



NDA 21999/S-018

**SUPPLEMENT APPROVAL**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: James Tan, Ph.D.  
Director, Regulatory Affairs  
1125 Trenton-Harbourton Road  
P.O. Box 200  
Titusville, NJ 08560-0200

Dear Dr. Tan:

Please refer to your supplemental new drug application dated January 22, 2010, received January 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega (paliperidone) extended-release tablets (NDA 21999).

We acknowledge receipt of your submission dated January 22, 2010.

This “Changes Being Effected” supplemental new drug application provides for the addition of 28 new adverse drug reactions (ADRs) identified in clinical studies performed by J&JPRD or based on spontaneous reports. Proposed changes to the labeling are as follows:

**3 DOSAGE FORMS AND STRENGTHS**

INVEGA<sup>®</sup> Extended-Release Tablets are available in the following strengths and colors: 1.5 mg (orange-brown), 3 mg (white), 6 mg (beige), and 9 mg (pink). All tablets are capsule shaped and are imprinted with either “PALI (b)(4) 1.5”, “PALI (b)(4) 3”, “PALI (b)(4) 6”, or “PALI (b)(4) 9”.

**Table 2: Adverse Drug Reactions Reported by > 2% of INVEGA-Treated Subjects With Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials**

Body System or Organ Class Dictionary-Derived Term	Placebo (N=202)	INVEGA® 3-6 mg once-daily fixed-dose range (N=108)	INVEGA® 9-12 mg once-daily fixed-dose range (N=98)	INVEGA® 3-12 mg once-daily flexible-dose (N=214)
<b>Nervous system disorders</b>				
Akathisia	4	4	6	6
Dysarthria	0	1	4	2
Extrapyramidal symptoms	8	20	17	12
Somnolence	5	12	12	8
<b>Psychiatric disorders</b>				
Sleep disorder	<1	2	3	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	1	1	3	1
Pharyngolaryngeal pain	<1	0	2	1

\* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from two studies. One study included once-daily INVEGA® doses of 6 mg (with the option to reduce to 3 mg) and 12 mg (with the option to reduce to 9 mg). The second study included flexible once-daily doses of 3 to 12 mg. Among the 420 subjects treated with INVEGA®, 230 (55%) received INVEGA® as monotherapy and 190 (45%) received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. Extrapyramidal symptoms includes the terms bradykinesia, drooling, dyskinesia, dystonia, hypertonia, muscle rigidity, muscle twitching, oculogyration, parkinsonian gait, parkinsonism, restlessness, and tremor.<sup>3</sup> Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. ~~All EPS-related terms are grouped under "extrapyramidal symptoms".~~

### 6.3 Other Adverse Reactions Observed During Premarketing Evaluation of INVEGA®

The following additional adverse reactions occurred in < 2% of INVEGA®-treated subjects in the above schizophrenia and schizoaffective disorder clinical trial datasets. The following also includes additional adverse reactions reported at any frequency by INVEGA®-treated subjects who participated in other clinical studies.<sup>4,5</sup>

**Cardiac disorders:** bradycardia, bundle branch block left, palpitations

Endocrine disorders: hyperprolactinemia

**Eye disorders:** vision blurred

**Gastrointestinal disorders:** abdominal pain, flatulence, small intestinal obstruction, swollen tongue

**General disorders:** edema, edema peripheral

**Immune system disorders:** anaphylactic reaction

Infections and infestations: urinary tract infection

Investigations: electrocardiogram abnormal<sup>6</sup>

Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity

**Nervous system disorders:** cerebrovascular accident, convulsion, dizziness postural, grand mal convulsion, lethargy, syncope, transient ischemic attack, additional extrapyramidal symptoms (cogwheel rigidity, muscle spasms, musculoskeletal pain, torticollis, trismus)

**Psychiatric disorders:** agitation, nightmare

**Reproductive system and breast disorders:** amenorrhea, breast discharge, breast engorgement, breast tenderness, breast pain, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular, retrograde ejaculation

Respiratory, thoracic and mediastinal disorders: nasal congestion, pneumonia aspiration

Skin and subcutaneous tissue disorders: pruritus, rash, rash papular

**Vascular disorders:** hypotension, ischemia

### 6.11 Postmarketing Experience

The following adverse reactions ~~has~~ have been identified during postapproval use of INVEGA<sup>®</sup>; because ~~this~~ these reactions ~~was~~ were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate ~~its~~ their frequency: angioedema<sup>7</sup>, priapism, swollen tongue<sup>8</sup>, tardive dyskinesia<sup>9</sup>, urinary incontinence<sup>10</sup>, urinary retention<sup>11</sup>.

## 10 OVERDOSAGE

### 10.1 Human Experience

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose.<sup>12</sup>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA® (paliperidone) Extended-Release Tablets are available in the following strengths and packages. All tablets are capsule-shaped.

1.5 mg tablets are orange-brown and imprinted with "PALI (b)(4)<sup>13</sup> 1.5", and are available in bottles of 30 (NDC 50458-554-01).

3 mg tablets are white and imprinted with "PALI 3", and are available in bottles of 30 (NDC 50458-550-01) and hospital unit dose packs of 100 (NDC 50458-550-10).

6 mg tablets are beige and imprinted with "PALI 6", and are available in bottles of 30 (NDC 50458-551-01) and hospital unit dose packs of 100 (NDC 50458-551-10).

9 mg tablets are pink and imprinted with "PALI 9", and are available in bottles of 30 (NDC 50458-552-01) and hospital unit dose packs of 100 (NDC 50458-552-10).

We have completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text.

## CONTENT OF LABELING

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in this supplemental application.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
5600 Fishers Lane, Room 12B05  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please email Ann Sohn, Regulatory Project Manager, at [ann.sohn@fda.hhs.gov](mailto:ann.sohn@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure  
Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21999	SUPPL-18	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	INVEGA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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THOMAS P LAUGHREN  
03/03/2010