Summary Basis of Decision (SBD)

PrINVEGA®* SUSTENNA™*
25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL paliperidone as paliperidone palmitate, suspension (extended release)

Janssen-Ortho Inc.
Submission Control Number: 127385

Date Issued | 2010/11/01

Health Products and Food Branch
Our mission is to help the people of Canada maintain and improve their health.

Health Canada

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- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), InvegaMD SustennaMC, palmitate de palipéridone, 25 mg/0,25 mL, 50 mg/0,5 mL, 75 mg/0,75 mL, 100 mg/1 mL et 150 mg/1,5 mL de palipéridone sous la forme de palmitate de palipéridone, Janssen-Ortho Inc. Numéro de contrôle de la présentation : 127385
FOREWORD

Health Canada’s Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within the evaluation reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the ‘Reader’s Guide to the Summary Basis of Decision - Drugs’ to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled ‘How Drugs are Reviewed in Canada’. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the ‘Summary Basis of Decision Initiative - Frequently Asked Questions’ document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events (AE), interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under ‘Related Links’ on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the ‘Management of Drug Submissions Guidance’.
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1 PRODUCT AND SUBMISSION INFORMATION

Brand Name: PrINVEGA® SUSTENNA™
Manufacturer/Sponsor: Janssen-Ortho Inc.
Medicinal Ingredient: Paliperidone palmitate
International Non-proprietary Name: Paliperidone palmitate
Strengths: 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL paliperidone as paliperidone palmitate
Dosage form: Suspension (extended release)
Route of Administration: Intramuscular
Drug Identification Numbers (DINs): Multiple DINs:
02354209 - 25 mg/0.25 mL
02354217 - 50 mg/0.5 mL
02354225 - 75 mg/0.75 mL
02354233 - 100 mg/1 mL
02354241 - 150 mg/1.5 mL

Therapeutic Classification: Antipsychotic agent

Non-medicinal Ingredients: Citric acid, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

Submission Type and Control Number: New Drug Submission, Control Number: 127385

Date of Submission: 2009/04/24
Date of Authorization: 2010/06/30

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2 NOTICE OF DECISION


Invega® Sustenna™ contains the medicinal ingredient paliperidone palmitate which is a long-acting injectable antipsychotic agent. Following intramuscular injection, paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the major metabolite of risperidone, an antipsychotic agent which has been authorized for treatment of schizophrenia since 1993. Similar to the parent drug risperidone, paliperidone is a strong antagonist towards dopamine Type 2 and serotonin Type 2 receptors.

Invega® Sustenna™ is indicated for the treatment of schizophrenia. In controlled clinical trials, Invega® Sustenna™ was found to improve the symptoms of schizophrenia.

The market authorization was based on quality, non-clinical, and clinical information submitted. The safety and efficacy of Invega® Sustenna™ were primarily evaluated in three 13-week double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for schizophrenia. Doses of Invega® Sustenna™ were given on Days 1, 8, 36, and 64, that is, at a weekly interval for the initial two doses and then every 4 weeks for maintenance. A total of 1498 patients were enrolled in the three studies, and the primary efficacy endpoint was evaluated using the Positive and Negative Syndrome Scale (PANSS). In all three studies, Invega® Sustenna™ was superior to placebo on the PANSS. Positive outcomes were also reported on the Clinical Global Impression-Severity (CGI-S) Scale. The safety profile of Invega® Sustenna™ was generally consistent with that of oral, paliperidone extended-release tablets (Invega®), currently marketed in Canada for the treatment of schizophrenia.

Invega® Sustenna™ (25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL paliperidone as paliperidone palmitate) is presented as an injectable extended-release suspension available in pre-filled syringes. For patients who have never taken oral paliperidone or oral/injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with Invega® Sustenna™. The recommended starting dose of Invega® Sustenna™ is 150 mg on treatment Day 1 and 100 mg on Day 8 (one week later), both administered in the deltoid muscle. The recommended subsequent monthly dose is 75 mg; this can be increased or decreased within the range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Following the initiation regimen, monthly doses can be administered in either the deltoid or gluteal muscle. Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release
characteristics of Invega® Sustenna™ should be considered, as the full effect of the dose adjustment may not be evident for several months. Dosing guidelines are available in the Product Monograph.

Invega® Sustenna™ is contraindicated in patients who are hypersensitive to paliperidone, risperidone, or to any ingredient in the formulation or component of the container.

A Black Box Warning in the Product Monograph states that Invega® Sustenna™ is not indicated in elderly patients with dementia. Invega® Sustenna™ should be administered under the conditions stated in the Product Monograph taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Invega® Sustenna™ are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Invega® Sustenna™ is favourable for the treatment of schizophrenia.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

Paliperidone palmitate, the medicinal ingredient of Invega® Sustenna™ is an antipsychotic agent indicated for the treatment of schizophrenia. The drug’s therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 and serotonin Type 2 receptor antagonism.

Manufacturing Process and Process Controls

The drug substance is synthetically derived.

The manufacturing process is considered to be adequately controlled within justified limits.
Characterization

The structure of paliperidone palmitate has been adequately elucidated and the representative spectra have been provided. Confirmation of the chemical structure was provided by elemental analysis and spectroscopic analysis.

Impurities and degradation products arising from manufacturing and/or storage were reported and characterized. These products were found to be within International Conference on Harmonisation (ICH) established limits and/or were qualified from toxicological studies and therefore are considered acceptable.

Control of Drug Substance

Copies of the analytical methods and, where appropriate, validation reports were provided and are considered satisfactory for all analytical procedures used for release and stability testing of paliperidone palmitate.

The specifications are considered acceptable for the drug substance. Data from the batch analyses were reviewed and are within the proposed acceptance criteria.

The proposed packaging components are considered acceptable.

Stability

Stability study results based on accelerated, long-term, and stress testing show that paliperidone palmitate is a stable compound when packaged as proposed over the proposed storage period.

3.1.2 Drug Product

Description and Composition

Invega® Sustenna™ (paliperidone palmitate) is an extended-release suspension available in pre-filled syringes as a white to off-white sterile aqueous suspension for intramuscular injection in dose strengths of 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, or 150 mg/1.5 mL paliperidone (as 39, 78, 117, 156 or 234 mg of paliperidone palmitate respectively). The product is supplied as a kit and contains a pre-filled syringe and two safety needles, a 1½-inch 22-gauge safety needle, and a 1-inch 23-gauge safety needle. The pre-filled syringes are for single-use only.
The non-medicinal ingredients in Invega® Sustenna™ are citric acid, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations. The compatibility of paliperidone palmitate with the excipients is demonstrated by the stability data presented on the proposed commercial formulation.

**Pharmaceutical Development**

Changes to the manufacturing process and formulation made throughout the pharmaceutical development are considered acceptable upon review.

**Manufacturing Process and Process Controls**

The method of manufacturing is considered acceptable and the process is considered adequately controlled within justified limits.

**Control of Drug Product**

Invega® Sustenna™ is tested to verify that its identity, appearance, content uniformity, assay, pH, particle size distribution, release rate, sterility, and levels of particulate matter, bacterial endotoxins, degradation products and impurities are within acceptance criteria. The test specifications and analytical methods are considered acceptable.

Validation reports submitted for all analytical procedures used for in-process and release testing of the drug product are considered satisfactory.

Data from final batch analyses were reviewed and are considered to be acceptable according to the specifications of the drug product.

**Stability**

Based on the long-term, accelerated, and stress stability data submitted, the proposed 24-month shelf-life at 15-30°C for Invega® Sustenna™ is considered acceptable when stored in its original package.

The container closure system met all validation test acceptance criteria.
3.1.3 Facilities and Equipment

The design, operations, and controls of the facilities and equipment that are involved in the production of Invega® Sustenna™ are considered suitable for the activities and products manufactured.

All of the proposed manufacturing sites comply with the requirements of Division 2 of the Food and Drug Regulations.

3.1.4 Adventitious Agents Safety Evaluation

Not applicable. The excipients used in the drug product formulation are not from animal or human origin.

3.1.5 Conclusion

The Chemistry and Manufacturing information submitted for Invega® Sustenna™ has demonstrated that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted and adequate controls are in place for the commercial processes.

3.2 Non-clinical Basis for Decision

3.2.1 Pharmacodynamics

Paliperidone palmitate is a prodrug of paliperidone (9-hydroxy-risperidone) formulated as an aqueous nanosuspension with long-acting properties for intramuscular (i.m.) administration. Paliperidone is the active metabolite of risperidone, which is a widely used atypical antipsychotic drug approved for the treatment of schizophrenia and other psychiatric disorders. Paliperidone and risperidone have similar pharmacological profiles. Similar to the parent drug risperidone, paliperidone is a strong antagonist towards dopamine Type 2 and serotonin Type 2 receptors. Paliperidone is also active as an antagonist at α1- and α2- adrenergic receptors and H1-histaminergic receptors.
3.2.2 Pharmacokinetics

The principle underlying the prolonged release of the paliperidone palmitate formulation is the very low aqueous solubility of the prodrug paliperidone palmitate. The slow dissolution of the prodrug and subsequent hydrolysis provide a prolonged release of paliperidone to the systemic circulation.

A cursory review of the submitted Level A In Vitro-In Vivo Correlation (IVIVC) model for Invega\(^\text{R}\) Sustenna\(^\text{TM}\) prolonged-release suspension for injection was conducted. The model was based on comparative bioavailability data and in vitro release data for three paliperidone palmitate formulations with different release rates. The IVIVC met the criteria for acceptable predictability on internal validation, based on median area under the curve (AUC) and maximum plasma concentration (C\(_{\text{max}}\)) values. The IVIVC is considered to be acceptable for the purpose of setting in vitro release specifications. Batches within the proposed upper and lower limit in vitro release specifications are expected to be bioequivalent based on the predicted difference in pharmacokinetic (PK) parameters.

In laboratory animals and humans, paliperidone palmitate is converted to paliperidone, with minimal systemic exposure to paliperidone palmitate. The PK characteristics of systemically available paliperidone have been adequately evaluated during the development of oral paliperidone (Invega\(^\text{R}\)). For additional information see the Summary Basis of Decision for Invega\(^\text{R}\). For Invega\(^\text{R}\) Sustenna\(^\text{TM}\), the emphasis of the non-clinical PK development program was to study the processes occurring between the i.m. injection of paliperidone palmitate as an aqueous nanosuspension and the appearance of paliperidone in the systemic circulation. Specifically, the following areas of the non-clinical PK of paliperidone palmitate were investigated: (i) PK characterization of the release profile of the paliperidone palmitate formulations through PK studies in various species, (ii) description of the disposition of paliperidone palmitate and paliperidone at the injection site following i.m. administration, and (iii) characterization of the hydrolysis step that results in the release of paliperidone from the prodrug.

Paliperidone showed a high bioavailability after i.m. dosing of the prodrug. The PK profile of paliperidone after i.m. or intralipomatous (i.l.) administration was similar, but paliperidone plasma concentrations after i.l. dosing were on average 28% lower as compared to i.m. administration. An intravenous (i.v.) administration of paliperidone palmitate, did not produce an immediate release of paliperidone, but resulted in measurable paliperidone plasma concentrations for a period of 9-41 days.
The disposition of paliperidone palmitate was studied in rats using the formulation intended for marketing. The fraction of paliperidone palmitate in plasma was up to 2.9 to 6.7% of the paliperidone plasma concentration. A study in which male rats received both radiolabelled paliperidone palmitate and paliperidone 3H-palmitate showed that an agglomerate of paliperidone palmitate nanoparticles formed in the muscle after i.m. injection. This agglomerate served as the depot from which the drug substance was released. The muscle was identified as the first site of hydrolysis. The inside core of the agglomerate did not show hydrolysis, whereas hydrolysis was observed in the muscle tissue surrounding the depot.

In vitro incubations showed that the liver and blood played a significant role in the hydrolysis of paliperidone palmitate. Serine esterases appeared to be the main enzymes involved in the hydrolysis of paliperidone palmitate, but a possible role of other esterases in the hydrolysis cannot be ruled out. There was no involvement of oxidoreductase enzymes (cytochrome P450 enzymes) in the hydrolysis.

Highest paliperidone concentrations were found at the injection site muscle, with the highest tissue-to-plasma (T/P) ratio of up to 489. The T/P ratios in the kidneys, lymph nodes, lungs, and liver were on average 6. Concentrations in the brain and in non-injected muscle were similar to the plasma concentrations.

### 3.2.3 Toxicology

Paliperidone palmitate is a long acting i.m. injectable prodrug of paliperidone. In humans as well as in laboratory animals, i.m. injected paliperidone palmitate was converted to paliperidone with minimal systemic exposure to paliperidone palmitate. Paliperidone was previously tested in an extensive series of toxicity experiments including single-and repeat-dose toxicity studies, genotoxicity studies, and reproductive and developmental toxicity studies focusing on the safety assessment of the oral route of administration of paliperidone. A 12-month repeat-dose toxicity study in dogs, and mouse and rat carcinogenicity studies were not conducted with paliperidone, but bridged to those previously conducted with oral risperidone in support of various Risperdal® (risperidone) formulations. These studies on paliperidone and risperidone were all submitted previously to support the clinical use of paliperidone extended-release tablets (Invega®).

A series of studies using i.m. injected paliperidone palmitate were conducted to study local tolerance at the i.m injection site. The toxicity program included single-dose toxicity studies in dogs, pigs, and minipigs; repeat-dose toxicity studies up to 6 months in
rats, 12 months in dogs, and 3 months in minipigs; *in vitro* genotoxicity assays; a rat carcinogenicity study; and a rat embryo-foetal developmental toxicity study.

**Single-Dose and Repeat-Dose Toxicity**

Single-dose toxicity studies were conducted in dogs and pigs in order to evaluate the local tolerance of various experimental formulations of paliperidone palmitate at the i.m. injection site. The doses tested in dogs were approximately 1-16 fold the maximum recommended human dose (MRHD), whereas in pigs, they were approximately 2-32 fold the MRHD. Injection site lesions were seen at all dose levels and in all of the animal species tested. This poor injection site tolerability does not translate to humans.

In the repeat dose-toxicity studies with i.m injected paliperidone palmitate, sedation, ptosis, body-weight changes, elevated levels of serum prolactin (PRL), and PRL-mediated tissue responses were observed. Sedation was most prominent on the first day of administration. Sedation and ptosis are considered to result from the exaggerated central dopamine D2-receptor antagonism of paliperidone, further potentiated by its $\alpha_1$-adrenergic receptor antagonism.

**Genotoxicity**

Paliperidone palmitate was not genotoxic in an Ames reverse mutation test and in an *in vitro* mouse lymphoma assay. An *in vivo* genotoxicity test was not conducted with paliperidone palmitate. This test was bridged to the test previously conducted *in vivo*, a rat micronucleus test with oral paliperidone which was not genotoxic.

**Carcinogenicity**

Carcinogenicity studies conducted with risperidone in mice and rats showed treatment-related tumour findings in the mammary gland, endocrine pancreas, and pituitary gland.

A rat carcinogenicity study with i.m. injected paliperidone palmitate was conducted to assess potential tumour formation at the i.m. injection site. The highest dose level had a systemic drug exposure of 2.2-fold and 3.1-fold higher than the MRHD, in male and female rats, respectively. Tumour responses were not reported at the injection sites or any peripheral tissue, except for the mammary glands. These mammary gland tumours are considered to be related to the enhanced PRL release. The human relevance of these non-genotoxic PRL-mediated tumours is considered minimal.
Reproductive and Developmental Toxicity

Oral paliperidone was tested in male and female fertility studies in rats, embryo-foetal developmental toxicity studies in rats and rabbits, and a pre-and post-natal developmental toxicity study in rats. Except for the embryo-foetal developmental toxicity study in rats, reproductive and toxicity studies were not conducted with paliperidone palmitate. These studies were bridged to those conducted previously with oral paliperidone.

In the embryo-foetal developmental toxicity study in rats, the highest dose provided a systemic exposure of approximately 4-fold higher than that achieved in humans at the MRHD. Maternal toxicity was evident at the medium and high dose as judged by a decrease in body weight gain, a loss of body weight, and reduced food consumption. Pregnancy parameters were not affected by the treatment, and no treatment-related effects on the foetuses were found.

3.2.4 Conclusion

The non-clinical studies for this new drug submission (NDS) are considered suitable. Paliperidone palmitate is the palmitate ester of paliperidone, and paliperidone is the drug substance in the authorized drug product Invega®. The pharmacological and toxicity profile of paliperidone has been adequately characterized and was evaluated in the Invega® NDS. Adequate statements are in place in the Invega® Sustenna™ Product Monograph to address the identified safety concerns. There are no pharmacological/toxicological issues within the submission which preclude approval of the requested product indication.

3.3 Clinical Basis for Decision

3.3.1 Pharmacodynamics

Paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the active metabolite of risperidone. As with other antipsychotic agents, both risperidone and paliperidone exert antipsychotic effects by blocking dopamine Type 2 receptors. In addition to dopamine D2 antagonist activity, paliperidone has also demonstrated predominant serotonergic 5-HT2A antagonistic activity, and is also active as an antagonist at α1 and α2 adrenergic receptors with lower affinity for H1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β1- and β2-adrenergic receptors. The pharmacological activity of the (+) - and (-) - paliperidone enantiomers are qualitatively and quantitatively similar.
3.3.2 Pharmacokinetics

Paliperidone palmitate is injected intramuscularly as an aqueous suspension. It is the extremely low solubility of paliperidone palmitate that allows formulation of this compound as a long-acting product. Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after i.m. injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation.

Absorption

Following a single i.m. dose of paliperidone palmitate, the plasma concentrations of paliperidone gradually reached $C_{\text{max}}$ at 13 days. The release of the drug started as early as Day 1 and lasted for as long as 126 days.

Following i.m. injection of single doses (25 mg - 150 mg) in the deltoid muscle, on average, a 28% higher $C_{\text{max}}$ was observed compared to an i.m. injection in the gluteal muscle. The two initial deltoid i.m. injections of 150 mg on Day 1 and 100 mg on Day 8 helped attain therapeutic concentrations rapidly.

The systemic exposure of paliperidone was on average slightly higher following a deltoid injection of paliperidone palmitate compared to a gluteal injection. The AUC levels for paliperidone following paliperidone palmitate administration was dose-proportional over a 25 mg - 150 mg dose range, and the $C_{\text{max}}$ levels were less than dose-proportional for doses exceeding 50 mg. The mean steady-state peak/trough ratio for a paliperidone palmitate dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent half-life of paliperidone following paliperidone palmitate administration increased over the dose range of 25 mg-150 mg from 25-49 days.

Distribution

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

The ester hydrolysis of paliperidone palmitate to paliperidone and palmitic acid has been studied only in vitro. The involvement of serine esterases in the hydrolysis of paliperidone palmitate was demonstrated, but a possible role of other esterases cannot be
ruled out. However, there was no involvement of cytochrome P450 (CYP) enzymes in the hydrolysis. The extent of hydrolysis \textit{in vitro} was highest in human liver fractions, and moderate in human muscle and kidney fractions. Only a limited fraction of paliperidone palmitate was hydrolyzed in human blood. Hydrolysis was negligible and often undetectable in healthy plasma samples.

In the drug submission for Invega\textsuperscript{*} extended-release tablets, it was reported that oral paliperidone was metabolized to a very limited extent in human liver matrices with possible involvement of CYP3A4 and CYP2D6, but not CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. Clinical studies showed that the cumulative urinary excretion of unchanged paliperidone amounted to 59%.

**Drug Interactions**

No CYP450 inhibition studies were performed with paliperidone palmitate given the low systemic exposure to paliperidone palmitate. Furthermore, as the incidence and the extent of the systemic exposure are so low, no systemic drug-drug interactions are expected.

The assessment of potential drug-drug interactions with paliperidone was submitted previously and information on this topic is contained in the Product Monograph.

**Special Population and Conditions**

**Geriatrics**
Paliperidone clearance is reduced with lower creatinine clearance. While no dosage adjustment is necessary based on age, dose reductions may be required because of age-related decreases in creatinine clearance.

**Renal Impairment**
Based on a limited number of observations with paliperidone palmitate in subjects with mild renal impairment as well as PK simulations, dose reductions may be required in patients with reduced renal clearance.

**3.3.3 Clinical Efficacy**

The efficacy of Invega\textsuperscript{®} Sustenna\textsuperscript{™} in the treatment of schizophrenia was primarily assessed in three Phase III, 13-week double-blind, randomized, placebo-controlled, fixed-dose studies (PSY 3003, 3004, and 3007) of acutely relapsed adult patients who met the DSM-IV criteria for schizophrenia. Doses of Invega\textsuperscript{®} Sustenna\textsuperscript{™} (25 mg/4 weeks to
150 mg/4 weeks) were given on Days 1, 8, 36, and 64, that is (i.e.) at a weekly interval for the initial two doses and then every 4 weeks for maintenance. A total of 1558 patients were enrolled in these three studies, of whom 1499 were included in the primary efficacy analysis, and the primary efficacy endpoint was evaluated using PANSS. In all three studies, Invega® Sustenna™ was superior to placebo in improving the PANSS total score. Positive outcomes were also reported on the CGI-S Scale.

Other efficacy studies included a 9-week randomized placebo-controlled double-blind Phase II/III clinical study (SCH-201) and a standard relapse prevention study (PSY-3001). These studies provided additional support for the efficacy of Invega® Sustenna™ in treatment of schizophrenia.

An additional efficacy study (Study 3005) was undertaken following results of a Phase I PK study that found that the C_{max} values of paliperidone were approximately 50% higher after deltoid administration compared with gluteal administration, although total drug exposure was comparable between the two sites. In Study 3005, steady-state blood levels for paliperidone were achieved earlier, when treatment was initiated using the deltoid site rather than the gluteal site.

The three acute Phase II/III studies (SCH-201, PSY-3003, and PSY-3004) showed evidence of a positive dose-response effect across the studied dosage range. The studies also indicated a high body mass index (BMI) associated with lower initial paliperidone plasma concentrations and less robust treatment response compared with normal BMI. In the longer duration Study PSY-3001 similar treatment efficacy was observed across all BMI categories. These results suggest that BMI does not affect efficacy once therapeutic plasma concentrations have been achieved.

Based on Phase I PK studies, PK data from Phase III studies, and PK modelling, the sponsor provided support for specific injection and dosing procedures, based on BMI and injection site, i.e. the use of a 1½-inch 22-gauge needle for patients ≥90 kg or 1-inch 23-gauge needle for patients <90 kg for deltoid injection, and a 1½-inch 22-gauge needle for gluteal injection regardless of patient weight.

In addition, use of a deltoid loading dose of 150 mg dose at Day 1 and a 100 mg dose at Day 8, was helpful in rapidly achieving therapeutic blood levels. This strategy also minimizes BMI effects once the monthly target dose is started. The utility and tolerability of this dosing strategy was confirmed in the Phase III Study PSY-3007. PK data and modelling shows that for the low end of the target maintenance dose range (i.e. 25 mg monthly), the loading dose somewhat ‘overshoots’ the steady-state concentration. Thus at these low maintenance doses, blood levels will decline somewhat over time until the
corresponding steady-state level is reached. Conversely at the highest recommended target maintenance dose (i.e. 150 mg monthly) the loading dose is not quite sufficient to achieve steady state, and thus blood levels gradually increase over time following the initial injections until the steady-state level is reached.

### 3.3.4 Clinical Safety

The combined cumulative exposure to Invega® Sustenna™ in all of the completed Phase II/III studies submitted for this New Drug Submission (NDS) was 1375.53 patient-years, based on 2770 who received at least one dose in the seven completed Phase II/III clinical studies included in the clinical program. In addition, 730 subjects received at least one dose of Invega® Sustenna™ in the ten completed Phase I studies. Current safety updates including studies completed since the submission of the NDS bring the total number of subjects treated with Invega® Sustenna™ in clinical studies to 4547. Among subjects who received Invega® Sustenna™ in studies completed at the time of NDS submission, 753 subjects received at least 28 weeks of exposure to Invega® Sustenna™, and 536 subjects received at least 52 weeks. Almost all of this exposure was at doses of 50 mg or higher.

With the exception of local adverse drug reactions related to the i.m. route of drug administration, the safety profile of Invega® Sustenna™ including the type and incidence of adverse events was generally consistent with that of oral paliperidone extended-release tablets, currently marketed in Canada as Invega®. For more information, see the Summary Basis of Decision for Invega®.

Although some individual PK profiles of paliperidone palmitate suggest a low incidence of inadvertent intravascular or partial intravascular administration of paliperidone palmitate, this was not associated with any serious or severe adverse events, likely because paliperidone palmitate is not pharmacologically active and paliperidone is not rapidly released even if paliperidone palmitate gets into the blood.

Injection site reactions with Invega® Sustenna™ were comparable to i.m. risperidone (Risperdal® Consta®). Moderate or severe injection site pain with Invega® Sustenna™ was reported in only isolated cases, and there were no injection site-related adverse events that were serious. Only four subjects in the clinical trial program discontinued treatment due to injection site-related adverse events, and only four subjects experienced injection site pain that was assessed as severe in intensity. Injection site reactions tended to be
more frequent with deltoid compared to gluteal injections, but when injection site reactions did occur, they tended to be mild. Overall Invega® Sustenna™ was well-tolerated.

### 3.4 Benefit/Risk Assessment and Recommendation

#### 3.4.1 Benefit/Risk Assessment

The efficacy of Invega® Sustenna™ with monthly i.m. doses (following two initial doses one week apart) in the treatment of symptoms of schizophrenia is well-supported by the submitted clinical trial program. Paliperidone is the active metabolite of risperidone. As such it avoids one metabolic step mediated by CYP 2D6, and thus has a reduced risk of drug-drug interactions related to this CYP iso-enzyme as compared to risperidone. The safety profiles of oral risperidone (Risperdal®) and oral paliperidone (Invega®) as well as long-acting i.m. risperidone (Risperdal® Consta®) are well-established in clinical use.

Invega® Sustenna™ offers some advantages compared to some other existing treatments. Invega® Sustenna™ provides a once-monthly treatment for schizophrenia, for those individuals where compliance with daily oral dosing is problematic. In addition, the use of thinner needles for injection of Invega® Sustenna™ compared to some other long-acting injectable antipsychotic medications may be better tolerated by patients. Currently the only second-generation antipsychotic drug marketed in a long-acting injectable form is Risperdal® Consta®, which requires once every-two-week dosing. In addition, the latter drug has a much-delayed onset of action (i.e., drug release only starts three weeks after the injection). This means that patients require oral supplementation for three weeks after the initial injection. In contrast, following an injection of Invega® Sustenna™, peak blood levels are reached within two weeks following the injection.

With the exception of local adverse drug reactions related to the i.m. route of drug administration, the safety profile of paliperidone palmitate (at doses of 25-150 mg) including the type and incidence of adverse events, was generally consistent with that of oral paliperidone extended-release tablets (Invega®), and with that of Risperdal® Consta®. Injection-site reactions tended to be more frequent with deltoid injections compared to gluteal injections; but, when injection site reactions did occur, they were usually mild. Overall, Invega® Sustenna™ was well-tolerated within the dose range of 25-150 mg i.m. given monthly following two initiation doses one week apart.
Based on the safety and efficacy profile, the benefits of Invega® Sustenna™ therapy seem to outweigh the risks. Invega® Sustenna™ shows a favourable risk-benefit profile.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Invega® Sustenna™ is favourable in the treatment of schizophrenia. The NDS complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance (NOC) pursuant to section C.08.004 of the Food and Drug Regulations.

4 SUBMISSION MILESTONES

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