose (56.7%) and high dose (62.2%) groups compared with the placebo group (40.2%).
- § The HAM-D-21, with a total score ranging from 0 to 63, where a higher score indicates a more severe condition, was assessed. In particular, changes from baseline HAM-D-21 total score for the subset of subjects in the ITT analysis set with a baseline HAM-D-21 total score  $\geq 16$  were determined. From baseline to end point, median and mean changes showed a decrease in HAM-D-21 total score in all treatment groups, indicating improvement of condition. The mean (SD) change from baseline to Week 6 LOCF end point was -9.9 (10.7) in the placebo group, -13.6 (9.2) in the paliperidone ER low dose group, and -14.5 (9.2) in the paliperidone ER high dose group.
- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in HAM-D-21 total score for subjects who had a baseline score of  $\geq 16$  in both the paliperidone ER low dose ( $p=0.013$ ) and high dose ( $p=0.032$ ) groups compared with the placebo group.
- § The YMRS, with a total score ranging from 0 to 60, where a higher score indicates a more severe condition, was assessed. In particular changes from the baseline in YMRS scores for the subset of subjects in the ITT analysis set with baseline YMRS total score  $\geq 16$  were determined. From baseline to end point, median and mean changes showed a decrease in YMRS total score in all treatment groups, indicating improvement of condition. The mean (SD) change from baseline to Week 6 LOCF end point was -11.5 (11.4) in the placebo group, -14.3 (11.8) in the paliperidone ER low dose group, and -19.4 (11.7) in the paliperidone ER high dose group.
- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in YMRS total score for subjects who had a baseline score of  $\geq 16$  for the paliperidone ER high dose group compared with the placebo group ( $p<0.001$ ), while the

paliperidone ER low dose group did not separate from placebo at the Week 6 LOCF end point.

**Study R076477-SCA-3002:** Multicentre, double-blind, randomised, placebo controlled parallel-group study.

Three hundred and eleven patients meeting the inclusion criteria were randomly assigned to receive either placebo (n = 95) or paliperidone ER (n = 216) in six countries (USA: 45%, Romania: 26%, India: 13%, Philippines: 75, Malaysia: 5%, South Korea: 4%). The inclusion criteria and the wash-out period were similar to those of study 3001. Of the 311 randomised patients, 309 patients (n = 214 for paliperidone group and n = 95 for placebo group) received at least one dose of double-blind study medication and, therefore, were included in the safety analysis set. Of the 309 subjects in the safety analysis set, 304 subjects (mean age  $37.6 \pm 9.2$  years, range 19- 61 years, male 55.9%, n = 211 for paliperidone group and n = 93 for placebo group) provided both baseline and at least 1 postbaseline PANSS assessment and, therefore, were included in the ITT analysis set. Subjects 210409, 210507 and 211616 in the paliperidone ER group and subjects 210206 and 210407 in the placebo group were excluded from the ITT analysis set because they had no efficacy data.

**Efficacy** was evaluated using similar assessment parameters at similar time periods to those stated for study 3001.

**Primary endpoint analyses:**

- § From baseline to end point (LOCF), median and mean changes showed a decrease in PANSS total scores in the paliperidone ER and placebo groups, indicating improvement in the severity of neuropsychiatric symptoms. The mean (SD) change from baseline to Week 6 LOCF end point was -10.8 (18.7) in the placebo group and -20.0 (18.9) in the paliperidone ER group.
- § The decrease from baseline in PANSS total scores for the paliperidone ER treatment group was significantly greater than that of the placebo group at Day 4 LOCF (p=0.010), Week 1 LOCF (p<0.001), Week 2 LOCF (p<0.001), Week 3 LOCF (p<0.001), Week 4 LOCF (p<0.001) and Week 6 LOCF (p<0.001).
- § A statistically significant treatment-by-baseline PANSS total score interaction was detected at the prespecified 10% significance level (p=0.009). In order to further evaluate the treatment-by-baseline PANSS total score interaction, unequal slopes models for each treatment were fit, and corresponding point estimates at 4 different baseline points were listed including at mean. Estimated treatment differences in each case were greater than 5 units in favour of paliperidone ER. The Gail-Simon test was used to test the consistency of treatment differences across 2 strata (<median and >=median for baseline PANSS total score) and separately across 4 strata (<25<sup>th</sup> percentile; >=25<sup>th</sup> percentile to <median; >=median to <75<sup>th</sup> percentile; >=75<sup>th</sup> percentile for baseline PANSS total score). The Gail-Simon test was based on the change score (paliperidone ER minus placebo). Both the 1-sided and 2-sided p-values show that there was no evidence of qualitative interaction between treatment and baseline PANSS total score (p>0.05).
- § No significant treatment-by-country, treatment-by-concomitant medication stratum, or treatment-by categorised country interactions were detected at the prespecified 10% significance level.
- § In the repeated measures analysis of PANSS total score, subjects in the paliperidone ER treatment group had a significantly larger decrease from baseline in the PANSS total score compared with placebo (p<0.001). The repeated measures estimated difference for the

change from baseline in the PANSS total score for treatment comparisons at Week 6 was -10.1 for paliperidone ER minus placebo.

- § A repeated measures analysis of the effect on PANSS total score of the interaction between treatment and the other fixed effect factors (country, concomitant medication stratum, and country classified as U.S or non-U.S.) and between treatment and baseline PANSS total score was investigated in addition to the various treatment-by-subgroup interactions were investigated. The Gail-Simon test was used to qualitatively test treatment difference across strata and no qualitative interactions were observed.
- § Results of the exploratory analysis of the change [Estimate (SE)] from baseline to Week 6 LOCF end point in the PANSS total score by concomitant medication [change = -20.7 (2.1) for paliperidone ER group vs. -12.9 (2.9) for placebo group] and by monotherapy or non concomitant medication [change = -24.0 (2.1) for paliperidone ER group vs. -12.9 (2.9) for the placebo group] was consistent with the lack of a significant interaction between treatment and concomitant medication strata ( $p = 0.486$ ), the mean improvement in the primary efficacy endpoint with paliperidone ER was consistently superior to placebo when administered either as monotherapy or in combination with antidepressants and/or mood stabilisers.
- § When given as monotherapy, the mean (SD) change from baseline to Week 6 LOCF end point was -22.4 (19.4) in the paliperidone ER group and -11.6 (20.1) in the placebo group. The LS mean difference from placebo was -11.0 for the paliperidone ER group (effect size of 0.60).
- § When administered in combination with antidepressants and/or mood stabilisers, the mean (SD) change from baseline to Week 6 LOCF end point was -17.7 (18.1) in the paliperidone ER group and -10.1 (17.5) in the placebo group. The LS mean difference from placebo was -7.8 (effect size of 0.43).
- § Results of exploratory analysis by subgroup baseline effective symptomatology (manic symptoms baseline YMRS  $\geq 16$  [ $n = 23$ ] or  $<16$  [ $n = 73$ ] for manic subgroup, depressive symptoms baseline HAM-D-21  $\geq 16$  [ $n = 210$ ] or  $<16$  [ $n = 94$ ] for depressive subgroups, mixed symptoms baseline YMRS  $\geq 16$  and HAM -D-21  $\geq 16$  [ $n = 137$ ] or YMRS and HAM-D-21  $\leq 16$  [ $n = 167$ ] were consistent in showing that paliperidone ER was more effective than placebo in improving the PANSS total score at Week 6 LOCF end point regardless of subjects' baseline affective symptomatology.

### **Secondary and other endpoint analyses:**

- § On the PANSS subscale scores, there was a statistically significant difference in LS mean change from baseline to Week 6 LOCF end point between the placebo group and the paliperidone ER treatment group for the PANSS positive subscale score ( $p < 0.001$ ), the PANSS negative subscale score ( $p < 0.001$ ), and the PANSS general psychopathology subscale score ( $p < 0.001$ ).
- § On the PANSS factor scores, there was a statistically significant difference in LS mean change from baseline to Week 6 LOCF end point between the placebo group and the paliperidone ER treatment group for all 5 of the PANSS factor scores (the PANSS positive factor score [ $p < 0.001$ ], the PANSS negative factor score [ $p < 0.001$ ], the PANSS disorganised thought factor score [ $p < 0.001$ ], the PANSS uncontrolled hostility/excitement factor score [ $p = 0.001$ ], and the PANSS anxiety/depression factor score [ $p = 0.016$ ]).

- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in CGI-S-SCA overall score for subjects in the paliperidone ER treatment group compared with the placebo group ( $p = 0.002$ ).
- § There was a statistically significant difference in LS mean change from baseline to Week 6 LOCF end point between the placebo group and the paliperidone ER treatment group for the CGI-S-SCA positive domain score ( $p = 0.003$ ), the CGI-S-SCA negative domain score ( $p = 0.042$ ), and the CGI-S-SCA depressive domain score ( $p < 0.001$ ).
- § There was a statistically significant difference at Week 6 LOCF end point in CGI-C-SCA overall score for the paliperidone ER treatment group ( $p < 0.001$ ) compared with the placebo group.
- § The responder rate, as per composite response, revealed at end point that there was a greater proportion of composite responders in the paliperidone ER treatment group (40.5%) compared with the placebo group (28.0%).
- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in HAM-D-21 total score for subjects who had a baseline score  $\geq 16$  in the paliperidone ER treatment group ( $p < 0.001$ ) compared with the placebo group.
- § There was a statistically significant improvement from baseline to Week 6 LOCF end point in YMRS total score for subjects who had a baseline score  $\geq 16$  for the paliperidone ER group compared with the placebo group ( $p < 0.001$ ).

## Safety

### Study R076477-SCA-3001

Safety analyses based on  $n = 313$  who had received at least one dose of double blind study medication showed the following:

The incidences of treatment-emergent adverse effects (TEAEs) in the paliperidone ER low dose (72.2%) and paliperidone ER high dose (69.4%) groups were similar and higher than that of the placebo group (57.0%).

The TEAEs reported at the highest incidences in the paliperidone ER groups were headache (13.6% of the total number of subjects in both dose groups), tremor (11.7%), nausea (8.3%) and insomnia (6.8%). Of the TEAEs that occurred in  $\geq 5\%$  of the subjects in any treatment group (see below) nasopharyngitis and somnolence occurred more frequently (that is  $\geq 3\%$  difference) in the paliperidone ER high dose group compared with the paliperidone ER low dose and placebo groups. Insomnia had a higher incidence (that is  $\geq 3\%$  difference) in the paliperidone ER high dose and placebo groups compared with the paliperidone ER low dose group. Among the common TEAEs, hypertonia, dry mouth, sedation, agitation, and schizoaffective disorder occurred more frequently (that is  $\geq 3\%$  difference) in the paliperidone ER low dose group compared with the paliperidone ER high dose group. All of these events also had a higher (0.9% to 5.5% difference) incidence in the paliperidone ER low dose group compared with placebo. Details are shown in Table 1 below.

Table 1. Treatment- Emergent Adverse Events in  $\geq 5\%$  of Subjects in Any Treatment Group by Preferred Term During Double –Blind Phase (Study R076477-SCA-3001: Safety Analysis Set)

MedDRA-System Organ Class/MedDRA-Preferred Term	Placebo (N=107) n (%)	PALI ER Low Dose (N=108) n (%)	PALI ER High Dose (N=98) n (%)	Total PALI ER (N=206) n (%)
Total no. subjects with adverse events	61 (57.0)	78 (72.2)	68 (69.4)	146 (70.9)
Gastrointestinal disorders	19 (17.8)	26 (24.1)	23 (23.5)	49 (23.8)
Constipation	2 (1.9)	4 (3.7)	5 (5.1)	9 (4.4)
Dry mouth	4 (3.7)	7 (6.5)	2 (2.0)	9 (4.4)
Dyspepsia	0	5 (4.6)	6 (6.1)	11 (5.3)
Nausea	8 (7.5)	9 (8.3)	8 (8.2)	17 (8.3)
Infections and infestations	10 (9.3)	11 (10.2)	11 (11.2)	22 (10.7)
Nasopharyngitis	2 (1.9)	2 (1.9)	5 (5.1)	7 (3.4)
Nervous system disorders	30 (28.0)	42 (38.9)	41 (41.8)	83 (40.3)
Akathisia	8 (7.5)	4 (3.7)	6 (6.1)	10 (4.9)
Dizziness	7 (6.5)	6 (5.6)	4 (4.1)	10 (4.9)
Headache	18 (16.8)	15 (13.9)	13 (13.3)	28 (13.6)
Hypertonia	3 (2.8)	9 (8.3)	4 (4.1)	13 (6.3)
Sedation	5 (4.7)	8 (7.4)	4 (4.1)	12 (5.8)
Somnolence	2 (1.9)	5 (4.6)	8 (8.2)	13 (6.3)
Tremor	4 (3.7)	13 (12.0)	11 (11.2)	24 (11.7)
Psychiatric disorders	24 (22.4)	20 (18.5)	20 (20.4)	40 (19.4)
Agitation	6 (5.6)	7 (6.5)	1 (1.0)	8 (3.9)
Insomnia	9 (8.4)	5 (4.6)	9 (9.2)	14 (6.8)
Schizoaffective disorder	3 (2.8)	6 (5.6)	0 (0.0)	6 (2.9)

#### *Deaths and Other Serious Reactions*

No subject died during the study. More subjects in the paliperidone ER low dose group (9.3%) experienced treatment – emergent serious adverse events (SAEs) compared with subjects in the placebo (5.6%) or paliperidone ER high dose (2.0%) groups. The most common SAEs were schizoaffective disorder (reported for 4 subjects [3.7%] in the paliperidone ER low dose group and 2 subjects [1.9%] in the placebo group) and psychotic disorder (reported for 2 subjects [1.9%] in the paliperidone ER low dose group and 1 subject [0.9%] in the placebo group).

One subject in the paliperidone ER low dose group experienced a SAE of suicidal behaviour and 1 subject in the placebo group experienced a SAE of suicidal ideation. Details are shown in Table 2 below:

**Table 2. Treatment- Emergent Serious Adverse Events by Preferred Term During Double –Blind Phase**  
(Study R076477-SCA-3001: Safety Analysis Set)

MedDRA-System Organ Class/MedDRA-Preferred Term	Placebo (N=107) n (%)	PALI ER Low Dose (N=108) n (%)	PALI ER High Dose (N=98) n (%)	Total PALI ER (N=206) n (%)
Total no. subjects with SAEs	6 (5.6)	10 (9.3)	2 (2.0)	12 (5.8)
Cardiac disorders	1 (0.9)	0	0	0
Supraventricular tachycardia	1 (0.9)	0	0	0
Infections and Infestations	0	2 (1.9)	0	2 (1.0)
Salpingitis	0	1 (0.9)	0	1 (0.5)
Urinary tract infection	0	1 (0.9)	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	1 (1.0)	1 (0.5)
Uterine leiomyoma	0	0	1 (1.0)	1 (0.5)
Nervous system disorders	0	1 (0.9)	0	1 (0.5)
Grand mal convulsion	0	1 (0.9)	0	1 (0.5)
Psychiatric disorders	5 (4.7)	8 (7.4)	1 (1.0)	9 (4.4)
Depressed mood	1 (0.9)	1 (0.9)	0	1 (0.5)
Depression	0	0	1 (1.0)	1 (0.5)
Psychotic disorder	1 (0.9)	2 (1.9)	0	2 (1.0)
Schizoaffective disorder	2 (1.9)	4 (3.7)	0	4 (1.9)
Suicidal behavior	0	1 (0.9)	0	1 (0.5)
Suicidal ideation	1 (0.9)	0	0	0
Reproductive system and breast disorders	0	0	1 (1.0)	1 (0.5)
Metrorrhagia	0	0	1 (1.0)	1 (0.5)

### Study R076477-SCA-3002

Safety analyses based on n = 309 who had received at least one (1) dose of double-blind study medication.

The incidence of TEAEs was higher in the paliperidone ER group (65.4%) compared with the placebo group (60.0%).

The TEAEs reported at the highest incidences in the paliperidone ER group were headache (15.0%) and dizziness (8.4%). Of the TEAEs that occurred in  $\geq 5\%$  of the subjects in either treatment group, akathisia and dizziness occurred more frequently (that is  $\geq 3\%$  difference) in paliperidone ER-treated subjects than in placebo-treated subjects. Details are shown in Table 3 below:



Table 3. Treatment –Emergent Adverse Events in  $\geq 5\%$  of Subjects in Any Treatment Group by Preferred Term During Double-Blind Phase (Study R076477-SCA-3002: Safety Analysis Set)

MedDRA-System Organ Class/MedDRA-Preferred Term	Placebo (N= 95) n (%)	PALI ER (N= 214) n (%)
Number of subjects with at least 1 TEAE	57 (60.0)	140 (65.4)
Gastrointestinal disorders	21 (22.1)	54 (25.2)
Dyspepsia	5 (5.3)	12 (5.6)
Nervous system disorders	26 (27.4)	84 (39.3)
Akathisia	1 (1.1)	13 (6.1)
Dizziness	5 (5.3)	18 (8.4)
Headache	12 (12.6)	32 (15.0)
Psychiatric disorders	24 (25.3)	39 (18.2)
Insomnia	5 (5.3)	14 (6.5)

#### *Deaths and Other Serious Reactions*

No subject died during the study. Fewer subjects in the paliperidone ER group (5.1%) experienced treatment-emergent SAEs compared with subjects in the placebo group (8.4%). The majority of SAEs coded to the Psychiatric Disorders SOC. The most common SAEs were schizoaffective disorder (reported for 5 subjects [2.3%] in the paliperidone ER group and 3 subjects [3.2%] in the placebo group) and mania (reported for 3 subjects [1.4%] in the paliperidone ER group and 2 subjects [2.1%] in the placebo group). One subject in the placebo group experienced an SAE of suicidal ideation. One subject in the paliperidone ER group experienced SAEs of accidental overdose and respiratory failure. One subject (Subject 211203 in the paliperidone ER group) had an SAE of small intestinal obstruction that the investigator considered at least possibly related to the study drug. Details are shown in Table 4 below:

Table 4. Treatment –Emergent Serious Adverse Events by Preferred Term During Double-Blind Phase (Study R076477-SCA-3002: Safety Analysis Set)

MedDRA-System Organ Class/MedDRA-Preferred Term	Placebo (N=95) n (%)	PALIPER (N=214) n (%)
Total no. subjects with SAEs	8 (8.4)	11 (5.1)
Gastrointestinal disorders	0	1 (0.5)
Small intestinal obstruction	0	1 (0.5)
Injury, poisoning and procedural complications	0	1 (0.5)
Accidental overdose	0	1 (0.5)
Psychiatric disorders	8 (8.4)	9 (4.2)
Anxiety	0	1 (0.5)
Mania	2 (2.1)	3 (1.4)
Persecutory delusion	0	1 (0.5)
Psychotic disorder	2 (2.1)	0
Schizoaffective disorder	3 (3.2)	5 (2.3)
Suicidal ideation	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.5)
Respiratory failure	0	1 (0.5)

## Clinical Summary and Conclusions

Two studies (**R076477-SCA-3001** and **R076477-SCA-3002**) were submitted for evaluation in support of the application. Both were multicentre, double-blind, randomised, placebo controlled, parallel group studies, enrolling patients/subjects (age range 18-61 years, mean age 37.3 years) with schizoaffective disorder (DSM IV 295.70).

For the **primary efficacy endpoint** (change in the PANSS total score from baseline to Week 6 LOCF end point), paliperidone ER caused a greater decrease in PANSS total score than placebo in both studies (indicating improvement in the severity of neuropsychiatric symptoms) although, this only reaches statistical significance for paliperidone ER high dose (12mg daily) ( $p = 0.003$ ) and not always for paliperidone ER low dose (3mg daily) in study 3001.

Regarding the effect of the interaction between treatment and the other fixed-effect factors (country, concomitant medication stratum and country classified as U.S or non-U.S) on PANSS total score, both studies detected no significant difference at the prescribed 10% significance level.

For the treatment-by-baseline PANSS total score interaction, no significant difference at the prescribed 10% significance level was found in Study 3001 while statistical significance ( $p = 0.009$ ) was established in Study 3002. However, further analysis using the Gail-Simon test revealed no evidence of qualitative interaction between treatment and baseline PANSS total score ( $p > 0.05$ , 1-sided and 2-sided  $p$ -values) in Study 3002. Exclusion of the data from the Indian trial site due to compliance deficiencies did not change the overall results of the primary efficacy outcome as per sensitivity analysis. Similar findings to the change in the PANSS total score from baseline to Week 6 LOCF endpoint, were established for the repeated measures analysis of PANSS total score and PANSS total score worsening LOCF at Week 6 LOCF end point assessment in both studies, that is, paliperidone ER especially high

dose, was better than placebo (**Note:** Post-hoc analysis of the effect of outlier observation data points on primary efficacy endpoint demonstrated that both paliperidone ER low dose and paliperidone ER high dose were statistically significantly different from placebo ( $p = 0.044$  and  $p < 0.001$ , respectively) in the change from baseline in PANSS total score at Week 6 LOCF endpoint. Other exploratory analyses of the change from baseline to Week 6 LOCF endpoint in the PANSS total score by (a) concomitant medication stratum (monotherapy or combination therapy with antidepressants and/or mood stabilisers), (b) region (U.S or outside U.S sites) and (c) baseline affective symptomatology (manic or depressive symptoms) yielded results consistent with (i) lack of significant interactions between treatment and concomitant medication stratum, region and baseline affective symptomatology and (ii) superiority of paliperidone ER, especially the high dose, over placebo in those subgroup analyses.

For the **secondary** endpoint analyses (PANSS subscale scores, PANSS factor scores, CGI-S-SCA scores, CGI-C-SCA scores, Responder rate as per composite response) and the additional/other endpoints analyses (HAM-D-21 total score, YMRS total score, Correlations among values in PANSS total score, HAM-D-21 and YMRS total scores), paliperidone ER especially the high dose, has generally performed significantly better than placebo.

Regarding the overall safety, the proposed amendments to the various tables on adverse drug reactions in the draft product information should be given adequate consideration and the adverse reactions data reviewed, in order to confirm the accuracy of the quoted percent for each adverse reaction. No new safety issues are apparent.

## **V. Pharmacovigilance Findings**

There were no pharmacovigilance data provided with the submission.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the Delegate's Request for ADEC Advice and recommendation.

### **Quality**

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

### **Non-Clinical**

No new nonclinical data were provided to support the proposed indication. An analytical report examining the influence of valproate on the solubility and dissolution rate of paliperidone in different solvents mimicking conditions in the gastrointestinal tract was submitted. This study report was not considered by the nonclinical evaluator to warrant changes to the Product Information.

### **Clinical**

#### **Efficacy**

Two clinical studies in subjects with acute exacerbation of schizoaffective disorder were submitted. Both were randomised, double-blind, placebo-controlled, parallel-group studies conducted over 6 weeks. Study 3001 had 3 treatment arms: paliperidone ER low dose (6 mg daily with an option to reduce to 3 mg daily); paliperidone ER high dose (12 mg daily with an option to reduce to 9 mg daily) and placebo. Study 3002 had 2 treatment arms: paliperidone ER flexibly dosed in the range of 3 to 12 mg daily and placebo. In both studies subjects given paliperidone could have their dose adjusted within the first 2 weeks of study only.

In Study 3001 the mean change in total PANSS from baseline to Week 6 for each dose group and for the pre-specified subgroups of monotherapy paliperidone and combination paliperidone with antidepressants and/ or mood stabilisers is summarised below:

**Mean (SD) change in total PANSS score from baseline to Week 6 (LOCF) modified ITT population**

	<b>Placebo</b>	<b>Paliperidone 3mg to 6 mg daily</b>	<b>Paliperidone 12 mg to 9 mg daily</b>
<b>Group Total</b>	-21.7 (21.4)	-27.4 (22.1)	-30.6 (19.1)*
<b>Monotherapy</b>	-20.6 (20.8)	-28.9 (20.8)	-31.0 (19.9)
<b>Combination Therapy</b>	-23.5 (22.5)	-24.7 (24.2)	-30.0 (17.9)

\* statistically significant vs placebo

The monotherapy and combination therapy sub-group analyses did not show statistically significant differences from placebo in mean change in total PANSS score from baseline to Week 6. Statistically significant differences were seen in the secondary endpoints of CGI-S-SCA, % treatment responders and improvements in YMRS and HAM-D-21 scores in the high dose paliperidone group compared with the placebo group. In the low dose paliperidone group there were statistically significant differences compared with placebo for % treatment responders, mean improvement in CGI-S-SCA score and HAM-D-21 score at Week 6. The responder rate was 62.2% for the paliperidone high dose group, 56.7% for the low dose group and 40.2% for the placebo group.

In Study 3002, the mean change in total PANSS from baseline to Week 6 for each dose group and for the pre-specified subgroups of monotherapy paliperidone and combination paliperidone with antidepressants and/ or mood stabilisers is summarised below:

**Mean (SD) change in total PANSS score from baseline to Week 6 (LOCF) modified ITT population**

	<b>Placebo</b>	<b>Paliperidone</b>	<b>95% CI for difference</b>
<b>Group Total</b>	-10.8 (18.7)	-20.0 (18.9)	-13.8; -4.9*
<b>Monotherapy</b>	-11.6 (20.08)	-22.4 (19.38)	-17.71; -3.78*
<b>Combination Therapy</b>	-10.1 (17.49)	-17.7 (18.15)	-14.03; -2.24*

\* statistically significant vs placebo

Statistically significant differences from placebo, favouring paliperidone were seen for PANSS subscales, improvements in CGI-S-SCA score and CGI-S-SCA score, treatment responders, reductions from baseline in HAM-D-21 and YMRS total scores. Of particular note the responder rates were 40.5% in the paliperidone group vs. 28.0% in the placebo group (p= 0.046).

**Safety**

Safety results from both studies were comprehensively presented in the clinical evaluation report. No new safety issues were apparent from extension of use of paliperidone to patients with schizoaffective disorder.

### **Risk-Benefit Analysis**

CPMP/EWP/559/95 *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia* states that extrapolation of data from a specific disorder (e.g. schizophrenia) to another disorder (e.g. delusional disorder) is not possible. At least one specific prospective study is required to establish efficacy in another psychotic disorder when efficacy has been established in schizophrenia. This is especially true for schizoaffective disorders. It was therefore appropriate to study these patients in separate studies and not include them as a sub-group in a larger study of patients with schizophrenia.

Multiple measuring instruments were used to assess the severity of illness in subjects enrolled in the 2 studies presented. Being considered mildly ill according to the CGI approximately corresponds to a PANSS total score of 58, moderately ill to a PANSS of 75, markedly ill to a PANSS of 95 and severely ill to a PANSS of 116<sup>1</sup>. Thus the subjects in these studies tended to be markedly ill at enrolment.

The studies demonstrated a statistically and clinically meaningful improvement in symptoms of schizophrenia for paliperidone given at the proposed dose, as either mono or combination therapy with antidepressants and/ or mood stabilizers.

A statistically significant advantage of paliperidone over placebo was demonstrated for the major measure of depression (HAM-D-21) in both studies in all dose groups of paliperidone and in the major measure of mania (YMRS) in study 3002 and in the high dose paliperidone group in study 3001. There was a high correlation between reduction in PANSS total score and reduction in HAM-D-21 total score and YMRS score. The clinical significance of the reductions in HAM-D-21 and YMRS scores were not addressed as a separate efficacy concern.

Very few subjects took concomitant mood stabilisers/ antiepileptic agents other than lithium and valproate. A wide range of antidepressants were taken concomitantly with selective serotonin reuptake inhibitors/serotonin-noradrenaline reuptake inhibitors most frequently taken.

The Delegate concluded that this data package is sufficient to support use of the proposed dose regimen of Invega for treatment of exacerbation of schizoaffective disorder but lacks data on the prevention of relapse or recurrence. Therefore long term use of Invega for patients with schizoaffective disorder is not supported. As a consequence, the Delegate proposed to reject the submission to extend the indications for paliperidone ER (Invega) to include

*Treatment of schizoaffective disorder as monotherapy and in combination with antidepressants and/ or mood stabilisers.*

because:

- Efficacy and safety has been demonstrated only in patients with acute exacerbation of schizoaffective disorder
- The proposal to not specify the antidepressants or mood stabilisers would permit broader concomitant medications than were used in the efficacy and safety studies.

The Delegate proposed an alternate indication, restricting use to patients with acute exacerbation of schizoaffective disorder and concomitant use to antidepressants and those

mood stabilisers that were predominantly used in the clinical trials. The proposed alternate indication is

*Treatment of acute exacerbation of schizoaffective disorder as monotherapy and in combination with antidepressants and/ or lithium or sodium valproate.*

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, agreed with the Delegate's proposal. In making this recommendation, the Committee notes that data were presented from two pivotal clinical trials which compared paliperidone with placebo in the treatment of acute exacerbations of schizoaffective disorder. Evidence of a statistically and clinically meaningful reduction from baseline to week 6 in PANSS score favouring paliperidone was seen in all but the low dose paliperidone group in study 3001. The Committee considers this negative finding might be explained by the higher placebo response rate observed in study 3001 which, in turn can be explained by the patients in study 3001 being less chronically ill than the patients in study 3002. Thus the results for the low dose group in study 3001 are likely to be biased against paliperidone and do not preclude a recommendation for approval.

The ADEC further agrees with the Delegate that, in the absence of data on prevention of relapse or recurrence, the indication should be restricted to treatment of acute exacerbations of schizoaffective disorder. The Committee additionally considers it appropriate to only allow treatment in combination with the mood stabilisers lithium and valproate, as very few subjects in either study took other concomitant mood stabilisers.

### **Outcome**

Based on review of quality, safety and efficacy data, TGA approved the extension of indications of paliperidone (Invega) tablets, modified release 3 mg, 6 mg, 9 mg and 12 mg for the indication:

*Treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers ( lithium and valproate).*

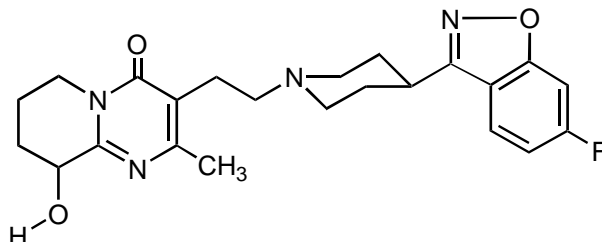
Attachment 1. Product Information

# INVEGA®

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Paliperidone is chemically identified as (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.



CAS:144598-75-4

C<sub>23</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>3</sub>

MW=426.49

### DESCRIPTION

INVEGA® (paliperidone) is a novel antipsychotic agent belonging to the benzisoxazole-derivatives class.

INVEGA® utilizes osmotic drug-release technology, whereby osmotic pressure delivers paliperidone from the dosage form at a controlled rate. The system, which resembles a capsule-shaped tablet in appearance, comprises an osmotically active trilayer core surrounded by a subcoat and semipermeable membrane. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There are two precision laser-drilled orifices on the drug-layer dome of the tablet. Each strength is identified by a unique colour overcoat and print markings. In an aqueous environment, such as the gastrointestinal tract, the water-dispersible colour overcoat erodes quickly. Water is then imbibed through the semipermeable, rate-controlling membrane. The membrane controls the rate at which water enters the tablet core, which, in turn, controls drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone that is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethylcellulose, macrogol, polyethylene oxide, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

### PHARMACOLOGY

#### Pharmacodynamics

Paliperidone is a centrally active dopamine D<sub>2</sub> antagonist with predominant serotonergic 5-HT<sub>2A</sub> antagonistic activity. Paliperidone is also active as an antagonist at α<sub>1</sub> and α<sub>2</sub> adrenergic receptors and H<sub>1</sub> histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β<sub>1</sub>- and β<sub>2</sub>-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar. Paliperidone is the major active metabolite of risperidone.

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is



unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D<sub>2</sub>) and serotonin Type 2 (5HT<sub>2A</sub>) receptor antagonism. Antagonism at receptors other than D<sub>2</sub> and 5HT<sub>2A</sub> may explain some of the other effects of paliperidone.

### Polysomnography:

Centrally-acting medications through their mechanism of action, drug-release profile, and/or time of dose administration may affect sleep. To evaluate the impact of morning dosing of INVEGA® on sleep architecture and continuity, a placebo-controlled study was conducted in 36 subjects with schizophrenia in which INVEGA® 9 mg or placebo was administered once daily for 14 days. The following observations were made (mean data compared with placebo): reduced latency to persistent sleep by 41.0 (SE 18.70) minutes, decreased sleep onset latency by 35.2 (SE 14.99) minutes, decreased number of awakenings after sleep onset by 7.0 (SE 3.88) events, increased total sleep time by 52.8 (SE 24.01) minutes, increased sleep period time by 41.7 (SE 18.75) minutes, and increased sleep efficiency index by 11.0% (SE 5.00). There was also a statistically significant decrease (relative to placebo) in Stage 1 sleep of 11.9 (SE 4.44) minutes and increase in Stage 2 sleep of 50.7 (SE 17.67) minutes. No clinically relevant effect on REM sleep was observed.

### **Pharmacokinetics**

Following a single dose, the plasma concentrations of paliperidone steadily rise to reach peak plasma concentration (C<sub>max</sub>) in approximately 24 hours after dosing. The pharmacokinetics of paliperidone following INVEGA® administration are dose-proportional within the recommended clinical dose range (3 to 12 mg). The terminal elimination half-life of paliperidone is approximately 23 hours.

Steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects. In a study comparing the steady-state pharmacokinetics following once-daily administration of 12 mg paliperidone (administered as prolonged-release tablets) with 4 mg immediate-release risperidone in schizophrenic subjects, the fluctuation indexes were 38% for paliperidone prolonged-release compared to 125% for risperidone immediate-release (Figure 1).

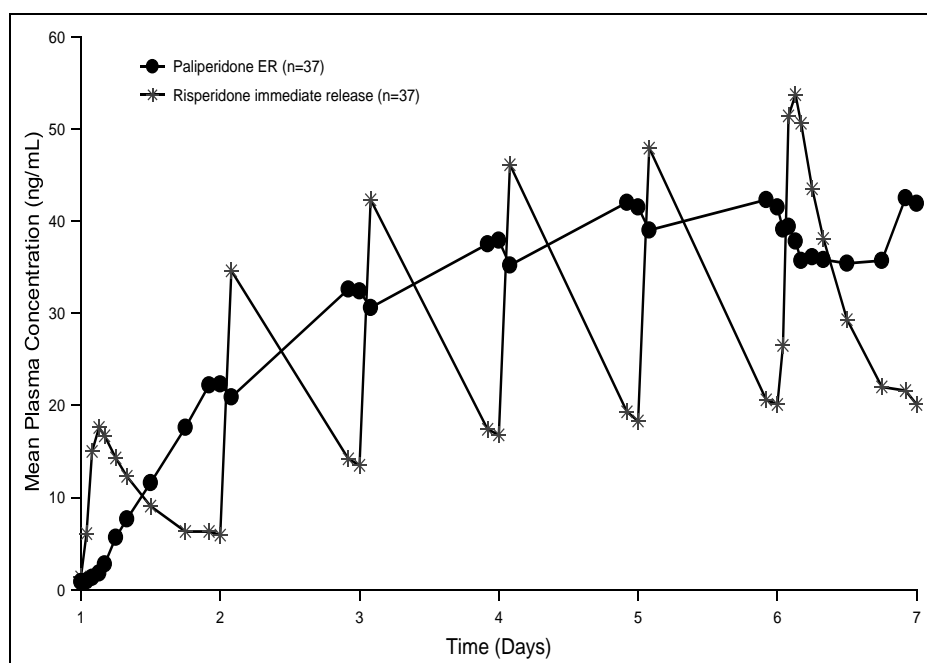


Figure 1. Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg prolonged-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone+risperidone concentrations are represented).

Following administration of INVEGA<sup>®</sup>, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6 at steady state.

#### Absorption:

The absolute oral bioavailability of paliperidone following INVEGA<sup>®</sup> administration is 28%. Following administration of a single 15 mg paliperidone prolonged-release tablet to healthy subjects, confined to bed for 36 hours, with a standard high-fat/high-caloric meal, the C<sub>max</sub> and AUC values increased by 42% and 46%, respectively, compared with administration under fasting conditions. (See **DOSAGE AND ADMINISTRATION**).

*In vitro* studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. (see **PRECAUTIONS** – Interactions with other medicines)

#### Distribution:

Paliperidone is rapidly distributed. Based on a population analysis, the apparent volume of distribution of paliperidone is 487 L. The plasma protein binding of paliperidone is 74%. It binds primarily to  $\alpha_1$ -acid glycoprotein and albumin. *In vitro*, high therapeutic concentrations of diazepam (3 mcg/mL), sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused a slight increase in the free fraction of paliperidone at 50 ng/mL. These changes are not expected to be of clinical significance.

#### Metabolism and Elimination:

One week following administration of a single oral dose of 1 mg immediate-release 14C-paliperidone, 59% (range 51% - 67%) of the dose was excreted unchanged into urine, 32% (26% - 41%) of the dose was recovered as metabolites, and 6% – 12% of the dose was not recovered. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. *In vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, however, *in vivo* results indicate that these isozymes play a limited role in the metabolism of paliperidone. Despite the large variation in the general population with regard to the ability to metabolize CYP2D6 substrates, population pharmacokinetic analyses indicated no discernable difference on the exposure and apparent clearance of paliperidone after administration of INVEGA<sup>®</sup> between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies using microsomal preparations of heterologous systems indicate that CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5 are not involved in the metabolism of paliperidone.

#### Hepatic Impairment:

In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Consequently, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

#### Renal Impairment:

The dose of INVEGA<sup>®</sup> should be reduced in patients with mild, moderate or severe renal impairment (see **DOSAGE AND ADMINISTRATION: Dosing in Special Populations**). The disposition of a single dose paliperidone 3 mg extended-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC<sub>inf</sub>) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal

function (CrCl  $\geq$  80 mL/min). (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

#### Gender:

The apparent clearance of paliperidone following INVEGA<sup>®</sup> administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance between men and women.

#### Elderly:

Data from a pharmacokinetic study in elderly subjects ( $\geq$  65 years of age, n = 26) indicated that the apparent steady-state clearance of paliperidone following INVEGA<sup>®</sup> administration was 20% lower compared to that of adult subjects (18-45 years of age, n = 28). However, there was no discernable effect of age in the population pharmacokinetic analysis involving schizophrenia subjects after correction of age-related decreases in CrCl. (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

#### Children and adolescents younger than 18 years of age:

No pharmacokinetics data on INVEGA<sup>®</sup> in patients < 18 years of age has been established.

#### Smoking Status:

Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. A population pharmacokinetic analysis showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance, though.

## **Clinical trials**

### Schizophrenia:

The efficacy of INVEGA<sup>®</sup> (3 to 15 mg once daily) in the treatment of schizophrenia was established in three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose trials in subjects who met DSM-IV-TR criteria for schizophrenia. The active control was included for assay sensitivity purposes. Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Efficacy was also evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains of behaviour (socially useful activities including work and study, personal and social relationships, self care, and disturbing and aggressive behaviours).

In the first placebo-controlled 6-week trial (n=605) comparing fixed doses of paliperidone (3, 9, and 15 mg/day) with placebo, all doses were superior to placebo on the PANSS, all PANSS factors, and the PSP scale.

In the second placebo-controlled 6-week trial (n=628) comparing fixed doses of paliperidone (6, 9, and 12 mg/day) with placebo, all doses were superior to placebo on the PANSS, all PANSS factors, and the PSP scale.

In the third placebo-controlled 6-week trial (n=432) comparing fixed doses of paliperidone (6 and 12 mg/day) with placebo, both doses were superior to placebo on the PANSS, with the 6 mg/day dose of paliperidone superior to placebo on the PSP scale.

Additionally, in a pooled analysis of the three trials, the superiority of INVEGA<sup>®</sup> versus placebo at each dose (3 to 15 mg once daily) was established on total PANSS (including all PANSS factors) and in the response measure of  $\geq$  30% reduction in PANSS total score. Each dose of INVEGA<sup>®</sup> also showed superiority to placebo on the PSP scale demonstrating an improvement in social functioning. An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of age, race, or gender.

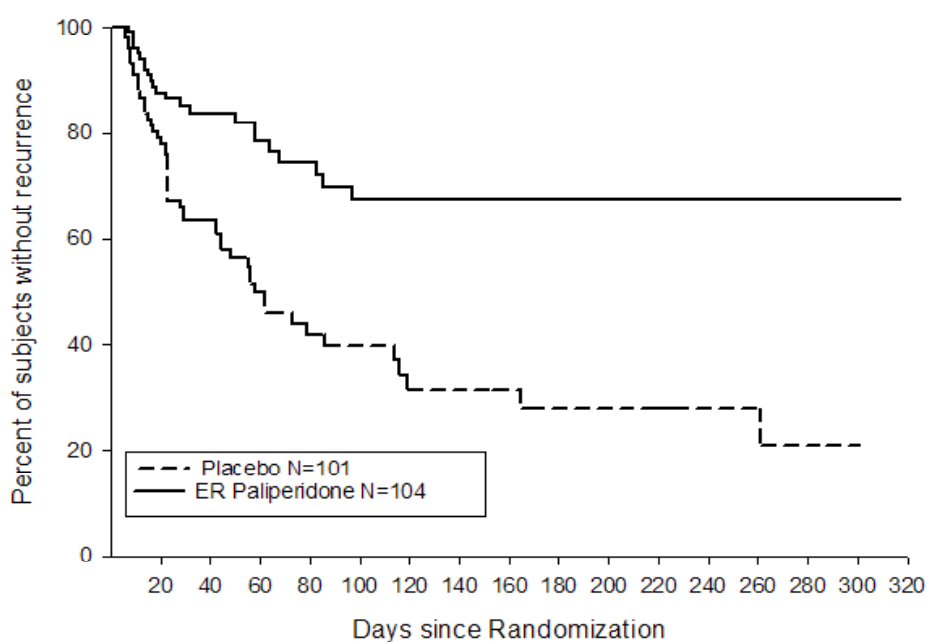
**Table 1: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set.**

	Placebo	INVEGA®			
		3 mg	6 mg	9 mg	12 mg
<b>R076477-SCH-303</b>	(N=126)		(N=123)	(N=122)	(N=129)
Mean baseline (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)
Mean change (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)
P-value (vs. Placebo)			<0.001	<0.001	<0.001
Diff. of LS Means (SE)			-13.7 (2.63)	-13.5 (2.63)	-18.9 (2.60)
95% CI			(-19.91;-7.53)	(-19.65;-7.25)	(-25.07;-12.82)
<b>R076477-SCH-304</b>	(N=105)		(N=111)		(N=111)
Mean baseline (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)
Mean change (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)
P-value (vs. Placebo)			0.006		<0.001
Diff. of LS Means (SE)			-7.0 (2.36)		-8.5 (2.35)
95% CI			(-12.27;-1.81)		(-13.75;-3.32)
<b>R076477-SCH-305</b>	(N=120)	(N=123)		(N=123)	
Mean baseline (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)	
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)		-16.3 (21.81)	
P-value (vs. Placebo)		< 0.001		<0.001	
Diff. of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)	
95% CI		(-17.17;-6.09)		(-18.42;-7.38)	

Note: Negative change in score indicates improvement. For all 3 studies, an active control (olanzapine at a dose of 10 mg) was included. LOCF = last observation carried forward. The 1-7 version of the PANSS was used. A 15 mg dose was also included in Study R076477-SCH-305, but results are not presented since this is above the maximum recommended daily dose of 12 mg.

In a long-term trial designed to assess the maintenance of effect, INVEGA® was significantly more effective than placebo in maintaining symptom control and preventing recurrence of schizophrenia symptoms. After having been treated for an acute episode for 6 weeks and stabilized for an additional 8 weeks with INVEGA® (doses ranging from 3 to 15 mg, flexible dosage regimen), patients were then randomised in a double-blind manner to either continue on INVEGA® or placebo until they experienced a recurrence of schizophrenia symptoms. Relapse was pre-defined as significant increase in PANSS (or pre-defined PANSS subscales), hospitalization, clinically significant suicidal or homicidal ideation, or deliberate injury to self or others. The trial was stopped early for efficacy reasons by showing a significantly longer time to recurrence in patients treated with INVEGA® compared to placebo ( $p < 0.001$ ) (Figure 2). INVEGA® was also significantly more effective than placebo in maintaining personal and social performance.

Figure 2. Kaplan-Meier Plot of Time to Recurrence



#### \*Schizoaffective Disorder

Efficacy of INVEGA<sup>®</sup> in the treatment of acute exacerbation of schizoaffective disorder was established in two placebo-controlled, 6-week trials conducted in adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale and/or Hamilton Rating Scale for Depression. The population included subjects with schizoaffective bipolar and depressive types.

Both studies included subjects who received INVEGA<sup>®</sup> either as monotherapy [no mood stabilizers and/or antidepressants (55%)] or in combination with mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. INVEGA<sup>®</sup> was taken in the morning without regard to meals.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. The primary efficacy end point was the change in the PANSS total score from baseline to week 6 last observation carried forward (LOCF) end point. Efficacy analyses were performed using the ITT analysis sets, which included subjects who received at least 1 dose of study medication, and both baseline and at least 1 post baseline PANSS assessment.

The safety and efficacy of INVEGA<sup>®</sup> in the prevention of relapse or recurrence of acute exacerbation of schizoaffective disorder has not been assessed.

In one of these trials subjects were permitted to have doses of INVEGA adjusted in the range of 3-12 mg once daily during the first 2 weeks, with doses fixed thereafter. The intent-to-treat (ITT) analysis set included 304 subjects (mean age: 37.6 years; range: 19-61 years), 186 subjects

completed the double blind treatment. Efficacy was assessed in 211 subjects who were assigned to at least 1 dose of active study medication, and had both baseline and at least 1 post baseline PANSS assessment.

In the other trial subjects received one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg or 12 mg with the option to reduce to 9 mg, once daily. The intent-to-treat (ITT) analysis set included 310 subjects (mean age: 37.3 years; range:18-61 years), 212 subjects completed the double blind treatment. Efficacy was assessed in 203 subjects who were assigned to at least 1 dose of study medication, and had both baseline and at least 1 post baseline PANSS assessment (n=105 INVEGA® 6 mg, with option to reduce to 3mg daily and n=98 INVEGA® 12 mg, with option to reduce to 9 daily).

**Table 2: Change in Positive and Negative Syndrome Scale (PANSS) Total Score From Baseline to Week 6 Last Observation Carried Forward (LOCF) ITT Population**

	Placebo	INVEGA®		
		6 mg, option to reduce to 3 mg	12 mg, option to reduce to 9 mg	3 mg to 12 mg
<b>R076477-SCA-3001</b>	(N=107)	(N=105)	(N=98)	
Mean baseline (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)	
Mean change (SD)	-21.7 (21.4)	-27.4 (22.1)	-30.6 (19.1)	
P-value (vs. Placebo)		0.187	0.003	
Diff. of LS Means (SE)		-3.6 (2.7)	-8.3 (2.8)	
95% CI		(-9.0;1.8)	(-13.8;-2.9)	
<b>R076477-SCA-3002</b>	(N=93)			(N=211)
Mean baseline (SD)	91.7 (12.1)			92.3 (13.5)
Mean change (SD)	-10.8 (18.7)			-20.0 (18.9)
P-value (vs. Placebo)				<0.001
Diff. of LS Means (SE)				-9.4 (2.3)
95% CI				(-13.8;-4.9)
<b>MONOTHERAPY</b>				
<b>R076477-SCA-3001</b>	(N=67)	(N=67)	(N=59)	
Mean baseline (SD)	89.6 (10.9)	96.6 (12.3)	90.1 (12.1)	
Mean change (SD)	-20.6 (20.8)	-28.9 (20.8)	-31.0 (19.9)	
P-value (vs. Placebo)		0.166	0.003	
Diff. of LS Means (SE)		-4.7 (3.4)	-10.1 (3.4)	
95% CI		(-11.3;2.0)	(-16.8;-3.5)	
<b>R076477-SCA-3002</b>	(N=44)			(N=102)
Mean baseline (SD)	92.9 (11.7)			92.7 (13.5)
Mean change (SD)	-11.6 (20.1)			-22.4 (19.4)
P-value (vs. Placebo)				0.003
Diff. of LS Means (SE)				-10.7 (3.5)
95% CI				(-17.7;-3.8)
<b>COMBINATION THERAPY</b>				
<b>R076477-SCA-3001</b>	(N=40)	(N=38)	(N=39)	
Mean baseline (SD)	95.0 (14.3)	94.8 (14.2)	96.6 (12.4)	
Mean change (SD)	-23.5 (22.5)	-24.7 (24.2)	-30.0 (17.9)	
P-value (vs. Placebo)		0.828	0.222	
Diff. of LS Means (SE)		-1.0 (4.7)	-5.7 (4.6)	
95% CI		(-10.3;8.2)	(-14.9;3.5)	

<b>R076477-SCA-3002</b>	(N=49)	(N=109)
Mean baseline (SD)	90.7 (12.5)	91.9 (13.6)
Mean change (SD)	-10.1 (17.5)	-17.7 (18.2)
P-value (vs. Placebo)		0.007
Diff. of LS Means (SE)		-8.1 (3.0)
95% CI		(-14.0;-2.2)

Note: Negative change in score indicates improvement.

The INVEGA<sup>®</sup> group in the study permitting dose adjustment for the first two weeks, followed by fixed dosing (in a range of 3-12 mg/day; mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA<sup>®</sup> in the 2 dose-level study (12 mg with option to reduce to 9 mg daily), were each superior to placebo in the PANSS. In the lower dose group of the 2 dose-level study (6 mg with option to reduce to 3 mg daily), INVEGA<sup>®</sup> was not significantly different from placebo as measured by the PANSS.

Taking the results of both studies together, INVEGA<sup>®</sup> improved the symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or in combination with antidepressants and/or mood stabilizers. An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age, or geographic region. There were insufficient data to explore differential effects based on race.

## INDICATIONS

INVEGA<sup>®</sup> is indicated for the treatment of schizophrenia, including acute treatment and recurrence prevention.

\*INVEGA<sup>®</sup> is indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/ or mood stabilizers (lithium and valproate).

## CONTRAINDICATIONS

INVEGA<sup>®</sup> (paliperidone) is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any components in the INVEGA<sup>®</sup> formulation.

## PRECAUTIONS

### Use in the elderly

The safety, tolerability, and efficacy of INVEGA<sup>®</sup> were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, 76 subjects received flexible doses of INVEGA<sup>®</sup> (3 to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA<sup>®</sup> (3 to 15 mg once daily, see **PHARMACOLOGY: Clinical Trials**).

Overall, of the total number of subjects in clinical studies of INVEGA<sup>®</sup> (n = 1796), including those who received INVEGA<sup>®</sup> or placebo, 125 (7.0%) were 65 years of age and older, of whom 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (also see Orthostatic Hypotension in this section).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION**).

### **Use in elderly patients with dementia**

INVEGA<sup>®</sup> has not been studied in elderly patients with dementia.

#### *Overall Mortality*

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. INVEGA<sup>®</sup> is not approved for the treatment of patients with dementia-related psychosis.

#### *Cerebrovascular Adverse Events*

In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo.

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischaemic attacks in patients (mean age 85 years, range 73-97) treated with risperidone compared to patients treated with placebo. The pooled data from six placebo-controlled trials in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96(1.33, 7.45).

### **QT Prolongation**

INVEGA<sup>®</sup> was not shown to result in any clinically significant increase in QTc intervals from baseline compared to placebo. However, as with other antipsychotics, caution should be exercised when INVEGA<sup>®</sup> is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other drugs known to increase the QTc interval particularly in elderly patients.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled (olanzapine 10 mg), 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n = 141), a suprathreshold dose of an immediate-release oral formulation (8 mg) resulted in a mean steady-state peak plasma concentration greater than twice the exposure observed with the maximum recommended INVEGA<sup>®</sup> dose of 12 mg ( $C_{max\ ss} = 113$  and  $45$  ng/mL, respectively). In the model-adjusted day-averaged linear-derived QT correction (QTcLD), there was a mean increase of 5.5 msec (90% CI: 3.66; 7.25) in the INVEGA<sup>®</sup> treatment group (n = 44). None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study. For the three fixed-dose efficacy studies, extensive electrocardiography (ECG) measurements were taken at 15 time points on specified days (including the times of expected  $C_{max}$ ) using a standardized methodology. Mean QTcLD increase did not exceed 5 msec in any treatment group at any time point, based on pooled data from 836 subjects treated with INVEGA<sup>®</sup>, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the INVEGA<sup>®</sup> 12 mg and olanzapine groups had a change exceeding 60 msec



at one time-point during these studies (changes of 62 and 110 msec, respectively). No subject receiving INVEGA<sup>®</sup> had a QTcLD exceeding 500 msec at any time in any of these three studies.

In the pooled double-blind safety analysis set, the largest mean increase in QTcLD interval, observed 22 hours after dose administration on Day 8, ranged between 1.6 to 4.4 msec across INVEGA<sup>®</sup> treatment groups.

In the overall phase 3 safety database (n=2054), which included both the double-blind and open-label extension studies, there were two patients with QTcLD prolongation > 500 msec.

## Extrapyramidal symptoms

As with other antipsychotics, EPS has been reported (see **ADVERSE EFFECTS**).

## Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

## Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome.

## **Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

## **Orthostatic Hypotension**

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3, 6, 9, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA®<sup>TM</sup> should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

As expected based on its pharmacologic profile, treatment with INVEGA® is associated with modest mean increases in heart rate at therapeutic doses.

Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

## **Seizures**

During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA<sup>®</sup> (3, 6, 9, 12 mg) and 0.25% of subjects treated with placebo. As with other antipsychotic drugs, INVEGA<sup>®</sup> should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

### **Hyperprolactinaemia**

As with other drugs that antagonize dopamine D<sub>2</sub> receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumourigenesis in humans; the available evidence is considered too limited to be conclusive at this time. (see **PRECAUTIONS**: Carcinogenicity)

### **Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA<sup>®</sup> and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

### **Weight gain**

As with other atypical antipsychotics, weight gain has been reported (see **ADVERSE EFFECTS**).

### **Suicide**

The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for INVEGA<sup>®</sup> should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

### **Potential for Cognitive and Motor Impairment**

Somnolence and sedation were reported in subjects treated with INVEGA<sup>®</sup> (see **ADVERSE EFFECTS**). Antipsychotics, including INVEGA<sup>®</sup> have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

### **Priapism**

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Severe priapism may require surgical intervention. Priapism has been reported with INVEGA<sup>®</sup> during postmarketing surveillance (see **ADVERSE EFFECTS**).

### **Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA<sup>®</sup> to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

## Gastrointestinal

Because the INVEGA<sup>®</sup> tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA<sup>®</sup> should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA<sup>®</sup> should only be used in patients who are able to swallow the tablet whole.

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.

## Antiemetic Effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdose with certain drugs or of conditions such as intestinal obstruction, Reye’s syndrome, and brain tumour.

## Use in patients with renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment and, therefore, dosage adjustment may be required in patients with mild (creatinine clearance  $\geq 50$  to  $< 80$  mL/min) and moderate to severe (creatinine clearance  $10$  to  $< 50$  mL/min) renal impairment (see **PHARMACOLOGY – Pharmacokinetics and DOSAGE AND ADMINISTRATION**). No data are available in patients with a creatinine clearance below 10 mL/min. Paliperidone should not be used in patients with creatinine clearance below 10 mL/min.

## Use in patients with hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if INVEGA<sup>®</sup> is used in such patients. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. (see **DOSAGE AND ADMINISTRATION**)

## Use in Children and adolescents younger than 18 years

Safety and effectiveness of INVEGA<sup>®</sup> in patients  $< 18$  years of age have not been studied.

## Use in Patients with Concomitant Illness

Clinical experience with INVEGA<sup>®</sup> in patients with certain concomitant illnesses is limited.

Patients with Parkinson’s Disease or Dementia with Lewy Bodies who receive antipsychotics, including INVEGA<sup>®</sup>, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medication. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

The safety of use of INVEGA<sup>®</sup> has not been evaluated in patients with relevant history of a significant or unstable cardiovascular or neurologic (including cerebrovascular) disease a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from

premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA<sup>®</sup>, caution should be observed in patients with known cardiovascular disease (see **PRECAUTIONS**: Orthostatic Hypotension).

### **Effects on fertility**

Mating and fertility of male and female rats was not affected at oral paliperidone doses up to 2.5 mg/kg/day (twice the maximum recommended clinical dose based on body surface area (mg/m<sup>2</sup>)). The 2.5 mg/kg/day dose produced slight maternal toxicity, increased pre-implantation loss and slightly reduced the number of live embryos; the no-effect dose was 0.63 mg/kg/day.

In rat fertility studies with risperidone, which is extensively converted to paliperidone in rats and humans, mating (but not fertility) was impaired at doses 0.2 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis, by an effect on females. In repeat dose toxicity studies in beagle dogs, risperidone at doses of 1 to 17 times the maximum human dose on a mg/m<sup>2</sup> basis was associated with adverse effects on the male reproductive system (inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog.

### **Use in pregnancy - Category B3**

The safety of INVEGA<sup>®</sup> during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate have been observed following the use of risperidone during the last trimester of pregnancy. Risperidone is extensively converted to paliperidone in humans. It is not known whether neonatal extrapyramidal effects will occur following the use of paliperidone near the end of pregnancy.

No teratogenic effect was noted in rats and rabbits following oral administration of paliperidone during the period of organogenesis at respective exposures up to 28- and 17-fold the maximal anticipated clinical exposure, based on plasma AUC. Maternotoxic doses in rabbits were associated with increased fetal mortality. Studies with risperidone also found no teratogenic effects in rats and rabbits following oral administration of risperidone during the period of organogenesis at doses up to nine times the human dose on a mg/m<sup>2</sup> basis. INVEGA<sup>®</sup> should only be used during pregnancy if the benefits outweigh the risks.

### **Use in lactation**

In animal studies with paliperidone and human studies with risperidone, paliperidone is excreted in milk. Women receiving INVEGA<sup>®</sup> should not breast feed.

Oral administration of paliperidone to rats from early gestation to lactation was associated with adverse effects in pups (clinical signs, reduced body weight gain and survival, impaired righting reflex) during lactation at doses similar to the maximal recommended clinical dose on mg/m<sup>2</sup> basis; the no-effect dose was less than the clinical dose. In risperidone studies in rats, oral administration of risperidone during late gestation and lactation was associated with increased pup deaths during early lactation at doses 0.2 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis (a no effect dose was not determined) and with reduced pup weight gain at doses fivefold or greater than the maximal recommended human dose on a mg/m<sup>2</sup> basis. There were also increases in stillborn rat pups at an oral risperidone dose 2.5 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis. It is not known whether these effects of risperidone and paliperidone resulted from a direct effect on the fetuses and pups and/or to an effect on the dams.

### **Alcohol**

Given the primary CNS effects of INVEGA<sup>®</sup>, patients should be advised to avoid alcohol while taking this medicine.

## Carcinogenicity

The carcinogenic potential of paliperidone has not been determined. Paliperidone is the major active metabolite of risperidone, which has been assessed for carcinogenic potential in rodents.

Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times (in mice) or 0.6, 2.5 and 10 times (in rats) the maximum human dose on a mg/m<sup>2</sup> basis.

There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies but measurements during repeat-dose toxicity studies showed that risperidone elevated serum prolactin levels by 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.

The relevance for human risk of the findings of prolactin mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL<sup>®</sup> elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, RISPERDAL<sup>®</sup> and INVEGA<sup>®</sup> should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia (see **ADVERSE EFFECTS**).

## Genotoxicity

No evidence of genotoxic potential for paliperidone was found in bacterial reverse mutation tests, forward mutation tests in mammalian cells (mouse lymphoma), or an *in vivo* chromosomal aberration assay (rat micronucleus test). Risperidone, which is metabolised to paliperidone in humans, was also negative in genotoxicity assays.

## Interactions with other medicines

The risks of using INVEGA<sup>®</sup> in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of INVEGA<sup>®</sup>, it should be used with caution in combination with other centrally acting drugs.

### Use with medicines known to cause QT prolongation:

Caution is advised when INVEGA<sup>®</sup> is used in combination with medicines known to cause QT prolongation e.g. class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine).

### Use with medicines containing risperidone:

Concomitant use of INVEGA<sup>®</sup> with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

### Potential for INVEGA<sup>®</sup> to affect other medicines:

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by

cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Given the primary CNS effects of paliperidone (see **ADVERSE EFFECTS**), INVEGA<sup>®</sup> should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Caution is advised when paliperidone is combined with medicines known to lower the seizure threshold. (e.g. phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.)

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA<sup>®</sup> is administered with other therapeutic agents that have this potential (see **PRECAUTIONS**: Orthostatic Hypotension).

#### Potential for other medicines to affect INVEGA<sup>®</sup>:

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone.

*In vitro* studies have shown that paliperidone is a P-gp substrate.

Paliperidone is metabolised to a limited extent by CYP2D6 (see **PHARMACOLOGY**: Pharmacokinetics – Metabolism and Elimination). In an interaction study in healthy males who were CYP2D6 extensive metabolisers, single doses of INVEGA<sup>®</sup> 3 mg were administered alone or after treatment with the potent CYP2D6 inhibitor paroxetine, 20 mg daily for 13 days. The mean peak plasma concentration and systemic exposure of unbound paliperidone were increased by 12% and 19%, respectively. This effect is unlikely to be clinically significant.

Co-administration of INVEGA<sup>®</sup> once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state  $C_{max}$  and AUC of paliperidone. The decrease may be greater with higher carbamazepine doses. On initiation of carbamazepine or when increasing the dose of carbamazepine, the dose of INVEGA<sup>®</sup> should be re-evaluated and increased if necessary. Conversely, on discontinuation or dose reduction of carbamazepine, the dose of INVEGA<sup>®</sup> should be re-evaluated and decreased if necessary.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Medicinal products affecting gastrointestinal transit time may affect the absorption of paliperidone, e.g. metoclopramide.

#### **Effect on ability to drive or operate machinery**

INVEGA<sup>®</sup> may interfere with activities requiring mental alertness and may have visual effects (see **ADVERSE EFFECTS**). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

### **\* ADVERSE EFFECTS**

#### **Clinical Trial Data**

*The safety of INVEGA<sup>®</sup> in the treatment of schizophrenia was evaluated in 1205 adult subjects with schizophrenia who participated in 3 double-blind, placebo-controlled 6-week trials, of whom 850 subjects received INVEGA<sup>®</sup> at fixed doses ranging from 3 mg to 12 mg once daily.*

The safety of INVEGA<sup>®</sup> was also evaluated in 622 subjects with schizoaffective disorder who participated in two double-blind, placebo-controlled, 6-week trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA<sup>®</sup>: 6 mg with the option to reduce to 3 mg (n = 108) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. In the other study, 214 subjects received doses of INVEGA<sup>®</sup> adjusted in the range of 3-12 mg once daily during the first 2 weeks (Mean Dose= 8.9 mg/day), with doses fixed thereafter. Both studies included subjects who received INVEGA<sup>®</sup> either as monotherapy or in combination with antidepressants and/or mood stabilizers.

The information in this section was derived from pooled data.

The majority of Adverse Drug Reactions (ADRs) were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data – Schizophrenia:

Adverse drug reactions reported by  $\geq 2\%$  of INVEGA<sup>®</sup> -treated subjects in the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia trials are shown in Table 3.

**Table 3. Adverse Drug Reactions Reported by  $\geq 2\%$  of INVEGA<sup>®</sup> -Treated Subjects with Schizophrenia in Three 6-Week Double-Blind, Placebo-Controlled, Fixed-Dose Clinical Trials**

System/Organ Class Adverse Reaction	INVEGA <sup>®</sup>				
	3 mg (N=127) %	6 mg (N=235) %	9 mg (N=246) %	12 mg (N=242) %	Placebo (N=355) %
<b>Nervous System Disorders</b>					
Headache	11	12	14	14	12
Dizziness	6	5	4	5	4
Extrapyramidal disorder	5	2	7	7	2
Somnolence	5	3	7	5	3
Akathisia	4	3	8	10	4
Tremor	3	3	4	3	3
Hypertonia	2	1	4	3	1
Dystonia	1	1	4	4	1
Sedation	1	5	3	6	4
Parkinsonism	0	<1	2	1	0
<b>Cardiac Disorders</b>					
Sinus tachycardia	9	4	4	7	4
Tachycardia	2	7	7	7	3
Bundle branch block	3	1	3	<1	2
Atrioventricular block first degree	2	0	2	1	1
<b>Vascular Disorders</b>					
Orthostatic hypotension	2	1	2	4	1
<b>Gastrointestinal Disorders</b>					
Dry mouth	2	3	1	3	1
Abdominal pain upper	1	3	2	2	1
Salivary hypersecretion	0	<1	1	4	<1
<b>General disorders</b>					
Asthenia	2	<1	2	2	1
Fatigue	2	1	2	2	1



Additional ADRs reported by <2% of INVEGA-treated subjects in the schizophrenia clinical double blind, placebo-controlled trial datasets are shown below:

**Table 4 Adverse Drug Reactions Reported by <2% of INVEGA-Treated Subjects in Short-Term, Placebo-Controlled Studies in Adult Subjects with Schizophrenia (SCH-303, SCH-304, SCH-305)**

<b>Adverse Events</b>
<b>Immune system disorders</b>
Anaphylactic reaction
<b>Metabolism and nutrition disorders</b>
Increased appetite
<b>Psychiatric disorders</b>
Nightmare
<b>Nervous system disorders</b>
Syncope, Dyskinesia, Dizziness postural, Grand mal convulsion
<b>Cardiac disorders</b>
Bradycardia, Palpitations
<b>Vascular disorders</b>
Hypotension, Ischaemia
<b>Musculoskeletal and connective tissue disorders</b>
Muscle rigidity
<b>Reproductive system and breast disorders</b>
Galactorrhoea, Amenorrhoea, Gynaecomastia, Erectile dysfunction, Breast discharge, Menstruation irregular
<b>General disorders and administration site conditions</b>
Oedema
<b>Investigations</b>
Weight increased, Electrocardiogram abnormal

Double-Blind, Placebo-Controlled Data – Schizoaffective Disorder:

ADRs reported by  $\geq 2\%$  of INVEGA<sup>®</sup>--treated subjects in the two placebo-controlled schizoaffective disorder trials are shown in Table 5.

**Table 5. Adverse Drug Reactions Reported by  $\geq 2\%$  of INVEGA<sup>®</sup>--Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials**

<b>System/Organ Class</b>	<b>INVEGA<sup>®</sup> 3-12 mg once daily (N=420)*</b>	<b>Placebo (N=202)</b>
<b>Adverse Reaction</b>	<b>%</b>	<b>%</b>
<b>Infections and Infestations</b>		
Nasopharyngitis	3	1
<b>Metabolism and Nutrition Disorders</b>		
Increased appetite	2	<1
<b>Nervous System Disorders</b>		
Tremor	8	3
Akathisia	5	4
Sedation	5	3

Somnolence	5	2
Hypertonia	5	2
Drooling	2	0
Dysarthria	2	0

**Gastrointestinal Disorders**

Nausea	6	6
Dyspepsia	5	2
Constipation	4	2

**Musculoskeletal and Connective Tissue Disorders**

Myalgia	2	<1
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**Investigations**

Weight increased	4	1
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\* Among the 420 subjects treated with INVEGA<sup>®</sup>, 230 (55%) received INVEGA<sup>®</sup> as monotherapy and 190 (45%) received INVEGA<sup>®</sup>, in combination with antidepressants and/or mood stabilizers.

Additional ADRs reported by <2% of INVEGA-treated subjects in the Schizoaffective Disorder clinical double blind, placebo-controlled trial datasets are shown below:

**Table 6: Adverse Drug Reactions Reported by <2% of INVEGA-Treated Subjects in Short-Term, Placebo-Controlled Studies in Adult Subjects with Schizoaffective Disorder (SCA-3001, SCA-3002)**

**Adverse Events**

**Infections and infestations**

Upper respiratory tract infection, Rhinitis

**Metabolism and nutrition disorders**

Decreased appetite

**Psychiatric disorders**

Restlessness, Sleep disorder

**Nervous system disorders**

Dystonia, Dyskinesia, Bradykinesia, Parkinsonism, Parkinsonian gait, Lethargy

**Eye disorders**

Vision blurred, Oculogyration

**Cardiac disorders**

Tachycardia, Bradycardia

**Vascular disorders**

Orthostatic hypotension

**Respiratory, thoracic and mediastinal disorders**

Cough, Pharyngolaryngeal pain

**Gastrointestinal disorders**

Abdominal discomfort/Abdominal pain upper, Stomach discomfort, Small intestinal obstruction

**Musculoskeletal and connective tissue disorders**

Back pain, Muscle rigidity, Muscle twitching

**Reproductive system and breast disorders**

Galactorrhoea, Erectile dysfunction, Breast discharge, Breast engorgement, Breast pain

**General disorders and administration site conditions**

Asthenia

Note: The following preferred terms (identified as ADRs in these studies) were combined: "ABDOMINAL DISCOMFORT/ABDOMINAL PAIN UPPER".

### *Monotherapy versus Combination Therapy:*

*The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA<sup>®</sup> as monotherapy and 190 (45%) subjects received INVEGA<sup>®</sup> in combination with antidepressants and/or mood stabilizers. When comparing these 2 subpopulations, only nausea occurred at a greater frequency ( $\geq 3\%$  difference) in subjects receiving INVEGA<sup>®</sup> as monotherapy.*

### **Discontinuations Due to Adverse Reactions**

#### Schizophrenia Trials:

The percentages of subjects who discontinued due to adverse reactions in the three placebo-controlled, 6-week, fixed-dose schizophrenia studies were 3% and 1% in INVEGA<sup>®</sup>- and placebo-treated subjects. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA<sup>®</sup>- and placebo-treated subjects, respectively).

#### *\*Schizoaffective Disorder Trials:*

*In a placebo-controlled, 6-week high- and low-dose study in subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of INVEGA<sup>®</sup> compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA<sup>®</sup> compared with subjects who received higher doses.*

### **Dose Related Adverse Events**

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose schizophrenia studies, adverse events that occurred with 2% or more incidence in the subjects treated with INVEGA<sup>®</sup>, the incidences of the following adverse events increased with dose: somnolence, orthostatic hypotension, salivary hypersecretion, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism. For most of these, the increased incidence was seen primarily at the 12 mg, and in some cases the 9 mg dose.

In the placebo-controlled, 6-week high- and low-dose study in subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of INVEGA<sup>®</sup> compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA<sup>®</sup> compared with subjects who received higher doses.

### **Extrapyramidal Symptoms (EPS)**

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia provided information regarding treatment-emergent EPS and dose-relatedness for EPS with the two higher doses of INVEGA<sup>®</sup> (9 and 12 mg once daily). Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates EPS-related symptoms, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale total score (mean change from baseline) which evaluates dyskinesia, (4) incidence of spontaneous reports of EPS, and (5) use of anticholinergic medications to treat emergent EPS. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there

was a dose-related increase observed for the 9 and 12 mg doses. There was no difference observed between placebo and INVEGA<sup>®</sup> 3 and 6 mg doses for any of these EPS measures.

**Table 7. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies**

EPS Group	Percentage of Patients				
	Placebo (N=355)	INVEGA <sup>®</sup> 3 mg once daily (N=127)	6 mg once daily (N=235)	9 mg once daily (N=246)	12 mg once daily (N=242)
Parkinsonism <sup>a</sup>	9	11	3	15	14
Akathisia <sup>b</sup>	6	6	4	7	9
Use of anticholinergic medications <sup>c</sup>	10	10	9	22	22

a: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items)

b: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score  $\geq 2$

c: Percent of patients who received anticholinergic medications to treat emergent EPS

**Table 8. Treatment-Emergent Extrapyramidal Symptoms (EPS)- Related Adverse Events by MedDRA Preferred Term– Schizophrenia Studies**

EPS Group	Percentage of Patients				
	Placebo (N=355)	INVEGA <sup>®</sup> 3 mg once daily (N=127)	6 mg once daily (N=235)	9 mg once daily (N=246)	12 mg once daily (N=242)
Overall percentage of patients with EPS- related AE	11.0	12.6	10.2	25.2	26.0
Dyskinesia	3.4	4.7	2.6	7.7	8.7
Dystonia	1.1	0.8	1.3	5.3	4.5
Hyperkinesia	3.9	3.9	3.0	8.1	9.9
Parkinsonism	2.3	3.1	2.6	7.3	6.2
Tremor	3.4	3.1	2.6	4.5	3.3

Dyskinesia group includes: Dyskinesia, Extrapyramidal disorder, Muscle twitching, Tardive dyskinesia

Dystonia group includes: Dystonia, Muscle spasms, Oculogyration, Trismus

Hyperkinesia group includes: Akathisia, Hyperkinesia

Parkinsonism group includes: Bradykinesia, Cogwheel rigidity, Drooling,

Hypertonia, Hypokinesia, Muscle rigidity, Musculoskeletal stiffness,

Parkinsonism

Tremor group includes: Tremor

\*Table 9 shows the EPS data from the pooled schizoaffective disorder trials.

**Table 9. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies**

<i>EPS Group</i>	<i>Placebo</i> (N=202)	<i>Percentage of Patients</i> <i>INVEGA®</i>		
		<i>3-6 mg</i> <i>once-daily</i> <i>fixed-dose</i> <i>range</i> (N=108)	<i>9-12 mg</i> <i>once-daily</i> <i>fixed-dose</i> <i>range</i> (N=98)	<i>3-12 mg</i> <i>once-daily</i> <i>flexible dose</i> (N=214)
<i>Overall percentage of patients with EPS-related AE</i>	11	23	22	17
<i>Dyskinesia</i>	1	3	1	1
<i>Dystonia</i>	1	2	3	2
<i>Hyperkinesia</i>	5	5	8	7
<i>Parkinsonism</i>	3	14	7	7
<i>Tremor</i>	3	12	11	5

*Dyskinesia group includes: Dyskinesia, muscle twitching*

*Dystonia group includes: Dystonia, muscle spasms, oculogyration*

*Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness*

*Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait, parkinsonism*

*Tremor group includes: Tremor*

Compared to data from the studies in schizophrenia, pooled data from the two placebo-controlled 6-week studies in subjects with schizoaffective disorder showed similar types and frequencies of EPS as measured by rating scales, anticholinergic medication use, and spontaneous reports of EPS-related adverse events. For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for Parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

## Laboratory Test Abnormalities

In the pooled data from the three placebo-controlled, 6-week, fixed-dose schizophrenia studies, a between-group comparison revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, haematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in haematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® was associated with increases in serum prolactin (see **PRECAUTIONS: Hyperprolactinaemia**).

## Weight Gain

In the pooled data from the three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose schizophrenia studies, the proportions of subjects meeting a weight gain criterion of  $\geq 7\%$  of body weight were compared. Weight gain incidence for INVEGA® 3 mg, 6 mg, 9 mg and 12 mg was 7%, 6%, 9% and 9% respectively. In comparison the incidence for placebo was 5%.

*\*In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, a higher percentage of INVEGA®-treated subjects (5%) had an increase in body weight of  $\geq 7\%$  compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of  $\geq 7\%$  was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.*

## Other Findings Observed During Clinical Studies

The safety of INVEGA<sup>®</sup> was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA<sup>®</sup> in adults with schizophrenia (see **PHARMACOLOGY** Clinical Trials). In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

### Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with INVEGA<sup>®</sup> are included in Table 10.

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports
Unknown	cannot be estimated from the available clinical trial data

<b>Table 10.</b> Adverse Drug Reactions Identified During Postmarketing Experience with INVEGA <sup>®</sup> by Frequency Category estimated from Clinical Trials
<b>Reproductive System and Breast Disorders</b>
Unknown Priapism

## Adverse Events Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse events reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone Product Information.

## DOSAGE AND ADMINISTRATION

The administration of INVEGA<sup>®</sup> should be standardised in relation to food intake (see **PHARMACOLOGY** – Pharmacokinetics). The patient should be instructed to always take INVEGA<sup>®</sup> in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state.

INVEGA<sup>®</sup> must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

### Schizophrenia

The recommended dose of INVEGA<sup>®</sup> for the treatment of schizophrenia is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the usual range of 3 to 9 mg once daily. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. If required the dose may be increased to the maximum recommended dose of 12 mg once daily.

### **\*Acute exacerbation of Schizoaffective Disorder**

*The recommended dose of INVEGA® for the treatment of schizoaffective disorder is 6 mg once daily, administered in the morning. While initial dose titration is not required, the patients would require dosage adjustment to lower or higher doses within the dose range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days.*

Concomitant use of INVEGA® with risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA®. Concomitant use of INVEGA® with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

## **Dosing in Special Populations**

### Hepatic Impairment:

No dose adjustment is required in patients with mild to moderate hepatic impairment. As INVEGA® has not been studied in patients with severe hepatic impairment, caution is recommended when using the medicine in such patients.

### Renal Impairment:

Dosing must be individualized according to the patient's renal function status. For patients with mild renal impairment (creatinine clearance  $\geq 50$  to  $< 80$  mL/min), the recommended initial dose is 3 mg once daily. The dose may be increased based on clinical response and tolerability.

For patients with moderate renal impairment (creatinine clearance  $\geq 30$  to  $< 50$  ml/min), the recommended dose of INVEGA® is 3 mg once daily. For patients with severe renal impairment (creatinine clearance  $\geq 10$  to  $< 30$  ml/min), the recommended initial dose of INVEGA® is 3 mg every other day, which may be increased to 3 mg once daily-after clinical reassessment. As INVEGA® has not been studied in patients with creatinine clearance below 10 ml/min, use is not recommended in such patients.

### Elderly:

In general, the same dosing recommendations apply for elderly patients with normal renal function as for adult patients with normal renal function (creatinine clearance  $\geq 80$  mL/min). However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal Impairment above).

### Children and adolescents younger than 18 years of age:

INVEGA® has not been studied in this patient group and should not be used in this age group.

## **OVERDOSAGE**

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation.

## **Management of Overdosage**

There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyride, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (adrenaline and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

## PRESENTATION AND STORAGE CONDITIONS

3 mg White, capsule shaped tablets imprinted with "PAL 3".  
Pack size: Blister pack of 28 tablets.

6 mg Beige, capsule shaped tablets imprinted with "PAL 6".  
Pack size: Blister pack of 28 tablets.

9 mg Pink, capsule shaped tablets imprinted with "PAL 9".  
Pack size: Blister pack of 28 tablets.

Store below 25°C.

## POISON SCHEDULE

S4 - Prescription Only Medicine

## SPONSOR

Janssen-Cilag Pty Ltd  
1-5 Khartoum Road, North Ryde, NSW, 2113, Australia  
NZ Office: Auckland, New Zealand.

**Date of TGA approval:** 16 November 2009

Please note changes (presented as *italicised text*) in Product Information.





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