INVEGA® PROLONGED RELEASE TABLETS (3 mg, 6 mg and 9 mg)
PRESCRIBING INFORMATION

ACTIVE INGREDIENT: 3 mg, 6 mg or 9 mg paliperidone.
Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATION: Treatment of schizophrenia in adults, and adolescents 15 years and older. **Adults only:** Treatment of schizoaffective disorder.

DOSAGE & ADMINISTRATION:
Adults (Schizophrenia and Schizoaffective disorder)
6 mg once daily in the morning with or without food (do **not** vary). Initial dose titration not required. Dosage adjustment, if indicated, only after clinical reassessment. Increments of 3 mg/day are recommended, generally at intervals of more than 4 days for schizoaffective disorder and more than 5 days for schizophrenia. Recommended range 3-12 mg for schizophrenia and 6-12 mg for schizoaffective disorder. Swallow tablets **whole** with liquid.
Adolescents 15 years and older (Schizophrenia)
3 mg once daily in the morning with or without food (do **not** vary).
Maximum recommended daily doses for adolescents < 51 kg is 6 mg and ≥ 51 kg is 12 mg.
Adjust dose within recommended range (after clinical reassessment), in increments of 3 mg/day at > 5 day intervals. Swallow tablets **whole** with liquid.
The efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established.
Elderly: Caution in elderly dementia patients with stroke risk factors. ***Renal impairment:*** **Mild** (creatinine clearance 50-80 ml/min): 3 mg once daily increasing to maximum of 6 mg once daily based on response and tolerability. **Moderate to Severe** (creatinine clearance 10-50 ml/min) 3 mg every other day recommended initial dose in severe renal impairment. May be increased to 3 mg once daily after clinical reassessment. Do not use in patients with creatinine clearance below 10 ml/min. ***Hepatic impairment:*** No dose adjustment for mild or moderate hepatic impairment. Caution in severe hepatic impairment.

CONTRAINDICATIONS: Hypersensitivity to paliperidone, risperidone, or excipients.

SPECIAL WARNINGS & PRECAUTIONS: ***Schizoaffective disorder:*** Monitor INVEGA treated patients carefully for potential switch from manic to depressive symptoms. ***Cardiovascular disease:*** Caution in patients with known cardiovascular disease, or family history of Q-T prolongation. INVEGA may induce orthostatic hypotension in some patients. Use with caution in cardiovascular disease, cerebrovascular disease and conditions that predispose patient to hypotension. ***Neuroleptic Malignant Syndrome:***

Discontinue all antipsychotics, including INVEGA if symptoms/signs develop. ***Tardive dyskinesia:*** If signs/symptoms appear, consider discontinuing all antipsychotics, including INVEGA. Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended. ***Leukopenia, neutropenia, and agranulocytosis:*** Events of leucopenia, neutropenia, and agranulocytosis reported with antipsychotics, including INVEGA - additional monitoring or cessation of treatment may be required. ***Weight gain:*** Monitor weight regularly. ***Hyperprolactinaemia:*** Use with caution in patients with possible prolactin-dependent tumours. ***Patients with diabetes mellitus/hyperglycaemia:*** Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment. Appropriate clinical monitoring is advisable. ***Patients with seizures:*** Caution where there is a history of seizures/other conditions that potentially lower the seizure threshold. ***Patients with dysphagia:*** Do not administer to patients with significant swallowing difficulty **or** known gastro-intestinal strictures. ***Patients with decreased gastro-intestinal transit time:*** Reduced absorption of paliperidone may result. ***Patients with renal impairment:*** See Dosage & Administration. Do not use in patients with creatinine clearance below 10 ml/min. ***Patients with hepatic impairment:*** See Dosage & Administration. Caution in severe hepatic impairment. ***Elderly patients with dementia:*** Use with caution in elderly dementia patients with risk factors for stroke. ***Parkinson's disease:*** Use with caution. ***Priapism:*** Reported during post-marketing surveillance (incidence not known). ***Body temperature regulation:*** Care when prescribing to patients experiencing conditions which may contribute to core body temperature elevation. ***Venous Thromboembolism:*** Identify all possible risk factors for VTE before and during treatment and take preventive measures. ***Anti-emetic effect:*** Observed in paliperidone preclinical studies; if occurs in human patients may mask signs and symptoms of overdosage with certain medicines, or of medical conditions such as intestinal obstruction, Reye's syndrome, brain tumour etc.

Paediatric population: monitor sedative effect of INVEGA closely (changing the time of administration may improve impact of sedation on patient). Potential effects of prolonged hyperprolactinemia- consider regular clinical evaluation of endocrinological status (height, weight, sexual maturation). Monitor regularly for extra-pyramidal symptoms, other movement disorders. ***Intraoperative floppy iris syndrome (IFIS)*** has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA. ***Lactose content (3 mg tablets only):*** Avoid in patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

SIDE EFFECTS:

Adults

Very common: headache, insomnia, sedation/somnolence, parkinsonism, akathisia, **Common:** bronchitis, upper respiratory tract infection, sinusitis,

urinary tract infection, influenza, weight increased, increased appetite, weight decreased, decreased appetite, mania, agitation, depression, anxiety, dystonia, dizziness, dyskinesia, tremor, vision blurred, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, tachycardia, orthostatic hypotension, hypertension, pharyngolaryngeal pain, cough, nasal congestion, abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache, transaminases increased, pruritus, rash, musculoskeletal, pain, back pain, arthralgia, amenorrhoea, pyrexia, asthenia and fatigue.

Extrapyramidal Symptoms (EPS): Schizophrenia: In clinical trials no difference observed between placebo and the 3 mg and 6 mg doses of INVEGA. Dose-relatedness for EPS seen with higher INVEGA doses (9 mg and 12 mg); ***Schizoaffective disorder:*** higher rate of EPS versus placebo in clinical trials in all dose groups without clear dose relationship. ***Hyperprolactinaemia:*** increased serum prolactin in 67% of INVEGA treated subjects in schizophrenia clinical trials; however prolactin-related adverse events reported in 2% of subjects overall. ***Weight gain:*** Schizophrenia clinical trials, similar incidence of weight gain (≥ 7%) for INVEGA 3 mg and 6 mg compared with placebo; higher incidence of weight gain for INVEGA 9 mg and 12 mg; in schizoaffective disorder trials, 5% of INVEGA treated subjects had a bodyweight increase of ≥ 7% compared to 1% of placebo group. ***Class effects:*** QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics. Cases of venous thromboembolism, including pulmonary embolism and deep vein thrombosis also reported. Rarely, drug withdrawal syndrome in neonates observed with antipsychotics.

Elderly: in a study conducted in elderly subjects with schizophrenia, safety profile was similar to non-elderly subjects. ***Paediatric population*****:** Overall safety profile in studies involving adolescents 12 years and older with schizophrenia similar to adults except for the following adverse drug reactions reported more frequently in INVEGA-treated adolescents: ***Very common:*** sedation/somnolence, parkinsonism, weight increase, upper respiratory tract infection, akathisia, and tremor. ***Common:*** abdominal pain, galactorrhoea, gynaecomastia, acne, dysarthria, gastroenteritis, epistaxis, ear infection, blood triglyceride increased, vertigo. ***Extrapyramidal Symptoms (EPS):*** incidence higher than placebo for all doses, and increased frequency at higher doses. ***Weight gain:*** higher incidence of ≥ 7% weight gain in INVEGA-treated subjects versus placebo in short-term study (no clear dose relationship). ***Prolactin:*** Adverse reactions suggestive of increased prolactin levels reported overall in 9.3% of subjects in an up to 2 year open label study. **Other side effects reported with risperidone (paliperidone is the active metabolite of risperidone):** Stevens-Johnson syndrome/toxic epidermal necrolysis.

Refer to SmPC for other side effects.

PREGNANCY: INVEGA should not be used during pregnancy unless clearly necessary.

LACTATION: INVEGA should not be used while breastfeeding.

INTERACTIONS: Caution prescribing INVEGA with medicines that prolong QT interval e.g., class IA and class III antiarrhythmics, some antihistaminics, some other antipsychotics, some antimalarials. ***Potential for INVEGA to affect other medicines:*** Not expected to cause clinically important pharmacokinetic interactions with medicines metabolized by cytochrome P-450 isozymes. Use with caution in conjunction with: centrally acting medicines e.g. anxiolytics, antipsychotics, hypnotics, opiates, or alcohol; medicines known to lower seizure threshold i.e., phenothiazines, butyrophenones, clozapine, tricyclics, SSRIs, tramadol, mefloquine etc; medicines capable of inducing orthostatic hypotension (an additive effect may be observed when INVEGA is co-administered); levodopa and other dopamine agonists (paliperidone may antagonize their effect - use the lowest effective dose of each treatment if this combination must be prescribed, e.g. end-stage Parkinson's disease). No interaction study between INVEGA and lithium has been performed, however pharmacokinetic interaction unlikely to occur. ***Potential for other medicines to affect INVEGA:*** Co-administration of INVEGA once daily with carbamazepine 200 mg twice daily decreases plasma concentration of paliperidone by 37%. Re-evaluate/increase INVEGA dose at carbemazepine initiation. Other P-gp inducers e.g. rifampicin, St. John's wort may have similar effects. No indications from *in vitro* and *in vivo* studies that isozymes CYP2D6 and CYP3A4 are significant in the metabolism of paliperidone. Metoclopramide and other medicines affecting G.I. transit time may alter paliperidone absorption. Consider reducing INVEGA dosage when co-administered with valproate (after clinical assessment). Do not use INVEGA with oral risperidone as additive paliperidone exposure may occur. ***Paediatric population:*** Interaction studies have only been performed in adults. The combined use of psychostimulants (e.g. methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either/both treatments.

Refer to SmPC for full details of interactions.

LEGAL CATEGORY: Prescription Only Medicine.

PRESENTATIONS, PACK SIZES, MARKETING AUTHORISATION NUMBERS & BASIC NHS COSTS:

Presentation	Pack Size	Product Licence Number	Basic NHS Cost
3 mg prolonged release tablets	Blister pack 28 tablets	PLGB 00242/0683	£97.28

6 mg prolonged release tablets		PLGB 00242/0684	£97.28
9 mg prolonged release tablets		PLGB 00242/0685	£145.92

MARKETING AUTHORISATION HOLDER:
Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG UK.

FURTHER INFORMATION IS AVAILABLE FROM: Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire HP12 4EG UK.

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Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com.