SCHEDULING STATUS

Schedule 5

1. NAME OF THE MEDICINE

INVEGA ® 3 mg Prolonged-Release Tablet.

INVEGA ® 6 mg Prolonged-Release Tablet.

INVEGA ® 9 mg Prolonged-Release Tablet.

INVEGA ® 12 mg Prolonged-Release Tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Excipient with known effect

Each 3 mg tablet contains 13.2 mg lactose

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged-Release tablet

Trilayer cylindrical-shaped longitudinal capsule-shaped tablets:

INVEGA 3 mg: White capsule shaped tablets printed with “PAL 3” in black ink along one side of the tablet. Two orifices may or may not be visible on one end of the tablet.

INVEGA 6 mg: Beige capsule shaped tablets printed with “PAL 6” in black ink along one side of the tablet. Two orifices may or may not be visible on one end of the tablet.

INVEGA 9 mg: Pink capsule shaped tablets printed with “PAL 9” in black ink along one side of the tablet. Two orifices may or may not be visible on one end of the tablet.

INVEGA 12 mg: Dark-yellow capsule shaped tablets printed with “PAL 12” in black ink along one side of the tablet. Two orifices may or may not be visible on one end of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INVEGA (paliperidone) is indicated for the treatment of schizophrenia. INVEGA has not been studied in patients unresponsive to risperidone.

INVEGA (paliperidone) is indicated for the treatment of schizophrenia in adolescents 12 – 17 years of age.

INVEGA (paliperidone) is indicated for the treatment of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilisers in adults. Efficacy beyond 6 weeks has not been demonstrated.

4.2 Posology and method of administration

Schizophrenia

Adults (≥ 18 years of age)

The recommended dose of INVEGA 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.

Adolescents (12 – 17 years of age)

The recommended dose of INVEGA for the treatment of schizophrenia in adolescents 12 – 17 years of age is 3 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from a higher dose of 6 mg to 12 mg/day. Dose increases should be made only after clinical reassessment and should occur at increments of 3 mg/day at intervals of more than 5 days.

Schizoaffective Disorder

Adults (≥ 18 years of age)

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. 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. There is no experience of treating schizoaffective disorder for more than 6 weeks.

Special populations

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 (see section 4.4).

Patients with renal impairment

For patients with mild renal impairment (creatinine clearance ≥ 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 ≥ 10 to < 50 mℓ/min), the recommended dose of INVEGA is 3 mg every other day which may then be increased to 3 mg once daily after clinical assessment.

As INVEGA has not been studied in patients with creatinine clearance below 10 mℓ/min, use is not recommended in such patients (see section 4.4).

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 are 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 4.4).

Adolescents and children

Safety and effectiveness of INVEGA for the treatment of schizophrenia in patients < 12 years of age have not been established. Safety and effectiveness of INVEGA for the treatment of schizoaffective disorder in patients < 18 years of age have not been studied.

Switching to other antipsychotic medicinal products

There are no systematically collected data to specifically address switching patients from INVEGA to other antipsychotic medicinal products.

Method of administration

INVEGA is for oral administration and can be administered with or without food. The administration of INVEGA should be standardised in relation to food intake.

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 (see section 5.2).

INVEGA must be swallowed whole with the aid of adequate amounts 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.

4.3 Contraindications

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

Severe renal impairment (CrCL < 10 mℓ/min) (see section 4.4)

Decreased gastro-intestinal transit time (see section 4.4)

Dementia or Parkinson's disease (see section 4.4)

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 a history of dysrhythmias, in patients with congenital long QT syndrome, and in concomitant use with medicines known 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 antipsychotics, including INVEGA. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, INVEGA should be discontinued.

Tardive Dyskinesia/extrapyramidal symptoms

Medicines with dopamine receptor antagonistic properties such as INVEGA 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 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 4.5)

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with INVEGA.

Patients with an established diagnosis of diabetes mellitus who are started on INVEGA should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with INVEGA should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with INVEGA should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when INVEGA was discontinued: however, some patients required continuation of anti-diabetic treatment despite discontinuation of INVEGA.

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when INVEGA is being used. Patients may be advised to refrain from overeating in view of the possibility of weight gain.

Orthostatic hypotension

INVEGA (paliperidone) may induce orthostatic hypotension based on its alpha-blocking activity. Based on pooled data from 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 a patient to hypotension (e.g. dehydration, hypovolaemia and treatment with antihypertensive medications).

Seizures

INVEGA should be used cautiously in patients with a history of seizures or other conditions that 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 pre-existing gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines with a non-absorbable shell.

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 INVEGA (see section 4.3).

Renal impairment

The plasma concentrations of INVEGA are increased in patients with renal impairment. Dosage adjustment may be required (see section 4.2 and section 5.2).

No data are available in patients with a creatinine clearance below 10 mℓ/min.

INVEGA 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 INVEGA is used in such patients.

Elderly

In a study conducted in elderly subjects with schizophrenia, the safety profile was similar to that seen in non-elderly subjects.

Elderly patients with Dementia

INVEGA has not been studied in elderly patients with dementia.

Overall Mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other antipsychotic medicines, 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 events (CAE)

In placebo-controlled trials in elderly patients with dementia, treated with some atypical antipsychotic medicines, including risperidone, aripiprazole and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo. INVEGA should be used with caution in elderly patients with dementia who have risk factors for stroke.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with INVEGA. Agranulocytosis has been reported during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leukopenia/neutropenia should be monitored during 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 significant neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue INVEGA and have their WBC followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with INVEGA. 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

INVEGA has not been studied in patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) (see section 4.3). These groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics such as INVEGA. 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, including INVEGA, have been reported to induce priapism. Priapism has been reported with INVEGA during post-marketing surveillance (See section 4.8: Post-marketing Data). Patients should be informed to seek urgent medical care in case priapism has not resolved within 3-4 hours.

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 INVEGA. This effect, although not demonstrated 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.

Class effects

QT prolongation, ventricular dysrythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics including INVEGA.

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, including INVEGA.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of INVEGA should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping INVEGA prior to cataract surgery has not been established and must be weighed against the risk of stopping INVEGA therapy.

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 examinations for extrapyramidal symptoms and other movement disorders should also be conducted. For specific posology recommendations in paediatric population see section 4.2

Events of particular interest to the class

Laboratory Tests: Serum Prolactin

In clinical trials, median increases in serum prolactin were observed with INVEGA in 67 % of subjects. Potentially prolactin-related adverse events (e.g., amenorrhoea, 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.

Lactose content (pertains only to the 3 mg INVEGA tablets)

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

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 antidysrhythmics (e.g., quinidine, disopyramide) and class III antidysrhythmics (e.g., amiodarone, sotalol), some antihistamines, some other antipsychotics and some antimalarials (e.g., mefloquine).

Potential for INVEGA to affect other medicines

INVEGA (paliperidone) is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450 isozymes. Formal interaction studies have not been performed.

INVEGA should be used with caution in combination with other centrally acting medicines e.g. anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol. INVEGA may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, 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 INVEGA is combined with other medicines known to lower the seizure threshold (i.e. phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.).
Co-administration of INVEGA at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2 000 mg once daily) did not affect the steady-state pharmacokinetics of valproate. (See below for effect of divalproex sodium on INVEGA).

Potential for other medicines to affect INVEGA

In vitro studies indicate that CYP2D6 and CYP3A4 may be 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 INVEGA.

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

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 drug 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.

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 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of INVEGA for use during human pregnancy has not been established.

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.

Neonates exposed to antipsychotic medicines (including INVEGA) 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. 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.

Breastfeeding

INVEGA is excreted in human breast milk. Therefore, women receiving INVEGA should not breastfeed.

4.7 Effects on ability to drive and use machines

INVEGA can have 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

Clinical Trial Data

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, increased weight, nausea, agitation, constipation, vomiting, fatigue, depression, dyspepsia, diarrhoea, dry mouth, toothache, musculoskeletal pain, hypertension, asthenia, back pain, prolonged electrocardiogram QT, 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 in Clinical Studies

The following are all ADRs that were reported with paliperidone by frequency category estimated from paliperidone palmitate clinical trials. The following terms and frequencies are applied: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000); and *not known* (cannot be estimated from the available data).

Summary of Adverse Reactions in Clinical Studies

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
Infections and infestations		bronchitis, upper respiratory tract infection, sinusitis, influenza	pneumonia, respiratory tract infection, urinary tract infection, cystitis, ear infection, tonsillitis, cellulitis	eye infection, onychomycosis, acarodermatitis	
Blood and lymphatic system disorders			anaemia, decreased haematocrit	decreased white blood cell count, increased eosinophil count	neutropenia
Immune system disorders			hypersensitivity	anaphylactic reaction	
Endocrine disorders			Hyper-prolactinaemia	glucose urine present	
Metabolism and nutrition disorders		increased weight, increased appetite, decreased	hyperglycaemia, anorexia, increased blood triglycerides, increased blood	polydipsia	Hyper-insulinaemia, increased waist circumference

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
		weight, decreased appetite	cholesterol		
Psychiatric disorders	insomnia[a]	agitation, depression, anxiety	sleep disorder, confusional state, decreased libido, anorgasmia, nightmare		blunted affect
Nervous system disorders	parkin-sonism[b], akathisia[b], somno-lence, headache	dystonia[b], dizziness, dyskinesia[b], tremor[b]	tardive dyskinesia, convulsion[a], syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, hypoaesthesia, paraesthesia	cerebrovascular accident, loss of consciousness, balance disorder, abnormal coordination	neuroleptic malignant syndrome, cerebro-vascular disorder, unresponsive to stimuli, depressed level of conscious-ness, diabetic coma, head titubation

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
Eye disorders		vision blurred	conjunctivitis, dry eye	glaucoma, eye movement disorder, photophobia, increased lacrimation, ocular hyperaemia	eye rolling
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders	tachycardia	atrio-ventricular block, conduction disorder, prolonged electro-cardiogram QT, bradycardia	sinus arrhythmia, abnormal electrocardiogram, palpitations		postural orthostatic tachycardia syndrome

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
Vascular disorders		orthostatic hypotension, hypertension	hypotension	ischaemia	flushing
Respiratory, thoracic and mediastinal disorders		pharyngo-laryngeal pain, cough, nasal congestion	dyspnoea, wheezing, epistaxis	hyperventilation, pneumonia aspiration, respiratory tract congestion, dysphonia	pulmonary congestion, rales
Gastro-intestinal disorders		abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	swollen tongue, gastroenteritis, dysphagia, flatulence	intestinal obstruction, faecal incontinence, cheilitis	faecaloma
Hepatobiliary disorders		increased trans-aminases	increased gamma-glutamyltransfer-ase, increased hepatic enzyme		

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
Skin and subcutan-eous tissue disorders		rash	urticaria, pruritus, eczema, dry skin, acne, seborrhoeic dermatitis	hyperkeratosis, erythema, skin discolouration	drug eruption
Musculo-skeletal and connective tissue disorders		musculo-skeletal pain, back pain, arthralgia	increased blood creatine phosphokinase, muscle spasms, joint stiffness, joint swelling, muscular weakness, neck pain		rhabdo-myolysis, abnormal posture
Renal and urinary disorders			urinary incontinence, pollakiuria, dysuria		
Reproductive system and breast disorders		amenorrhoea, galactorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder[a],	breast engorgement	delayed menstruation, breast enlargement

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
			gynaecomastia, sexual dysfunction, breast discomfort, breast discharge, vaginal discharge		
General disorders		pyrexia, asthenia, fatigue	face oedema, oedema[a], chills, increased body temperature, thirst, chest discomfort, malaise	abnormal gait	decreased body temperature, drug withdrawal syndrome, induration
Injury, poisoning and procedural complica-tions			fall		

[a] **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

[b] **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 includes: 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.

Post-marketing data

Adverse Reactions Identified During Post-marketing Experience

Blood and lymphatic system disorders

Agranulocytosis, thrombocytopenia

Endocrine disorders

Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders

Diabetes mellitus, water intoxication, diabetic ketoacidosis, hypoglycaemia

Psychiatric disorders

Catatonia

Mania

Somnambulism

Sleep-related eating disorder

Nervous system disorders

Dysgeusia

Eye disorders

Floppy iris syndrome

Cardiac disorders

Atrial fibrillation

Vascular disorders

Deep vein thrombosis, pulmonary embolism

Respiratory, thoracic and mediastinal disorders

Sleep apnoea syndrome

Gastrointestinal disorders

Pancreatitis, paralytic ileus

Hepatobiliary disorders

Jaundice

Skin and subcutaneous tissue disorders

Alopecia, angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis

Renal and urinary disorders

Urinary retention

Pregnancy, puerperium and perinatal conditions

Neonatal drug withdrawal syndrome

Reproductive system and breast disorders

Priapism

General disorders

Hypothermia

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 ≥ 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 ≥ 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 ≥ 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 arrythmias (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 (≥ 1/10) in adolescents; abdominal pain, galactorrhoea, gynaecomastia, acne, dysarthria, gastroenteritis, epistaxis, ear infection, increased blood triglyceride, and vertigo were reported commonly (≥ 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 ≥ 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, disturbances, gynaecomastia) were reported overall in 9,3 % of subjects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the :"**6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Expected signs and symptoms are those resulting from an exaggeration of the known pharmacological effects of INVEGA, i.e. drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Tosade de pointes and ventricular fibrillation have been reported. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment is supportive and symptomatic.

Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. There is no antidote to INVEGA. 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 dysrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures. Administration of

activated charcoal together with a laxative should be considered. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacologic classification: A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Paliperidone, the active metabolite of risperidone, is an atypical antipsychotic. Paliperidone binds strongly to serotonergic 5-HT_2- and dopaminergic D_2-receptors.

Paliperidone also blocks $alfa_1$-adrenergic receptors and, slightly less, H_1-histaminergic and $alfa_2$-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.
Paliperidone is not bound to cholinergic receptors.

5.2 Pharmacokinetic properties

The pharmacokinetics of paliperidone following administration is dose proportional within the recommended clinical dose range (3 to 12 mg).

Absorption

Following a single dose, paliperidone 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 paliperidone, 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 paliperidone ER result in peak-trough fluctuations of 38 %.

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

Administration of a 12 mg paliperidone extended release tablet to healthy ambulatory subjects with a standard high fat/high calorific meal gave a mean C_{max} and AUC value of paliperidone that were increased by 60 % and 54 % respectively, compared with administration under fasting conditions. Clinical trials establishing the safety and efficacy of paliperidone ER OROS were carried out in subjects without regard to the timing of meals. The presence of food at the time of paliperidone ER OROS administration may increase exposure to paliperidone.

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 a_1-acid glycoprotein and albumin.

Biotransformation and Elimination

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. 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 paliperidone 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. However formal interaction studies are limited (see section 4.5)

In vitro studies indicated that paliperidone is not an inducer of CYP1A2, 2C19 or 3A4 activity.
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 after a single dose of 1 mg of paliperidone, in subjects with moderate hepatic impairment (Child Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment (Child Pugh C).

Renal impairment

Elimination of paliperidone decreased with decreasing renal function. Total clearance after a single dose of 3 mg 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). Paliperidone has not been studied in patients with CrCl < 10 mℓ/min.

Adolescents

Paliperidone systemic exposure in adolescent subjects was comparable to that in adults. In adolescents weighing < 51 kg, a 23 % higher exposure was observed than in adolescents weighing ≥ 51 kg; this is considered not to be clinically significant. Age alone did not influence the paliperidone exposure.

Elderly

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

Gender

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients of INVEGA are butyl hydroxytoluene (E321), carnauba wax, cellulose acetate, hydroxyethyl cellulose, hypromellose, iron oxides (E172), polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, and titanium dioxide (E171). INVEGA 3 mg tablets also contain lactose monohydrate and triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C. Protect from moisture.

Bottles: Keep the bottle tightly closed to protect from moisture.

Blisters: Keep tablets in the original package (i.e. blisters) to protect from moisture until required for use.

6.5 Nature and contents of container

INVEGA prolonged-release tablets are packed in bottles or blister presentations.

Bottles

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

Pack sizes: 75 mℓ size bottle (30 tablets); 160 mℓ size bottle (350 tablets).

Blisters:

Pack sizes of 28, 30, 49, 56, 98 (not all pack sizes may be marketed) in:

- Polyvinyl chloride (PVC) laminated with polychloro-trifluoroethylene (PCTFE)/aluminium push-through layer

Or

- White polyvinyl chloride (PVC) laminated with polychloro-trifluoroethylene (PCTFE)/paper- aluminium push-through layer

Or

- Oriented Polyamide (OPA)-aluminium-polyvinyl chloride (PVC)/aluminium push-through layer

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg.No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand 1685, South Africa

MedinfoZA@its.jnj.com

8. REGISTRATION NUMBER(S)

INVEGA 3 mg: 42/2.6.5/0284

INVEGA 6 mg: 42/2.6.5/0285

INVEGA 9 mg: 42/2.6.5/0286

INVEGA 12 mg: 42/2.6.5/0287

Namibia Reg. No.:
INVEGA 3 mg: 11/2.6.5/0079
INVEGA 6 mg: 11/2.6.5/0080
INVEGA 9 mg: 11/2.6.5/0081
NS 3

9. DATE OF FIRST AUTHORISATION

- Date on the registration certificate: 3 mg, 6 mg, 9mg and 12 mg – 01 October 2010

10. DATE OF REVISION OF THE TEXT

19 October 2023