**NAME OF THE MEDICINAL PRODUCT**
INVEGA® 3 mg extended-release tablets
INVEGA® 6 mg extended-release tablets
INVEGA® 9 mg extended-release tablets

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
INVEGA® contains 3 mg, 6 mg or 9 mg of paliperidone.

FOR THE 3 MG TABLETS:
Excipient: Each tablet contains 13.2 mg lactose.

For a full list of excipients, see section List of excipients

**PHARMACEUTICAL FORM**
Extended-release tablet

3 mg: white capsule-shaped tablet imprinted with "PAL 3"
6 mg: beige tablets printed with "PAL 6"
9 mg: pink tablets printed with "PAL 9"

**CLINICAL PARTICULARS**

**Therapeutic indications**

INVEGA® is indicated for the treatment of schizophrenia**.**

INVEGA® is indicated for the acute treatment of schizoaffective disorder as monotherapy and as an adjunct to antidepressants and/or mood stabilizers

**Posology and method of administration**

INVEGA® is for oral administration. INVEGA® must be swallowed whole with the aid of liquids, 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.

*Adults*

Schizophrenia

The recommended dose of INVEGA® is 6 mg once daily, administered in the morning. The administration of INVEGA® should be standardized in relation to food intake (see section on Pharmacokinetic properties). 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. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days.

Schizoaffective Disorder

The recommended dose of INVEGA® for the treatment of schizoaffective disorder 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 dose range of 3 to 12 mg once daily. A general trend for greater effects was seen with higher doses. This trend must be weighed against dose-related increase in adverse reactions. Dosage adjustment, if indicated, should occur only after clinical reassessment. Dose increases, if indicated, generally should occur at intervals of more than 4 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

*Patients with 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.

*Patients with renal impairment*
For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 ml/min), the recommended initial dose of INVEGA® is 3 mg once daily. The dose may be increased to 6mg once daily based on clinical response and tolerability.

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

*Elderly*
Dosing recommendations for elderly patients with normal renal function (≥ 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 Patients with Renal Impairment above). INVEGA® should be used with caution in elderly patients with dementia with risk factors for stroke (see section on Special warnings and special precautions for use).

*Pediatrics*
Safety and effectiveness of INVEGA® in patients < 18 years of age have not been studied. There is no experience in children.

*Other special populations*
No dose adjustment for INVEGA® is recommended based on gender, race, or smoking status. (For pregnant women and breast-feeding mothers, see section on Pregnancy and lactation)

*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.

**Contraindications**

- Hypersensitivity to paliperidone or to any of the excipients.
- Hypersensitivity to risperidone since paliperidone is an active metabolite of risperidone,

**Special Warnings and Special Precautions for Use**

*QT interval*

As with other antipsychotics, 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), characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics, including 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 characterized 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.

*Extrapyramidal symptoms and psychostimulants*
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 one or both treatments should be considered (see section on Interaction with other medicinal products and other forms of interaction).

*Hyperglycemia and Diabetes Mellitus*
Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including INVEGA® should be monitored for symptoms of hyperglycemia and diabetes mellitus. (See section on Undesirable Effects).

*Weight*
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

*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 ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications).

*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 diarrhea, 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 section on Posology and method of administration and on Pharmacokinetic properties). 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.

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

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

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

*Venous Thromboembolism*
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. 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.

*Parkinson's disease and dementia with Lewy bodies*
Physicians should weigh the risks versus the benefits when prescribing antipsychotic medicinal products, including 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*
Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance (see section on Undesirable Effects).

*Body temperature regulation*
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. 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.

*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 overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

*Intraoperative Floppy Iris Syndrome*
Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA® (see section on Undesirable Effects).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

*Lactose content (pertains only to the 3 mg tablets)*
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

*Leukopenia, Neutropenia, and Agranulocytosis*
Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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 <1000/mm$^3$) should discontinue INVEGA® and have their WBC followed until recovery.

**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 metabolized by cytochrome P-450 isozymes.

In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. In vitro studies indicated that paliperidone is not an inducer of CYP1A2, 2C19, or 3A4 activity.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Given the primary CNS effects of paliperidone (see section on Undesirable effects), 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 antagonize 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 on Special warnings and special precautions for use), 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, tricyclics or SSRIs, tramadol, mefloquine, etc.).

Pharmacokinetic interaction between INVEGA® and lithium is unlikely.

Co-administration of INVEGA® at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

*Potential for other medicines to affect INVEGA®*

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. *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-gp substrate.

Paliperidone is metabolized to a limited extent by CYP2D6 (see section on Pharmacokinetic properties: *Biotransformation and Elimination*). In an interaction study in healthy subjects in which INVEGA® was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of INVEGA® once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state Cmax 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 drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. 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.

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

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

Co-administration of a single dose of INVEGA® 12 mg with divalproex sodium extended-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 the emergence of extrapyramidal symptoms upon change of either or both treatments (see section on Special warnings and special precautions for use).

**Pregnancy and lactation**

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

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. Paliperidone, the active metabolite of risperidone, was not specifically evaluated in this study. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95%

CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

Laboratory animals treated with a high dose of paliperidone showed a slight increase in fetal deaths. This high dose was toxic to the mothers. The offspring was not affected at exposures 20 to 34-fold the maximum human exposure.

Other types of reproductive toxicity were seen (see section on Preclinical safety data).

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

INVEGA® should only be used during pregnancy if the benefits outweigh the risks. The effect of INVEGA® on labor and delivery in humans is unknown. If discontinuation during pregnancy is necessary, it should not be done abruptly.

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

**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 on Undesirable effects). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to INVEGA® is known.

**Undesirable effects**

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

*Clinical Trial Data*

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

The safety of INVEGA® was also evaluated in 622 subjects with schizoaffective disorder who participated in two double-blind, placebo-controlled, 6-week trials. In one of these trials, 206 subjects

were assigned to one of two dose levels of INVEGA® 6 mg with the option to reduce to 3 mg (n=108) or 12 mg with the option to reduce to 9 mg (n=98) once daily. In the other study, 214 subjects received flexible doses of INVEGA® (3-12 mg once daily). Both studies included subjects who received INVEGA® either as monotherapy or in combination with antidepressants and/or mood stabilizers.

The information in this section was derived from pooled data.

The majority of adverse reactions were mild to moderate in severity.

*Double-Blind, Placebo-Controlled Data – Schizophrenia*

Adverse drug reactions (ADRs) reported by ≥ 2% of INVEGA® -treated subjects in the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia trials are shown in Table 1.

**Table 1 Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizophrenia in Three 6-Week Double-Blind, Placebo-Controlled, Fixed-Dose Clinical Trials**

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

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

Adverse reactions reported by ≥ 2% of INVEGA®-treated subjects in the two placebo-controlled schizoaffective disorder trials are shown in Table 2.

**Table 2 Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials**

| | Percentage of Patients | |
|---|---|---|
| **System/Organ Class** Adverse Reaction | **INVEGA® 3-12 mg once daily (N=420)*** **%** | **Placebo (N=202)** **%** |
| **Infections and Infestations** | | |
| Nasopharyngitis | 3 | 1 |
| **Metabolism and Nutrition Disorders** | | |
| Increased appetite | 2 | <1 |
| **Nervous System Disorders** | | |
| Tremor | 8 | 3 |
| Akathisia | 5 | 4 |
| Sedation | 5 | 3 |
| Somnolence | 5 | 2 |
| Hypertonia | 5 | 2 |
| Drooling | 2 | 0 |
| Dysarthria | 2 | 0 |
| **Gastrointestinal Disorders** | | |
| Nausea | 6 | 6 |
| Dyspepsia | 5 | 2 |
| Constipation | 4 | 2 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Myalgia | 2 | <1 |
| **Investigations** | | |
| Weight increased | 4 | 1 |

*Among the 420 subjects treated with INVEGA®, 230 (55%) received INVEGA® as monotherapy and 190 (45%) received INVEGA® in combination with antidepressants and/or mood stabilizers.

*Monotherapy versus Combination Therapy*

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

*Dose-Related Adverse Reactions*

*Schizophrenia Trials*

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia,

parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

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

***Other Clinical Trials Data***

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. Hence, a comprehensive listing of adverse reactions across paliperidone and risperidone products provides relevant safety information for these related products. Adverse reactions detected for one formulation of risperidone or paliperidone were considered as relevant safety information for the other formulation of the same compound unless the adverse reactions were unique to either the formulation or the route of administration. Adverse reactions for one compound that were not listed for the other compound were also added to the label for the other compound unless no meaningful new safety information could be derived from the additional adverse reactions (i.e., the term was vague or the medical concept was already found in the current label). All adverse reactions and their frequencies of occurrence in patients on INVEGA® are reflected in the Adverse reaction tables below.

Adverse reactions reported with paliperidone and/or risperidone by ≥ 2% of INVEGA®-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 3.

**Table 3. Additional Adverse Reactions Reported with Paliperidone and/or Risperidone by ≥2% of INVEGA®-Treated Subjects[i]. (The Terms within each System Organ Class are Sorted Alphabetically)**

| System/Organ Class<br>Adverse Reaction |
|---|
| **Infections and Infestations** |
| Upper respiratory tract infection |
| **Psychiatric Disorders** |
| Insomnia* |
| **Nervous System Disorders** |
| Akathisia*, Dystonia*, Parkinsonism* |
| **Gastrointestinal Disorders** |
| Abdominal discomfort, Diarrhea |
| **Musculoskeletal and Connective Tissue Disorders** |
| Musculoskeletal pain |

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Dystonia includes**: blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness.
[1] Frequencies calculated based on a pooled dataset of the 9 double- blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects).

Adverse reactions reported with paliperidone and/or risperidone by <2% of INVEGA®-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 4.

**Table 4. Additional Adverse reactions Reported with Paliperidone and/or Risperidone by <2% of INVEGA®-Treated Subjects[1] (The Terms within each System Organ Class are Sorted Alphabetically)**

| System/Organ Class<br>Adverse Reaction |
|---|
| **Infections and Infestations**<br>Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Tonsillitis, Urinary tract infection |
| **Blood and Lymphatic System Disorders**<br>Anemia, Hematocrit decreased, Neutropenia, White blood cell count decreased |
| **Immune System Disorders**<br>Anaphylactic reaction, Hypersensitivity |
| **Endocrine Disorders**<br>Hyperprolactinemia |
| **Metabolism and Nutritional Disorders**<br>Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Weight decreased |
| **Psychiatric Disorders**<br>Anorgasmia, Depression, Libido decreased, Nightmare, Sleep disorder |
| **Nervous System Disorders**<br>Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dyskinesia*, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia |
| **Eye Disorders**<br>Conjunctivitis, Dry eye, Lacrimation increased, Photophobia |
| **Ear and Labyrinth Disorders**<br>Ear pain, Tinnitus, Vertigo |
| **Cardiac Disorders**<br>Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations |

| System/Organ Class<br>Adverse Reaction |
|---|
| **Vascular Disorders**<br>Flushing, Hypertension, Hypotension, Ischemia |
| **Respiratory, Thoracic and Mediastinal Disorders**<br>Cough, Dyspnea, Hyperventilation, Nasal congestion, Pharyngolaryngeal pain, Wheezing |
| **Gastrointestinal Disorders**<br>Cheilitis, Dysphagia, Fecal incontinence, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue, Toothache |
| **Hepatobiliary Disorders**<br>Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased |
| **Skin and Subcutaneous Tissue Disorder**<br>Acne, Dry skin, Eczema, Erythema, Pruritus, Rash, Seborrheic dermatitis, Skin discoloration |
| **Musculoskeletal and Connective Tissue Disorders**<br>Arthralgia, Back pain, Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Neck pain |
| **Renal and Urinary Disorders**<br>Dysuria, Pollakiuria, Urinary incontinence |
| **Reproductive System and Breast Disorders**<br>Breast discharge, Breast discomfort, Breast engorgement, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge |
| **General Disorders**<br>Body temperature increased, Chest discomfort, Chills, Face edema, Gait abnormal, Edema*, Pyrexia, Thirst |
| **Injury, Poisoning and Procedural Complications**<br>Fall |

*__Convulsion includes:__ __g__rand mal convulsion; __Dyskinesia includes:__ athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; __Menstrual disorder includes:__ menstruation irregular, oligomenorrhoea__; Edema includes:__ generalised edema, edema peripheral, pitting edema.

[1] Frequencies calculated based on a pooled dataset of the 9 double- blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects).

Adverse reactions reported with paliperidone and/or risperidone in other clinical trials but not reported by INVEGA® (3-12 mg)-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 5.

**Table 5. Additional Adverse Reactions Reported with Paliperidone and/or Risperidone in Other Clinical Trials but not Reported by INVEGA® (3-12 mg)-treated Subjects in Trials Listed in Tables 3 and4.[1] (The Terms within each System Organ Class are Sorted Alphabetically)**

| System/Organ Class<br>Adverse Reaction |
|---|
| **Infections and Infestations** |
| Eye infection |
| **Blood and Lymphatic System Disorders** |
| Eosinophil count increased |
| **Endocrine Disorders** |
| Glucose urine present |
| **Metabolism and Nutritional Disorders** |
| Hyperinsulinemia, Polydipsia |
| **Psychiatric Disorders** |
| Blunted affect, Confusional state |
| **Nervous System Disorders** |
| Balance disorder, Cerebrovascular disorder, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Neuroleptic malignant syndrome, Unresponsive to stimuli |
| **Eye Disorders** |
| Eye movement disorder, Eye rolling, Glaucoma, Ocular hyperemia |
| **Cardiac Disorders** |
| Postural orthostatic tachycardia syndrome |
| **Respiratory, Thoracic and Mediastinal Disorders** |
| Dysphonia, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory tract congestion |
| **Gastrointestinal Disorders** |
| Fecaloma |
| **Skin and Subcutaneous Tissue Disorders** |
| Drug eruption, Hyperkeratosis, Urticaria |
| **Musculoskeletal and Connective Tissue Disorders** |
| Posture abnormal, Rhabdomyolysis |
| **Reproductive System and Breast Disorders** |
| Breast enlargement, Menstruation delayed |
| **General Disorders** |
| Body temperature decreased, Drug withdrawal syndrome, Induration, Malaise |

[1] Frequencies of ADRs listed in Tables 3 and 4 were calculated from 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects). The ADRs listed in the table above were not observed in these studies, but were observed in other, nonpivotal clinical trials with INVEGA® or in clinical studies with another risperidone- or paliperidone-containing product.

*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 on Special warnings and special precautions for use).

*Events of Particular interest to the class*
*Extrapyramidal Symptoms (EPS).* In clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of INVEGA®. Dose-relatedness for EPS was seen with the two higher doses of INVEGA® (9 and 12 mg). EPS included a pooled analysis of the following terms: dyskinesia, dystonia, hyperkinesia, Parkinsonism, and tremor.

For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

*Weight Gain.* In clinical trials, the proportions of subjects meeting a weight gain criterion of ≥ 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.

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

*Laboratory Tests: Serum Prolactin.* In clinical trials, median increases in serum prolactin were observed with INVEGA® in 67% of subjects, however, potentially prolactin-related adverse events (e.g., amenorrhea, galactorrhoea, 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.

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements.

Class effects
QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics.

Postmarketing Data

In addition to the adverse reactions reported during clinical trials and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Table 6). The frequencies are provided according to the following convention:

| | |
|---|---|
| Very common | ≥1/10 |
| Common | ≥1/100 to <1/10 |
| Uncommon | ≥1/1000 to <1/100 |
| Rare | ≥1/10000 to <1/1000 |
| Very rare | <1/10000, including isolated reports |
| Not known | Cannot be estimated from the available data |

In Table 6, adverse reactions are presented by frequency category based on spontaneous reporting rates.

**Table 6. Adverse Reactions Identified During Postmarketing Experience with Paliperidone and/or Risperidone. (The Frequency Is Based on Spontaneous Reporting Rates with Paliperidone)**

| | |
|---|---|
| **Blood and Lymphatic System Disorders** | |
| *Very rare* | Agranulocytosis, Thrombocytopenia |
| **Endocrine Disorders** | |
| *Not known* | Inappropriate antidiuretic hormone secretion |
| **Metabolism and Nutrition Disorders** | |
| *Very rare* | Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia |
| *Not known* | Water intoxication |
| **Psychiatric Disorders** | |
| *Very rare* | Catatonia, Mania, Somnambulism |
| *Not known* | Sleep-related eating disorder |
| **Nervous System Disorders** | |
| *Very rare* | Dysgeusia |
| Eye Disorders | |
| Not known | Floppy iris syndrome (intraoperative) |
| **Cardiac Disorders** | |
| *Very rare* | Atrial fibrillation |
| **Vascular Disorder** | |
| *Very rare* | Deep vein thrombosis, Pulmonary embolism |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| *Very rare* | Sleep apnea syndrome |
| **Gastrointestinal Disorders** | |
| *Very rare* | Pancreatitis |
| *Very rare* | Ileus |
| **Hepatobiliary Disorders** | |
| *Not known* | Jaundice |
| **Skin and Subcutaneous Tissue Disorders** | |
| *Rare* | Angioedema |
| *Very rare* | Alopecia |
| *Not known* | Stevens-Johnson syndrome/Toxic epidermal necrolysis |
| **Renal and Urinary Disorder** | |
| *Very rare* | Urinary retention |
| **Pregnancy, Puerperium and Perinatal Conditions** | |
| *Very rare* | Drug withdrawal syndrome neonatal |
| **Reproductive System and Breast Disorders** | |
| *Very rare* | Priapism |
| General Disorders | |
| *Very rare* | Hypothermia |

**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 the setting of overdose with oral paliperidone. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Consideration should be given to the extended-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.

PHARMACOLOGICAL PROPERTIES

**Pharmacodynamic properties**

*Pharmacologic group: Antipsychotics, 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-$HT_2$- and dopaminergic $D_2$-receptors. Paliperidone also blocks $\alpha_1$-adrenergic receptors and, slightly less, $H_1$-histaminergic and $\alpha_2$-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 $D_2$-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions less than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

*Pharmacodynamic Effects*

*Clinical Efficacy*
*Schizophrenia*
The efficacy of INVEGA® 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 decrease in total Positive and Negative Syndrome Scale (PANSS) scores as shown in the following table. 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.

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 | 3 mg | 6 mg | 9 mg | 12 mg |
|---|---|---|---|---|---|
| **R076477-SCH-303** | (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) |
| **R076477-SCH-304** | (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) |
| **R076477-SCH-305** | (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.

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 stabilized for an additional 8 weeks with INVEGA® (doses ranging from 3 to 15 mg once daily) patients were then randomized in a double-blind manner to either continue on INVEGA® or to 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 acute efficacy of INVEGA® (3 mg to 12 mg once daily) in the treatment 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 and/or Hamilton Rating Scale for Depression. 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 [no mood stabilizers and/or antidepressants (55%)] or as an adjunct to mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and

SNRIs. INVEGA® was dosed in the morning without regard to meals. Studies were carried out in the United States, Eastern Europe, Russia, and Asia.

Efficacy was evaluated using the PANSS, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

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. Numerical improvements in mood symptoms were also observed, as measured by the HAM-D-21 and YMRS. 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.

Taking the results of both studies together, INVEGA® improved the symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. 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.

**Pharmacokinetic properties**

The pharmacokinetics of paliperidone following INVEGA® administration are dose proportional within the available dose range (3 to 9 mg).

*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 (Cmax) 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 extended-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 α1-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 in 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 discernable difference on the apparent clearance of paliperidone after administration of INVEGA® between extensive metabolisers and poor metabolisers of CYP2D6 substrates. 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 metabolized 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 (CrCl = 50 to < 80 ml/min), 64% in moderate (CrCl = 30 to < 50 ml/min), and 71% in severe (CrCl =10 to < 30 ml/min) renal impairment. 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.

*Race*
No dosage adjustment is recommended based on race. Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA® administration. No differences in pharmacokinetics were observed in a pharmacokinetics study conducted in Japanese and Caucasian subjects

*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 utilizing 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.

**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 with risperidone, which is extensively converted

to paliperidone in rats and humans, adverse effects were seen on 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 tumors can be related to prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown.

## PHARMACEUTICAL PARTICULARS

### List of excipients

*For the 3 mg tablet:*
Coated tablet core:
Butyl hydroxytoluene E321, Cellulose acetate, Ferric oxide (yellow) E172, Ferric oxide (red) E172, Hydroxyethyl cellulose, Polyethylene glycol 3350, Polyethylene oxide 200K, Polyethylene oxide 7000K, Povidone (K29-32), Sodium chloride, Stearic acid

Colour overcoat:
Carnauba wax, Hypromellose, Lactose monohydrate, Titanium dioxide E171, Triacetin

Printing ink:
Hypromellose, Iron oxide (black) E172, Propylene glycol

*For the 6 mg tablet:*
Coated tablet core:
Butyl hydroxytoluene E321, Cellulose acetate, Ferric oxide (red) E172, Hydroxyethyl cellulose, Polyethylene glycol 3350, Polyethylene oxide 200K, Polyethylene oxide 7000K, Povidone (K29-32), Sodium chloride, Stearic acid

Colour overcoat:
Carnauba wax, Ferric oxide (yellow) E172, Ferric oxide (red) E172, Hypromellose, Polyethylene glycol 400, Titanium dioxide E171

Printing ink:
Hypromellose, Iron oxide (black) E172, Propylene glycol

*For the 9 mg tablet:*
Coated tablet core:
Butyl hydroxytoluene E321, Cellulose acetate, Ferric oxide (red) E172, Hydroxyethyl cellulose, Iron oxide (black) E172, Polyethylene glycol 3350, Polyethylene oxide 200K, Polyethylene oxide 7000K, Povidone (K29-32), Sodium chloride, Stearic acid

Colour overcoat:
Carnauba wax, Ferric oxide (red) E172, Hypromellose, Polyethylene glycol 400, Titanium dioxide E171

Printing ink:
Hypromellose, Iron oxide (black) E172, Propylene glycol

### Incompatibilities

Not applicable

**Special precautions for storage**

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

Keep out of reach of children.

**Nature and contents of container**

Blisters:

• Oriented polyamide (OPA)-aluminium-polyvinyl chloride (PVC)/aluminium push-through child-resistant (CR) layer.
Pack sizes of 7, 28, 49, 56, and 98 extended-release tablets.

Not all pack sizes may be marketed.

**Special precautions for disposal**

No special requirements.

**PRODUCT REGISTRANT**
Johnson & Johnson International (Singapore) Pte Ltd
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

**BATCH RELEASER**
Janssen Cilag S.p.A
Via C. Janssen
04100 Borgo San Michele
Latina, Italy

**DATE OF REVISION OF THE TEXT**
15 September 2022 (CCDS 07 April 2020)