

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

INVEGA 3 mg prolonged-release tablets  
INVEGA 6 mg prolonged-release tablets  
INVEGA 9 mg prolonged-release tablets  
INVEGA 12 mg prolonged-release tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each prolonged-release tablet contains 3 mg of paliperidone.  
Each prolonged-release tablet contains 6 mg of paliperidone.  
Each prolonged-release tablet contains 9 mg of paliperidone.  
Each prolonged-release tablet contains 12 mg of paliperidone.

### Excipient with known effect

Each 3 mg tablet contains 13.2 mg lactose.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Prolonged-release tablet

Trilayer capsule-shaped white tablets of 11 mm in length and 5 mm in diameter printed with “PAL 3”  
Trilayer capsule-shaped beige tablets of 11 mm in length and 5 mm in diameter printed with “PAL 6”  
Trilayer capsule-shaped pink tablets of 11 mm in length and 5 mm in diameter printed with “PAL 9”  
Trilayer capsule-shaped yellow tablets of 11 mm in length and 5 mm in diameter printed with “PAL 12”

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

INVEGA is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

INVEGA is indicated for the treatment of schizoaffective disorder in adults.

### **4.2 Posology and method of administration**

#### Posology

##### *Schizophrenia (adults)*

The recommended dose of INVEGA for the treatment of schizophrenia in adults 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 recommended range of 3 mg 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 5 days.

##### *Schizoaffective disorder (adults)*

The recommended dose of INVEGA for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from higher doses within the recommended range of 6 mg 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.

#### *Switching to other antipsychotic medicinal products*

There are no systematically collected data to specifically address switching patients from INVEGA to other antipsychotic medicinal products. Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic medicinal products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

#### *Elderly*

Dosing recommendations for elderly patients with normal renal function ( $\geq 80$  mL/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal impairment below). INVEGA should be used with caution in elderly patients with dementia with risk factors for stroke (see section 4.4). Safety and efficacy of INVEGA in patients  $> 65$  years of age with schizoaffective disorder have not been studied.

#### *Hepatic impairment*

No dose adjustment is required in patients with mild or moderate hepatic impairment. As INVEGA has not been studied in patients with severe hepatic impairment, caution is recommended in such patients.

#### *Renal impairment*

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 to 6 mg once daily based on clinical response and tolerability.

For patients with moderate to severe renal impairment (creatinine clearance  $\geq 10$  to  $< 50$  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.

#### *Paediatric population*

*Schizophrenia:* The recommended starting dose of INVEGA for the treatment of schizophrenia in adolescents 15 years and older is 3 mg once daily, administered in the morning.

Adolescents weighing  $< 51$  kg: the maximum recommended daily dose of INVEGA is 6 mg.

Adolescents weighing  $\geq 51$  kg: the maximum recommended daily dose of INVEGA is 12 mg.

Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more. The safety and efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made. There is no relevant use of INVEGA in children aged less than 12 years.

*Schizoaffective disorder:* The safety and efficacy of INVEGA in the treatment of schizoaffective disorder in patients aged 12 to 17 years has not been studied or established. There is no relevant use of INVEGA in children aged less than 12 years.

#### *Other special populations*

No dose adjustment for INVEGA is recommended based on gender, race, or smoking status.

#### Method of administration

INVEGA is for oral administration. It must be swallowed whole with liquid, and must not be chewed, divided, or crushed. The active substance is contained within a non-absorbable shell designed to

release the active substance 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.

The administration of INVEGA should be standardised in relation to food intake (see section 5.2). The patient should be instructed to always take INVEGA 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.

### **4.3 Contraindications**

Hypersensitivity to the active substance, risperidone, or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

Patients with schizoaffective disorder treated with paliperidone should be carefully monitored for a potential switch from manic to depressive symptoms.

#### QT interval

Caution should be exercised when INVEGA is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicines thought to prolong the QT interval.

#### Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotics, including INVEGA, should be discontinued.

#### Tardive dyskinesia/extrapyramidal symptoms

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including INVEGA, should be considered.

Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

#### Leucopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including INVEGA. Agranulocytosis has been reported very rarely (< 1/10 000 patients) during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of INVEGA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 10<sup>9</sup>/L) should discontinue INVEGA and have their WBC followed until recovery.

#### Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with paliperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including INVEGA, should

be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

#### Weight gain

Significant weight gain has been reported with INVEGA use. Weight should be monitored regularly.

#### Hyperprolactinaemia

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with possible prolactin-dependent tumours.

#### Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. Based on pooled data from the three, placebo-controlled, 6-week, fixed-dose trials with INVEGA (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with INVEGA compared with 0.8% of subjects treated with placebo. INVEGA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolaemia).

#### Seizures

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

#### Potential for gastrointestinal obstruction

Because the INVEGA tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, INVEGA should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable controlled-release formulations. Due to the controlled-release design of the dosage form, INVEGA should only be used in patients who are able to swallow the tablet whole.

#### Conditions with decreased gastro-intestinal transit time

Conditions leading to shorter gastrointestinal transit time, e.g., diseases associated with chronic severe diarrhoea, may result in a reduced absorption of paliperidone.

#### Renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment and, therefore, dosage adjustment may be required in some patients (see sections 4.2 and 5.2). 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.

#### Hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if paliperidone is used in such patients.

#### Elderly patients with dementia

INVEGA has not been studied in elderly patients with dementia. The experience from risperidone is considered valid also for paliperidone.

#### *Overall mortality*

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an

increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

#### *Cerebrovascular adverse reactions*

An approximately 3-fold increased risk of cerebrovascular adverse reactions have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known. INVEGA should be used with caution in elderly patients with dementia who have risk factors for stroke.

#### Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing INVEGA to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

#### Priapism

Antipsychotic medicinal products (including risperidone) with  $\alpha$ -adrenergic blocking effects have been reported to induce priapism. During post-marketing surveillance priapism has also been reported with paliperidone, which is the active metabolite of risperidone. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3-4 hours.

#### Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing INVEGA 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.

#### Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA and preventive measures undertaken.

#### 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 medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

#### Paediatric population

The sedative effect of INVEGA should be closely monitored in this population. A change in the time of administration of INVEGA may improve the impact of sedation on the patient.

Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with INVEGA regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in the paediatric population see section 4.2.

### Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha 1a-adrenergic antagonist effect, such as INVEGA (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha 1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

### Excipients

#### Lactose content (*pertains only to the 3 mg tablets*)

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e., essentially sodium-free.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Caution is advised when prescribing INVEGA with medicines known to prolong the QT interval, 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).

### Potential for INVEGA to affect other medicines

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450 isozymes. *In vitro* studies indicate that paliperidone is not an inducer of CYP1A2 activity.

Given the primary CNS effects of paliperidone (see section 4.8), INVEGA should be used with caution in combination with other centrally acting medicines, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when INVEGA is administered with other therapeutic agents that have this potential, e.g., other antipsychotics, tricyclics.

Caution is advised if paliperidone is combined with other medicines known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, clozapine, tricyclics or SSRIs, tramadol, mefloquine, etc.).

No interaction study between INVEGA and lithium has been performed, however, a pharmacokinetic interaction is unlikely to occur.

Co-administration of INVEGA 12 mg once daily with divalproex sodium prolonged-release tablets (500 mg to 2,000 mg once daily) did not affect the steady-state pharmacokinetics of valproate. Co-administration of INVEGA with divalproex sodium prolonged-release tablets increased the exposure to paliperidone (see below).

#### Potential for other medicines to affect INVEGA

*In vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of INVEGA with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone. *In vitro* studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate.

Co-administration of INVEGA 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. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of INVEGA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA should be re-evaluated and decreased if necessary. It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer the effect wears off over a similar time period. Other medicinal products or herbals which are inducers, e.g., rifampicin and St. John's wort (*Hypericum perforatum*) may have similar effects on paliperidone.

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

Co-administration of a single dose of INVEGA 12 mg with divalproex sodium prolonged-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the  $C_{max}$  and AUC of paliperidone. Dosage reduction for INVEGA should be considered when INVEGA is co-administered with valproate after clinical assessment.

#### Concomitant use of INVEGA with risperidone

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.

#### Concomitant use of INVEGA with psychostimulants

The combined use of psychostimulants (e.g., methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no adequate data from the use of paliperidone during pregnancy.

Paliperidone was not teratogenic in animal studies, but other types of reproductive toxicity were observed (see section 5.3). Neonates exposed to antipsychotics (including paliperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. INVEGA should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.



### Breast-feeding

Paliperidone is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if therapeutic doses are administered to breast-feeding women. INVEGA should not be used while breast feeding.

### Fertility

There were no relevant effects observed in the non-clinical studies.

## **4.7 Effects on ability to drive and use machines**

Paliperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to INVEGA is known.

## **4.8 Undesirable effects**

### Adults

#### *Summary of the safety profile*

The adverse drug reactions (ADRs) most frequently reported in clinical trials with adults were headache, insomnia, sedation/somnolence, parkinsonism, akathisia, tachycardia, tremor, dystonia, upper respiratory tract infection, anxiety, dizziness, weight increased, nausea, agitation, constipation, vomiting, fatigue, depression, dyspepsia, diarrhoea, dry mouth, toothache, musculoskeletal pain, hypertension, asthenia, back pain, electrocardiogram QT prolonged, and cough.

The ADRs that appeared to be dose-related included headache, sedation/somnolence, parkinsonism, akathisia, tachycardia, dystonia, dizziness, tremor, upper respiratory tract infection, dyspepsia, and musculoskeletal pain.

In the schizoaffective disorder studies, a greater proportion of subjects in the total INVEGA dose group who were receiving concomitant therapy with an antidepressant or mood stabiliser experienced adverse events as compared to those subjects treated with INVEGA monotherapy.

### Tabulated list of adverse reactions

The following are all the ADRs that were reported in clinical trials and post-marketing experience with paliperidone by frequency category estimated from INVEGA clinical trials in adults. The following terms and frequencies are applied: *very common* ( $\geq 1/10$ ), *common* ( $\geq 1/100$  to  $< 1/10$ ), *uncommon* ( $\geq 1/1\,000$  to  $< 1/100$ ), *rare* ( $\geq 1/10\,000$  to  $< 1/1\,000$ ), *very rare* ( $< 1/10\,000$ ), and *not known* (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
<b>Infections and infestations</b>		bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, influenza	pneumonia, respiratory tract infection, cystitis, ear infection, tonsillitis	eye infection, onychomycosis, cellulitis, acarodermatitis	
<b>Blood and lymphatic system disorders</b>			white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased	agranulocytosis <sup>c</sup> , neutropenia, eosinophil count increased	
<b>Immune system disorders</b>				anaphylactic reaction, hypersensitivity	

<b>Endocrine disorders</b>			hyperprolactinaemia <sup>a</sup>	inappropriate antidiuretic hormone secretion <sup>c</sup> , glucose urine present	
<b>Metabolism and nutrition disorders</b>		weight increased, increased appetite, weight decreased, decreased appetite	diabetes mellitus <sup>d</sup> , hyperglycaemia, waist circumference increased, anorexia, blood triglycerides increased	water intoxication, diabetic ketoacidosis <sup>c</sup> , hypoglycaemia, polydipsia, blood cholesterol increased	hyperinsulinaemia <sup>a</sup>
<b>Psychiatric disorders</b>	insomnia <sup>c</sup>	mania, agitation, depression, anxiety	sleep disorder, confusional state, libido decreased, anorgasmia, nervousness, nightmare	catatonia, somnambulism, blunted affect <sup>c</sup>	
<b>Nervous system disorders</b>	parkinsonism <sup>b</sup> , akathisia <sup>b</sup> , sedation/somnolence, headache	dystonia <sup>b</sup> , dizziness, dyskinesia <sup>b</sup> , tremor <sup>b</sup>	tardive dyskinesia, convulsion <sup>c</sup> , syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paresthesia	neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli <sup>c</sup> , loss of consciousness, depressed level of consciousness <sup>c</sup> , diabetic coma <sup>c</sup> , balance disorder, coordination abnormal, head titubation <sup>c</sup>	
<b>Eye disorders</b>		vision blurred	photophobia, conjunctivitis, dry eye	glaucoma, eye movement disorder <sup>c</sup> , eye rolling <sup>c</sup> , lacrimation increased, ocular hyperaemia	
<b>Ear and labyrinth disorders</b>			vertigo, tinnitus, ear pain		
<b>Cardiac disorders</b>		atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, tachycardia	sinus arrhythmia, electrocardiogram abnormal, palpitations	atrial fibrillation, postural orthostatic tachycardia syndrome <sup>c</sup>	
<b>Vascular disorders</b>		orthostatic hypotension, hypertension	hypotension	pulmonary embolism, venous thrombosis, ischaemia, flushing	
<b>Respiratory, thoracic and mediastinal disorders</b>		pharyngolaryngeal pain, cough, nasal congestion	dyspnoea, wheezing, epistaxis	sleep apnoea syndrome, hyperventilation, pneumonia aspiration, respiratory tract congestion, dysphonia	pulmonary congestion
<b>Gastrointestinal disorders</b>		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	swollen tongue, gastroenteritis, dysphagia, flatulence	pancreatitis <sup>c</sup> , intestinal obstruction, ileus, faecal incontinence, faecaloma <sup>c</sup> , cheilitis	

<b>Hepatobiliary disorders</b>		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
<b>Skin and subcutaneous tissue disorders</b>		pruritus, rash	urticaria, alopecia, eczema, acne	angioedema, drug eruption <sup>c</sup> , hyperkeratosis, dry skin, erythema, skin discolouration, seborrhoeic dermatitis, dandruff	
<b>Musculoskeletal and connective tissue disorders</b>		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, joint swelling, muscular weakness, neck pain	rhabdomyolysis <sup>c</sup> , posture abnormal <sup>c</sup>	
<b>Renal and urinary disorders</b>			urinary incontinence, pollakiuria, urinary retention, dysuria		
<b>Pregnancy, puerperium and perinatal conditions</b>				drug withdrawal syndrome neonatal (see section 4.6) <sup>c</sup>	
<b>Reproductive system and breast disorders</b>		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder <sup>c</sup> , galactorrhoea, sexual dysfunction, breast pain, breast discomfort	priapism <sup>c</sup> , menstruation delayed <sup>c</sup> , gynaecomastia, breast engorgement, breast enlargement <sup>c</sup> , breast discharge, vaginal discharge	
<b>General disorders</b>		pyrexia, asthenia, fatigue	face oedema, oedema <sup>c</sup> , chills, body temperature increased, gait abnormal, thirst, chest pain, chest discomfort, malaise	hypothermia <sup>c</sup> , body temperature decreased <sup>c</sup> , drug withdrawal syndrome <sup>c</sup> , induration <sup>c</sup>	
<b>Injury, poisoning and procedural complications</b>			fall		

<sup>a</sup> Refer to 'Hyperprolactinaemia' below.

<sup>b</sup> Refer to 'Extrapyramidal symptoms' below.

<sup>c</sup> Not observed in INVEGA clinical studies but observed in post-marketing environment with paliperidone.

<sup>d</sup> In placebo-controlled pivotal trials, diabetes mellitus was reported in 0.05% in INVEGA-treated subjects compared to a rate of 0% in placebo group. Overall incidence from all clinical trials was 0.14% in all INVEGA-treated subjects.

<sup>e</sup> **Insomnia includes:** initial insomnia, middle insomnia; **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema; **Menstrual disorder includes:** menstruation irregular, oligomenorrhoea.

#### Undesirable effects noted with risperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reactions have been noted with the use of risperidone products and can be expected to occur with INVEGA.

**Psychiatric disorders:** sleep-related eating disorder

**Nervous system disorders:** cerebrovascular disorder

**Eye disorders:** floppy iris syndrome (intraoperative)

**Respiratory, thoracic and mediastinal disorders:** rales

**Skin and subcutaneous tissue disorders:** Stevens-Johnson syndrome/toxic epidermal necrolysis

### Description of selected adverse reactions

#### *Extrapyramidal symptoms (EPS)*

In schizophrenia clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of INVEGA. Dose dependence for EPS was seen with the two higher doses of INVEGA (9 and 12 mg). In the schizoaffective disorder studies, the incidence of EPS was observed at a higher rate than placebo in all dose groups without a clear relationship to dose.

EPS included a pooled analysis of the following terms: Parkinsonism (includes salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), akathisia (includes akathisia, restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor. It should be noted that a broader spectrum of symptoms are included that do not necessarily have an extrapyramidal origin.

#### *Weight gain*

In schizophrenia clinical trials, the proportions of subjects meeting a weight gain criterion of  $\geq 7\%$  of body weight were compared, revealing a similar incidence of weight gain for INVEGA 3 mg and 6 mg compared with placebo, and a higher incidence of weight gain for INVEGA 9 mg and 12 mg compared with placebo.

In schizoaffective disorder clinical trials, 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 two dose groups (see section 5.1), the increase in body weight of  $\geq 7\%$  was 3% in the lower-dose (3-6 mg) group, 7% in the higher-dose (9-12 mg) group, and 1% in the placebo group.

#### *Hyperprolactinaemia*

In schizophrenia clinical trials, increases in serum prolactin were observed with INVEGA in 67% of subjects. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 2% of subjects. Maximum mean increases of serum prolactin concentrations were generally observed on day 15 of treatment, but remained above baseline levels at study endpoint.

### Class effects

QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics. Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs - Frequency unknown.

Paliperidone is the active metabolite of risperidone. The safety profile of risperidone may be pertinent.

### Elderly

In a study conducted in elderly subjects with schizophrenia, the safety profile was similar to that seen in non-elderly subjects. INVEGA has not been studied in elderly patients with dementia. In clinical trials with some other atypical antipsychotics, increased risks of death and cerebrovascular accidents have been reported (see section 4.4).

### Paediatric population

#### *Summary of the safety profile*

In one short-term and two longer-term studies with paliperidone prolonged-release tablets conducted in adolescents 12 years and older with schizophrenia, the overall safety profile was similar to that seen in adults. In the pooled adolescent schizophrenia population (12 years and older, N = 545) exposed to INVEGA, the frequency and type of undesirable effects were similar to those in adults except for the

following ADRs that were reported more frequently in adolescents receiving INVEGA than adults receiving INVEGA (and more frequently than placebo): sedation/somnolence, parkinsonism, weight increase, upper respiratory tract infection, akathisia, and tremor were reported very commonly ( $\geq 1/10$ ) in adolescents; abdominal pain, galactorrhoea, gynaecomastia, acne, dysarthria, gastroenteritis, epistaxis, ear infection, blood triglyceride increased, and vertigo were reported commonly ( $\geq 1/100$ ,  $< 1/10$ ) in adolescents.

#### *Extrapyramidal Symptoms (EPS)*

In the short-term, placebo-controlled, fixed-dose adolescent study, the incidence of EPS was higher than placebo for all doses of INVEGA with an increased frequency of EPS at higher doses. Across all adolescent studies, EPS was more common in adolescents than in adults for each INVEGA dose.

#### *Weight gain*

In the short-term, placebo-controlled, fixed-dose adolescent study, a higher percentage of INVEGA-treated subjects (6-19% depending on dose) had an increase in body weight of  $\geq 7\%$  compared to placebo-treated subjects (2%). There was no clear dose relationship. In the long-term 2-year study, the subjects who were exposed to INVEGA during both the double-blind and open-label studies reported a modest weight gain (4.9 kg).

In adolescents, weight gain should be assessed against that expected with normal growth.

#### *Prolactin*

In the up to 2-year, open-label treatment study of INVEGA in adolescents with schizophrenia, incidence of elevated serum prolactin levels occurred in 48% of females and 60% of males. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 9.3% of subjects.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## **4.9 Overdose**

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in association with overdose. In the case of acute overdosage, the possibility of multiple medicinal product involvement should be considered.

Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. Administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

*Pharmacologic group:* Psycholeptics, other antipsychotics, ATC code: N05AX13

INVEGA contains a racemic mixture of (+)- and (-)-paliperidone.

### Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT<sub>2</sub>- and dopaminergic D<sub>2</sub>-receptors. Paliperidone also blocks  $\alpha$ <sub>1</sub>-adrenergic receptors and blocks, to a lesser extent, H<sub>1</sub>-histaminergic and  $\alpha$ <sub>2</sub>-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D<sub>2</sub>-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions to a lesser extent than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

### Clinical efficacy

#### *Schizophrenia*

The efficacy of INVEGA in the treatment of schizophrenia was established in three multi-centre, placebo-controlled, double-blind, 6-week trials in subjects who met DSM-IV criteria for schizophrenia. INVEGA doses, which varied across the three studies, ranged from 3 to 15 mg once daily. The primary efficacy endpoint was defined as a decrease in total Positive and Negative Syndrome Scale (PANSS) scores as shown in the following table. The PANSS is a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression. All tested doses of INVEGA separated from placebo on day 4 ( $p < 0.05$ ). Predefined secondary endpoints included the Personal and Social Performance (PSP) scale and the Clinical Global Impression – Severity (CGI-S) scale. In all three studies, INVEGA was superior to placebo on PSP and CGI-S. Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score  $\geq 30\%$ ) as a secondary endpoint.

Schizophrenia Studies: 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	INVEGA 6 mg	INVEGA 9 mg	INVEGA 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)
<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)
<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)	

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.

Schizophrenia Studies: Proportion of Subjects with Responder Status at LOCF End Point Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set					
	Placebo	INVEGA 3 mg	INVEGA 6 mg	INVEGA 9 mg	INVEGA 12 mg
<b>R076477-SCH-303</b>					
N	126		123	122	129
Responder, n (%)	38 (30.2)		69 (56.1)	62 (50.8)	79 (61.2)
Non-responder, n (%)	88 (69.8)		54 (43.9)	60 (49.2)	50 (38.8)
P value (vs Placebo)	--		< 0.001	0.001	< 0.001
<b>R076477-SCH-304</b>					
N	105		110		111
Responder, n (%)	36 (34.3)		55 (50.0)		57 (51.4)
Non-responder, n (%)	69 (65.7)		55 (50.0)		54 (48.6)
P value (vs Placebo)	--		0.025		0.012
<b>R076477-SCH-305</b>					
N	120	123		123	
Responder, n (%)	22 (18.3)	49 (39.8)		56 (45.5)	
Non-responder, n (%)	98 (81.7)	74 (60.2)		67 (54.5)	
P value (vs Placebo)	--	0.001		< 0.001	

In a long-term trial designed to assess the maintenance of effect, INVEGA was significantly more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode for 6 weeks and stabilised for an additional 8 weeks with INVEGA (doses ranging from 3 to 15 mg once daily) patients were then randomised in a double-blind manner to either continue on INVEGA or on placebo until they experienced a relapse in schizophrenia symptoms. The trial was stopped early for efficacy reasons by showing a significantly longer time to relapse in patients treated with INVEGA compared to placebo (p=0.0053).

#### *Schizoaffective disorder*

The efficacy of INVEGA in the acute treatment of psychotic or manic symptoms of schizoaffective disorder was established in two placebo-controlled, 6-week trials in non-elderly 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 (YMRS) and/or Hamilton Rating Scale 21 for Depression (HAM-D 21). The population included subjects with schizoaffective bipolar and depressive types. In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of INVEGA (3-12 mg once daily). In the other study, efficacy was assessed in 203 subjects who were assigned to one of two dose levels of INVEGA: 6 mg with the option to reduce to 3 mg (n = 105) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. Both studies included subjects who received INVEGA either as monotherapy or in combination with mood stabilisers and/or antidepressants. Dosing was in the morning without regard to meals. Efficacy was evaluated using the PANSS.

The INVEGA group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS at 6 weeks. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), INVEGA was not significantly different from placebo as measured by the PANSS. Only few subjects received the 3 mg dose in both studies and efficacy of this dose could not be established. Statistically superior improvements in manic symptoms as measured by YMRS (secondary efficacy scale) were observed in patients from the flexible-dose study and the INVEGA higher dose in the second study.

Taking the results of both studies together (pooled study-data), INVEGA improved the psychotic and manic symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or in combination with mood stabilisers and/or antidepressants. However, overall the magnitude of effect in regard to PANSS and YMRS observed on monotherapy was larger than that observed with concomitant antidepressants and/or mood stabilisers. Moreover, in the pooled population, INVEGA was not efficacious in patients concomitantly receiving mood stabiliser and antidepressants in regard to the psychotic symptoms, but this population was small (30 responders in

the paliperidone group and 20 responders in the placebo group). Additionally, in study SCA-3001 in the ITT population the effect on psychotic symptoms measured by PANSS was clearly less pronounced and not reaching statistical significance for patients receiving concomitantly mood stabilisers and/or antidepressants. An effect of INVEGA on depressive symptoms was not demonstrated in these studies, but has been demonstrated in a long-term study with the long-acting injectable formulation of paliperidone (described further down in this section).

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. Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score  $\geq$  30% and CGI-C Score  $\leq$  2) as a secondary endpoint.

Schizoaffective Disorder Studies: Primary Efficacy Parameter, PANSS Total Score Change from Baseline from Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set				
	Placebo	INVEGA Lower Dose (3-6 mg)	INVEGA Higher Dose (9-12 mg)	INVEGA Flexible Dose (3-12 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)	
<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 (20.23)
P-value (vs. Placebo)				< 0.001
Diff. of LS Means (SE)				-13.5 (2.63)

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

Schizoaffective Disorder Studies: Secondary Efficacy Parameter, Proportion of Subjects with Responder Status at LOCF End Point: Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set				
	Placebo	INVEGA Lower Dose (3-6 mg)	INVEGA Higher Dose (9-12 mg)	INVEGA Flexible Dose (3-12 mg)
<b>R076477-SCA-3001</b>				
N	107	104	98	
Responder, n (%)	43 (40.2)	59 (56.7)	61 (62.2)	
Non-responder, n (%)	64 (59.8)	45 (43.3)	37 (37.8)	
P value (vs Placebo)	--	0.008	0.001	
<b>R076477-SCA-3002</b>				
N	93			210
Responder, n (%)	26 (28.0)			85 (40.5)
Non-responder, n (%)	67 (72.0)			125 (59.5)
P value (vs Placebo)	--			0.046

Response defined as decrease from baseline in PANSS Total Score  $\geq$  30% and CGI-C Score  $\leq$  2

In a long-term trial designed to assess the maintenance of effect, the long-acting injectable formulation of paliperidone was significantly more effective than placebo in maintaining symptom control and delaying relapse of psychotic, manic, and depressive symptoms of schizoaffective disorder. After having been successfully treated for an acute psychotic or mood episode for 13 weeks and stabilised for an additional 12 weeks with the long-acting injectable formulation of paliperidone (doses ranging from 50 to 150 mg) patients were then randomised to a 15-month double-blind relapse prevention period of the study to either continue on the long-acting injectable formulation of paliperidone or on placebo until they experienced a relapse of schizoaffective symptoms. The study showed a significantly longer time to relapse in patients treated with the long-acting injectable formulation of paliperidone compared to placebo ( $p < 0.001$ ).



### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with INVEGA in all subsets of the paediatric population in the treatment of schizoaffective disorders. (See section 4.2 for information on paediatric use).

### **The efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established.**

The efficacy of INVEGA in adolescent subjects with schizophrenia (INVEGA N = 149, placebo N = 51) was studied in a randomised, double-blind, placebo-controlled, 6-week study using a fixed-dose weight-based treatment group design over the dose range of 1.5 mg/day to 12 mg/day. Subjects were 12-17 years of age and met DSM-IV criteria for schizophrenia. Efficacy was evaluated using PANSS. This study demonstrated the efficacy of INVEGA of the medium dose group in adolescent subjects with schizophrenia. Secondary by dose analysis demonstrated the efficacy of 3 mg, 6 mg, and 12 mg dose given once daily.

Adolescent Schizophrenia Study: R076477-PSZ-3001: 6-week, fixed-dose, placebo-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline				
	Placebo N=51	INVEGA Low Dose 1.5 mg N=54	INVEGA Medium Dose 3 or 6 mg* N=48	INVEGA High Dose 6 or 12 mg** N=47
<b>Change in PANSS Score</b>				
Mean baseline (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Mean change (SD)	-7.9 (20.15)	-9.8 (16.31)	-17.3 (14.33)	-13.8 (15.74)
P-value (vs Placebo)		0.508	0.006	0.086
Diff. of LS Means (SE)		-2.1 (3.17)	-10.1 (3.27)	-6.6 (3.29)
<b>Responder Analysis</b>				
Responder, n (%)	17 (33.3)	21 (38.9)	31 (64.6)	24 (51.1)
Non-responder, n (%)	34 (66.7)	33 (61.1)	17 (35.4)	23 (48.9)
P value (vs Placebo)		0.479	0.001	0.043

Response defined as decrease from baseline in PANSS Total Score  $\geq$  20%

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

\* Medium dose group: 3 mg for subjects < 51 kg, 6 mg for subjects  $\geq$  51 kg

\*\* High dose group: 6 mg for subjects < 51 kg, 12 mg for subjects  $\geq$  51 kg

Efficacy of INVEGA over a flexible dose range of 3 mg/day to 9 mg/day in adolescent subjects (12 years and older) with schizophrenia (INVEGA N = 112, aripiprazole N = 114) was also evaluated in a randomised, double-blind, active-controlled study that included an 8-week, double-blind acute phase and an 18-week, double-blind maintenance phase. The changes in PANSS total scores from baseline to week 8 and week 26 were numerically similar between the INVEGA and aripiprazole treatment groups. In addition, the difference in the percentage of patients demonstrating  $\geq$  20% improvement in PANSS total score at week 26 between the two treatment groups was numerically similar.

Adolescent Schizophrenia Study: R076477-PSZ-3003: 26-week, flexible-dose, active-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline		
	INVEGA 3-9 mg N=112	Aripiprazole 5-15 mg N=114
<b>Change in PANSS Score 8 week, acute endpoint</b>		
Mean baseline (SD)	89.6 (12.22)	92.0 (12.09)
Mean change (SD)	-19.3 (13.80)	-19.8 (14.56)
P-value (vs aripiprazole)	0.935	
Diff. of LS Means (SE)	0.1 (1.83)	

<b>Change in PANSS Score</b>		
<b>26 week endpoint</b>		
Mean baseline (SD)	89.6 (12.22)	92.0 (12.09)
Mean change (SD)	-25.6 (16.88)	-26.8 (18.82)
P-value (vs aripiprazole)	0.877	
Diff. of LS Means (SE)	-0.3 (2.20)	
<b>Responder Analysis</b>		
<b>26 week endpoint</b>		
Responder, n (%)	86 (76.8)	93 (81.6)
Non-responder, n (%)	26 (23.2)	21 (18.4)
P value (vs aripiprazole)	0.444	

Response defined as decrease from baseline in PANSS Total Score  $\geq$  20%

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of paliperidone following INVEGA administration are dose proportional within the available dose range.

### Absorption

Following a single dose, INVEGA exhibits a gradual ascending release rate, allowing the plasma concentrations of paliperidone to steadily rise to reach peak plasma concentration ( $C_{max}$ ) approximately 24 hours after dosing. With once-daily dosing of INVEGA, steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

Paliperidone is the active metabolite of risperidone. The release characteristics of INVEGA result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone (fluctuation index 38% versus 125%).

The absolute oral bioavailability of paliperidone following INVEGA administration is 28% (90% CI of 23%-33%).

Administration of paliperidone prolonged-release tablets with a standard high-fat/high-caloric meal increases  $C_{max}$  and AUC of paliperidone by up to 50-60% compared with administration in the fasting state.

### Distribution

Paliperidone is rapidly distributed. The apparent volume of distribution is 487 L. The plasma protein binding of paliperidone is 74%. It binds primarily to  $\alpha$ 1-acid glycoprotein and albumin.

### Biotransformation and elimination

One week following administration of a single oral dose of 1 mg immediate-release  $^{14}C$ -paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised by the liver. 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. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of INVEGA between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. The terminal elimination half-life of paliperidone is about 23 hours.

*In vitro* studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

### Hepatic impairment

Paliperidone is not extensively metabolised in the liver. 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. No data are available in patients with severe hepatic impairment (Child-Pugh class C).

### Renal impairment

Elimination of paliperidone decreased with decreasing renal function. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (Creatinine Clearance [CrCl] = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = < 30 mL/min) renal impairment. 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 ≥ 80 mL/min).

### Elderly

Data from a pharmacokinetic study in elderly subjects (≥ 65 years of age, n = 26) indicated that the apparent steady-state clearance of paliperidone following INVEGA 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.

### Adolescents

Paliperidone systemic exposure in adolescent subjects (15 years and older) was comparable to that in adults. In adolescents weighing < 51 kg, a 23% higher exposure was observed than in adolescents weighing ≥ 51 kg. Age alone did not influence the paliperidone exposure.

### Race

Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA administration.

### Gender

The apparent clearance of paliperidone following INVEGA 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.

### 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.

## **5.3 Preclinical safety data**

Repeat-dose toxicity studies of paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. Paliperidone was not teratogenic in rat and rabbit. In rat reproduction studies using risperidone, which is extensively converted to paliperidone in rats and humans, a reduction was observed in the birth weight and survival of the offspring. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. Paliperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

In a 7-week juvenile toxicity study in rats administered oral doses of paliperidone up to 2.5 mg/kg/day, corresponding to an exposure approximately equal to the clinical exposure based on AUC, no effects

on growth, sexual maturation and reproductive performance were observed. Paliperidone did not impair the neurobehavioural development in males at doses up to 2.5 mg/kg/day. At 2.5 mg/kg/day in females, an effect on learning and memory was observed. This effect was not observed after discontinuation of treatment. In a 40-week juvenile toxicity study in dogs with oral doses of risperidone (which is extensively converted to paliperidone) up to 5 mg/kg/day, effects on sexual maturation, long bone growth and femur mineral density were observed from 3 times the clinical exposure based on AUC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **3 mg**

##### *Core*

Polyethylene oxide 200K  
Sodium chloride  
Povidone (K29-32)  
Stearic acid  
Butyl hydroxytoluene (E321)  
Ferric oxide (yellow) (E172)  
Polyethylene oxide 7000K  
Ferric oxide (red) (E172)  
Hydroxyethyl cellulose  
Polyethylene glycol 3350  
Cellulose acetate

##### *Overcoat*

Hypromellose  
Titanium dioxide (E171)  
Lactose monohydrate  
Triacetin  
Carnauba wax

##### *Printing ink*

Iron oxide (black) (E172)  
Propylene glycol  
Hypromellose

#### **6 mg**

##### *Core*

Polyethylene oxide 200K  
Sodium chloride  
Povidone (K29-32)  
Stearic acid  
Butyl hydroxytoluene (E321)  
Polyethylene oxide 7000K  
Ferric oxide (red) (E172)  
Hydroxyethyl cellulose  
Polyethylene glycol 3350  
Cellulose acetate

##### *Overcoat*

Hypromellose  
Titanium dioxide (E171)  
Polyethylene glycol 400  
Ferric oxide (yellow) (E172)

Ferric oxide (red) (E172)  
Carnauba wax

*Printing ink*

Iron oxide (black) (E172)  
Propylene glycol  
Hypromellose

**9 mg**

*Core*

Polyethylene oxide 200K  
Sodium chloride  
Povidone (K29-32)  
Stearic acid  
Butyl hydroxytoluene (E321)  
Polyethylene oxide 7000K  
Ferric oxide (red) (E172)  
Iron oxide (black) (E172)  
Hydroxyethyl cellulose  
Polyethylene glycol 3350  
Cellulose acetate

*Overcoat*

Hypromellose  
Titanium dioxide (E171)  
Polyethylene glycol 400  
Ferric oxide (red) (E172)  
Carnauba wax

*Printing ink*

Iron oxide (black) (E172)  
Propylene glycol  
Hypromellose

**12 mg**

*Core*

Polyethylene oxide 200K  
Sodium chloride  
Povidone (K29-32)  
Stearic acid  
Butyl hydroxytoluene (E321)  
Polyethylene oxide 7000K  
Ferric oxide (red) (E172)  
Ferric oxide (yellow) (E172)  
Hydroxyethyl cellulose  
Polyethylene glycol 3350  
Cellulose acetate

*Overcoat*

Hypromellose  
Titanium dioxide (E171)  
Polyethylene glycol 400  
Ferric oxide (yellow) (E172)  
Carnauba wax

*Printing ink*

Iron oxide (black) (E172)

Propylene glycol  
Hypromellose

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years

## **6.4 Special precautions for storage**

Bottles: Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.  
Blisters: Do not store above 30°C. Store in the original package in order to protect from moisture.

## **6.5 Nature and contents of container**

Bottles:

White high-density polyethylene (HDPE) bottle with induction sealing and polypropylene child-resistant closure. Each bottle contains two 1 g dessicant silica gel (silicone dioxide) pouches (pouch is food approved polyethylene).

Pack sizes of 30 and 350 prolonged-release tablets.

Blisters:

Oriented polyamide (OPA)-aluminium-polyvinyl chloride (PVC)/aluminium push-through child-resistant blister.

Pack sizes of 14, 28, 49, 56, and 98 prolonged-release tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7. MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

## **8. MARKETING AUTHORISATION NUMBER(S)**

### **3 mg**

EU/1/07/395/041 - 044

EU/1/07/395/057 - 058

EU/1/07/395/067

### **6 mg**

EU/1/07/395/045 - 048

EU/1/07/395/059 - 060

EU/1/07/395/070

**9 mg**

EU/1/07/395/049 - 052

EU/1/07/395/061 - 062

EU/1/07/395/073

**12 mg**

EU/1/07/395/053 - 056

EU/1/07/395/063 - 064

EU/1/07/395/076

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 June 2007

Date of latest renewal: 14 May 2012

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**



#### **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA  
Via C. Janssen  
IT-04100 Borgo San Michele  
Latina  
Italy

#### **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

#### **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

#### **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR OPA-ALUMINIUM-PVC/ALUMINIUM BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

INVEGA 3 mg prolonged-release tablets  
INVEGA 6 mg prolonged-release tablets  
INVEGA 9 mg prolonged-release tablets  
INVEGA 12 mg prolonged-release tablets

paliperidone

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each prolonged-release tablet contains 3 mg paliperidone  
Each prolonged-release tablet contains 6 mg paliperidone  
Each prolonged-release tablet contains 9 mg paliperidone  
Each prolonged-release tablet contains 12 mg paliperidone

**3. LIST OF EXCIPIENTS**

3 mg tablets

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 prolonged-release tablets  
28 prolonged-release tablets  
49 prolonged-release tablets  
56 prolonged-release tablets  
98 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use  
Swallow whole, do not chew, divide or crush.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

3 mg

14 prolonged-release tablets - EU/1/07/395/067

28 prolonged-release tablets - EU/1/07/395/041

49 prolonged-release tablets - EU/1/07/395/042

56 prolonged-release tablets - EU/1/07/395/043

98 prolonged-release tablets - EU/1/07/395/044

6 mg

14 prolonged-release tablets - EU/1/07/395/070

28 prolonged-release tablets - EU/1/07/395/045

49 prolonged-release tablets - EU/1/07/395/046

56 prolonged-release tablets - EU/1/07/395/047

98 prolonged-release tablets - EU/1/07/395/048

9 mg

14 prolonged-release tablets - EU/1/07/395/073

28 prolonged-release tablets - EU/1/07/395/049

49 prolonged-release tablets - EU/1/07/395/050

56 prolonged-release tablets - EU/1/07/395/051

98 prolonged-release tablets - EU/1/07/395/052

12 mg

14 prolonged-release tablets - EU/1/07/395/076

28 prolonged-release tablets - EU/1/07/395/053

49 prolonged-release tablets - EU/1/07/395/054

56 prolonged-release tablets - EU/1/07/395/055

98 prolonged-release tablets - EU/1/07/395/056

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

invega 3 mg  
invega 6 mg  
invega 9 mg  
invega 12 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**7 TABLET OPA-ALU-PVC/ALU BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

INVEGA 3 mg prolonged-release tablets  
INVEGA 6 mg prolonged-release tablets  
INVEGA 9 mg prolonged-release tablets  
INVEGA 12 mg prolonged-release tablets

paliperidone

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV

**3. EXPIRY DATE**

EXP MM/YYYY

**4. BATCH NUMBER**

Lot

**5. OTHER**

Mon, Tue, Wed, Thu, Fri, Sat, Sun

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**BOTTLE CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

INVEGA 3 mg prolonged-release tablets  
INVEGA 6 mg prolonged-release tablets  
INVEGA 9 mg prolonged-release tablets  
INVEGA 12 mg prolonged-release tablets

paliperidone

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each prolonged-release tablet contains 3 mg paliperidone  
Each prolonged-release tablet contains 6 mg paliperidone  
Each prolonged-release tablet contains 9 mg paliperidone  
Each prolonged-release tablet contains 12 mg paliperidone

**3. LIST OF EXCIPIENTS**

3 mg tablets

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 prolonged-release tablets  
350 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use  
Swallow whole, do not chew, divide or crush.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}



**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C

Keep the bottle tightly closed in order to protect from moisture

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

3 mg

30 prolonged-release tablets - EU/1/07/395/057

350 prolonged-release tablets - EU/1/07/395/058

6 mg

30 prolonged-release tablets - EU/1/07/395/059

350 prolonged-release tablets - EU/1/07/395/060

9 mg

30 prolonged-release tablets - EU/1/07/395/061

350 prolonged-release tablets - EU/1/07/395/062

12 mg

30 prolonged-release tablets - EU/1/07/395/063

350 prolonged-release tablets - EU/1/07/395/064

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

<b>16. INFORMATION IN BRAILLE</b>
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invega 3 mg  
invega 6 mg  
invega 9 mg  
invega 12 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****BOTTLE****1. NAME OF THE MEDICINAL PRODUCT**

INVEGA 3 mg prolonged-release tablets  
INVEGA 6 mg prolonged-release tablets  
INVEGA 9 mg prolonged-release tablets  
INVEGA 12 mg prolonged-release tablets

paliperidone

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each prolonged-release tablet contains 3 mg paliperidone  
Each prolonged-release tablet contains 6 mg paliperidone  
Each prolonged-release tablet contains 9 mg paliperidone  
Each prolonged-release tablet contains 12 mg paliperidone

**3. LIST OF EXCIPIENTS**

3 mg tablets

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENT**

30 prolonged-release tablets  
350 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

Swallow whole, do not chew, divide or crush.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C

Keep the bottle tightly closed in order to protect from moisture

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

3 mg

30 prolonged-release tablets - EU/1/07/395/057

350 prolonged-release tablets - EU/1/07/395/058

6 mg

30 prolonged-release tablets - EU/1/07/395/059

350 prolonged-release tablets - EU/1/07/395/060

9 mg

30 prolonged-release tablets - EU/1/07/395/061

350 prolonged-release tablets - EU/1/07/395/062

12 mg

30 prolonged-release tablets - EU/1/07/395/063

350 prolonged-release tablets - EU/1/07/395/064

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

**B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

**INVEGA 3 mg prolonged-release tablets**  
**INVEGA 6 mg prolonged-release tablets**  
**INVEGA 9 mg prolonged-release tablets**  
**INVEGA 12 mg prolonged-release tablets**  
Paliperidone

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet:**

1. What INVEGA is and what it is used for
2. What you need to know before you take INVEGA
3. How to take INVEGA
4. Possible side effects
5. How to store INVEGA
6. Contents of the pack and other information

## **1. What INVEGA is and what it is used for**

INVEGA contains the active substance paliperidone which belongs to the class of antipsychotic medicines.

INVEGA is used to treat schizophrenia in adults and in adolescents aged 15 years and older.

Schizophrenia is a disorder with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech, and behaviour and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense.

INVEGA is also used to treat schizoaffective disorder in adults.

Schizoaffective disorder is a mental condition in which a person experiences a combination of schizophrenia symptoms (as listed above) in addition to mood disorder symptoms (feeling very high, feeling sad, feeling agitated, distracted, sleeplessness, talkativeness, losing interest in everyday activities, sleeping too much or too little, eating too much or too little, and recurrent thoughts of suicide).

INVEGA can help alleviate the symptoms of your disease and stop your symptoms from coming back.

## **2. What you need to know before you take INVEGA**

### **Do not take INVEGA**

- if you are allergic to paliperidone, risperidone, or any of the other ingredients of this medicine (listed in section 6).

### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before taking INVEGA.

- Patients with schizoaffective disorder treated with this medicine should be carefully monitored for a potential switch from manic to depressive symptoms.
- This medicine has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death. (see section 4, possible side effects).
- if you have Parkinson's disease or Dementia.
- if you have ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome).
- if you have ever experienced abnormal movements of the tongue or face (Tardive Dyskinesia). You should be aware that both of these conditions may be caused by this type of medicine.
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- if you are diabetic or prone to diabetes.
- if you have heart disease or heart disease treatment that makes you prone to low blood pressure.
- if you have epilepsy.
- if you have a swallowing, stomach or intestinal disorder that reduces your ability to swallow or pass foods by normal bowel movements.
- if you have diseases associated with diarrhoea.
- if you have kidney problems.
- if you have liver problems.
- if you have prolonged and/or painful erection.
- if you have difficulty controlling core body temperature or overheating.
- if you have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour.
- if you or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose or monitor you for a while.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking INVEGA, your doctor may check your white blood cell counts.

INVEGA may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking INVEGA, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

### **Children and adolescents**

INVEGA is not for use in children and adolescents under 15 years for the treatment of schizophrenia.

INVEGA is not for use in children and adolescents who are under 18 years for the treatment of schizoaffective disorder.

This is because it is not known if INVEGA is safe or effective in these age groups.

### **Other medicines and INVEGA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.



Abnormalities of electrical function in the heart may occur when this medicine is taken with certain heart medicines that control heart rhythm, or some other types of medicines such as antihistamines, antimalarials, or other antipsychotics.

Since this medicine works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to additive effect on brain function.

Since this medicine can lower blood pressure, care should be taken when this medicine is taken with other medicines that lower blood pressure.

This medicine can reduce the effect of medicines against Parkinson's disease and restless legs syndrome (e.g., levodopa).

The effects of this medicine may be affected if you are taking medicines that affect the speed of movement in the gut (e.g., metoclopramide).

Dosage reduction for this medicine should be considered when this medicine is co-administered with valproate.

The use of oral risperidone together with this medicine is not recommended as the combination of the two medicines may lead to increased side effects.

INVEGA should be used with caution with medicines that increase the activity of the central nervous system (psychostimulants such as methylphenidate).

#### **INVEGA with alcohol**

Alcohol should be avoided when taking this medicine.

#### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take this medicine during pregnancy unless this has been discussed with your doctor. The following symptoms may occur in newborn babies of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

You should not breastfeed when taking this medicine.

#### **Driving and using machines**

Dizziness and vision problems may occur during treatment with this medicine (see section 4, possible side effects). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

#### **The 3 mg tablet of INVEGA contains lactose**

The 3 mg tablet of this medicine contains lactose, a type of sugar. If you have been told by a doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

#### **INVEGA contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

### **3. How to take INVEGA**

Take this medicine exactly as the doctor, pharmacist or nurse has told you to.

**Use in adults**

The recommended dose in adults is 6 mg once a day taken in the morning. The dose may be increased or decreased by your doctor within the dose range of 3 mg to 12 mg once a day for schizophrenia or 6 mg to 12 mg once a day for schizoaffective disorder. This depends on how well the medicine works for you.

**Use in adolescents**

The recommended starting dose for treating schizophrenia in adolescents 15 years and older is 3 mg once a day taken in the morning.

For adolescents weighing 51 kg or more the dose may be increased within the range of 6 mg to 12 mg once a day.

For adolescents weighing less than 51 kg the dose may be increased to 6 mg once a day.

Your doctor will decide how much to give you. The amount you take depends on how well the medicine works for you.

**How and when to take INVEGA**

This medicine must be taken by mouth, swallowed whole with water or other liquids. It must not be chewed, broken, or crushed.

This medicine should be taken every morning with breakfast or without breakfast, but in the same way every day. Do not alternate between taking this medicine with breakfast one day and without having breakfast the next day.

The active ingredient, paliperidone, dissolves once swallowed and the tablet shell is passed out of the body as waste.

**Patients with kidney problems**

Your doctor may adjust your dose of this medicine based upon your kidney function.

**Elderly**

Your doctor may reduce your dose of medicine if your kidney function is reduced.

**If you take more INVEGA than you should**

Contact your doctor right away. You may experience sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats.

**If you forget to take INVEGA**

Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose on the day following the missed dose. If you miss two or more doses, contact your doctor.

**If you stop INVEGA**

Do not stop taking this medicine since you will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor immediately if you:**

- experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately.
- have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.
- experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called “Neuroleptic Malignant Syndrome”). Immediate medical treatment may be needed.
- are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed.
- experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed.
- experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an ‘anaphylactic reaction’).

**Very common: may affect more than 1 in 10 people**

- difficulty falling or staying asleep
- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- restlessness
- feeling sleepy or less alert
- headache.

**Common side effects: may affect up to 1 in 10 people**

- infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, feeling like you have the flu
- weight gain, increased appetite, weight loss, decreased appetite
- elated mood (mania), irritability, depression, anxiety
- dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw.
- dizziness
- dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching.
- tremor (shaking)
- blurry vision
- an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, rapid heart rate
- low blood pressure upon standing (consequently, some people taking INVEGA may feel faint, dizzy, or may pass out when they stand up or sit up suddenly), high blood pressure
- sore throat, cough, stuffy nose
- abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, indigestion, dry mouth, toothache
- increased liver transaminases in your blood
- itching, rash
- bone or muscle ache, back pain, joint pain
- loss of menstrual periods
- fever, weakness, fatigue (tiredness).

**Uncommon side effects: may affect up to 1 in 100 people**

- pneumonia, infection of the breathing passages, bladder infection, ear infection, tonsillitis
- white blood cell count decreased, decrease in platelets (blood cells that help you stop bleeding), anaemia, decrease in red blood cells
- INVEGA can raise your levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include: (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction, (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle.
- diabetes or worsening diabetes, high blood sugar, increased waist size, loss of appetite resulting in malnutrition and low body weight, high blood triglycerides (a fat)
- sleep disorder, confusion, decreased sexual drive, inability to reach orgasm, nervousness, nightmares
- tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of INVEGA may be needed.
- convulsion (fits), fainting, a restless urge to move parts of your body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin
- oversensitivity of the eyes to light, eye infection or "pink eye", dry eye
- a sensation of spinning (vertigo), ringing in the ears, ear pain
- irregular heartbeat, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)
- low blood pressure
- shortness of breath, wheezing, nosebleeds
- swollen tongue, stomach or intestinal infection, difficulty swallowing, excessive passing of gas or wind
- increased GGT (a liver enzyme called gamma-glutamyltransferase) in your blood, increased liver enzymes in your blood
- hives (or "nettle rash"), hair loss, eczema, acne
- an increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown, muscle spasms, joint stiffness, joint swelling, muscle weakness, neck pain
- incontinence (lack of control) of urine, frequent passing of urine, inability to pass urine, pain when passing urine
- erectile dysfunction, ejaculation disorder
- missed menstrual periods or other problems with your cycle (females), leakage of milk from the breasts, sexual dysfunction, breast pain, breast discomfort
- swelling of the face, mouth, eyes, or lips, swelling of the body, arms or legs
- chills, an increase in body temperature
- a change in the way you walk
- feeling thirsty
- chest pain, chest discomfort, feeling unwell
- fall.

**Rare side effects: may affect up to 1 in 1,000 people**

- eye infection, fungal infection of the nails, infection of the skin, skin inflammation caused by mites
- dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood
- decrease in the type of white blood cells that help to protect you against infection, increase in eosinophils (a type of white blood cell) in your blood
- severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure, allergic reaction
- sugar in the urine

- inappropriate secretion of a hormone that controls urine volume
- life-threatening complications of uncontrolled diabetes
- dangerously excessive intake of water, low blood sugar, excessive drinking of water, increased cholesterol in your blood
- sleep walking
- not moving or responding while awake (catatonia)
- lack of emotion
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness)
- loss of consciousness, balance disorder, abnormal coordination
- blood vessel problems in the brain, coma due to uncontrolled diabetes, unresponsive to stimuli, low level of consciousness, shaking of the head
- glaucoma (increased pressure within the eyeball), increased tears, redness of the eyes, problems with movement of your eyes, eye rolling
- atrial fibrillation (an abnormal heart rhythm), rapid heartbeat upon standing
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately
- decreased oxygen in parts of your body (because of decreased blood flow), flushing
- trouble breathing during sleep (sleep apnea), fast, shallow breathing
- pneumonia caused by inhaling food, congestion of breathing passages, voice disorder
- a blockage in the bowels, stool incontinence, very hard stool, lack of bowel muscle movement that causes blockage
- yellowing of the skin and the eyes (jaundice)
- inflammation of the pancreas
- serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing
- thickening of the skin, dry skin, skin redness, skin discolouration, flaky itchy scalp or skin, dandruff
- breakdown of muscle fibers and pain in muscles (rhabdomyolysis), abnormal posture
- priapism (a prolonged penile erection that may require surgical treatment)
- development of breasts in men, enlargement of the glands in your breasts, discharge from the breasts, vaginal discharge
- a delay in menstrual periods, breast enlargement
- very low body temperature, a decrease in body temperature
- symptoms of drug withdrawal.

**Not known: frequency cannot be estimated from the available data**

- lung congestion
- increased insulin (a hormone that controls blood sugar levels) in your blood.

The following side effects have been seen with the use of another medicine called risperidone that is very similar to paliperidone, so these can also be expected with INVEGA: sleep-related eating disorder, other types of blood vessel problems in the brain, crackly lung sounds, and severe or life-threatening rash with blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body (Stevens-Johnson syndrome/toxic epidermal necrolysis). Eye problems during cataract surgery may also occur. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken INVEGA. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken this medicine.

**Additional side effects in adolescents**

Adolescents generally experienced side effects that were similar to those seen in adults except the following side effects were seen more commonly:

- feeling sleepy or less alert

- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- weight gain
- common cold symptoms
- restlessness
- tremor (shaking)
- stomach pain
- leaking milk from the breasts in girls
- breast swelling in boys
- acne
- problems with speech
- stomach or intestinal infection
- nose bleeds
- ear infection
- high blood triglycerides (a fat)
- sensation of spinning (vertigo).

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store INVEGA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister/bottle and carton after EXP. The expiry date refers to the last day of that month.

Bottles: Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.

Blisters: Do not store above 30°C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## **6. Contents of the pack and other information**

### **What INVEGA contains**

The active substance is paliperidone

Each INVEGA 3 mg prolonged-release tablet contains 3 mg of paliperidone.

Each INVEGA 6 mg prolonged-release tablet contains 6 mg of paliperidone.

Each INVEGA 9 mg prolonged-release tablet contains 9 mg of paliperidone.

Each INVEGA 12 mg prolonged-release tablet contains 12 mg of paliperidone.

The other ingredients are:

Coated tablet core:

Polyethylene oxide 200K

Sodium chloride

Povidone (K29-32)

Stearic acid

Butyl hydroxytoluene (E321)  
Ferric Oxide (Yellow) (E172) (3, 12 mg tablet only)  
Polyethylene Oxide 7000K  
Ferric Oxide (Red) (E172)  
Hydroxyethyl Cellulose  
Polyethylene glycol 3350  
Cellulose acetate  
Iron oxide (Black) (E172) (9 mg tablet only)

Colour overcoat:

Hypromellose  
Titanium dioxide (E171)  
Polyethylene glycol 400 (6, 9 and 12 mg tablet only)  
Ferric Oxide (Yellow) (E172) (6, 12 mg tablet only)  
Ferric Oxide (Red) (E172) ( 6, 9 mg tablet only)  
Lactose monohydrate (3 mg tablet only)  
Triacetin (3 mg tablet only)  
Carnauba wax

Printing ink:

Iron oxide (Black) (E172)  
Propylene glycol  
Hypromellose

#### **What INVEGA looks like and contents of the pack**

INVEGA prolonged-release tablets are capsule shaped. The 3 mg tablets are white and printed with “PAL 3”, the 6 mg tablets are beige and printed with “PAL 6”, the 9 mg tablets are pink and printed with “PAL 9”, and the 12 mg tablets are dark yellow and printed with “PAL 12”. All tablets are available in the following pack sizes:

- Bottles: The tablets are supplied in a plastic bottle with a child-resistant plastic cap. Each bottle contains either 30 tablets or 350 tablets. Each bottle contains two silica gel pouches which are provided to absorb moisture and keep the tablets dry.
- Blisters: The tablets are supplied in blisters packed in cartons of 14, 28, 49, 56, and 98 tablets.

Not all pack sizes may be marketed.

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<https://www.ema.europa.eu>.