

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207946Orig1s000

PHARMACOLOGY REVIEW(S)

SUPERVISORY MEMORANDUM

NDA# 207946
Supporting Document(s): SDN 1, Sequence 0000
Drug: Invega Trinza (Paliperidone palmitate extended release injectable suspension)
Sponsor: Janssen Pharmaceuticals
Indication: Treatment of schizophrenia
Division: Psychiatry Products
Reviewer: Elzbieta Chalecka-Franaszek, Ph.D.
Team Leader: Aisar Atrakchi, Ph.D.
Date: April 28, 2015

Paliperidone palmitate 3-month extended release injectable suspension is the subject drug of NDA 207946 it is the palmitate ester of paliperidone and is hydrolyzed to paliperidone. Paliperidone is the pharmacologically active metabolite of risperidone the latter was approved for the treatment of schizophrenia in 1993.

Paliperidone, Invega (NDA 21999 and 22043), was approved in 2006 as extended release oral tablets. Paliperidone palmitate, Invega Sustenna (NDA 22264), was approved in 2009 as a once monthly extended release injectable suspension for intramuscular (im), use.

The mechanism of action of paliperidone in schizophrenia is unknown. Paliperidone is a selective dopamine D2 and serotonin 5HT_{2A} antagonist of the “atypical” (second generation) antipsychotic drugs.

Paliperidone palmitate 3-month injectable suspension (PP3M), contains the same API and excipients as well as (b) (4) as the previously approved paliperidone palmitate 1-month injectable suspension (PP1M), Invega Sustenna. The difference between the 2 formulations is (b) (4)

Based on the similarities between the approved and current formulation, limited nonclinical toxicology studies were needed as agreed to between the Division and the sponsor (regulatory history/meetings; pre-IND (2007), EOP2/pre-Phase3 (2011), and pre-NDA (2014)). Therefore, for this current application only 2 local tolerability studies in the minipig were conducted to determine the potential adverse effects of the higher concentration of the drug in the 3-month injectable suspension as compared to the 1-month formulation.

Dr. Chalecka-Franaszek reviewed the above 2 nonclinical studies and she concluded that there are no nonclinical concerns that would affect approval of this drug application. She recommended new text to be included in section 13.2 of the label describing adverse reactions at the site of injection that were more advanced than those observed with the 1-month injectable suspension. I agree with her conclusion and to include this information in the label. Dr. Chalecka-Franaszek also recommended updating the DMF to limit the level of two mutagenic impurities: (b) (4) and (b) (4) to not more than (b) (4) ug per injection or (b) (4) ppm in the maximum recommended human dose (MRHD), of 819 mg paliperidone palmitate. I disagree with this assessment and this memo provides explanation.

The above 2 mutagenic impurities are not new to the API they are present and have been previously identified in the approved paliperidone palmitate 1-month injectable suspension drug substance and their level is limited in the drug substance to the appropriate specification. At that time the recommended limit of (b) (4) ug was based on the CDER draft guidance of 2008: “Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches”. As of June 2014 ICH M7 has been published: “Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential of carcinogenic risk” and is the current guidance to be followed for assessing and determining limits for mutagenic impurities. These are impurities that test positive in the bacterial Ames mutation assay of which the above impurities were shown to be positive. Section 7.3 in M7 “Acceptable intakes in relation to LTL (less than lifetime), Exposure” discusses the approach to LTL exposure to mutagenic impurities in pharmaceuticals in which the cumulative lifetime dose (1.5 ug/day x 25,550 days = 38.3 mg), is uniformly distributed over the total number of exposure days during the LTL exposure. Such approach allow higher “daily” intake of mutagenic impurity than would be the case for lifetime exposure but still maintain comparable cancer risk (1 in 100,000), for daily and non-daily dosing regimens. The text continues to state:

“In the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses were administered and that number of dosing days should be related to the relevant duration category in Table 2. For example, a drug administered once per week for 2 years (i.e., 104 dosing days) would have an acceptable intake per dose of 20µg.”

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

The LTL calculation is based on Haber’s principle in toxicology where the carcinogenic risk is based on both dose and duration of exposure (Note 6, Figure 1 below):

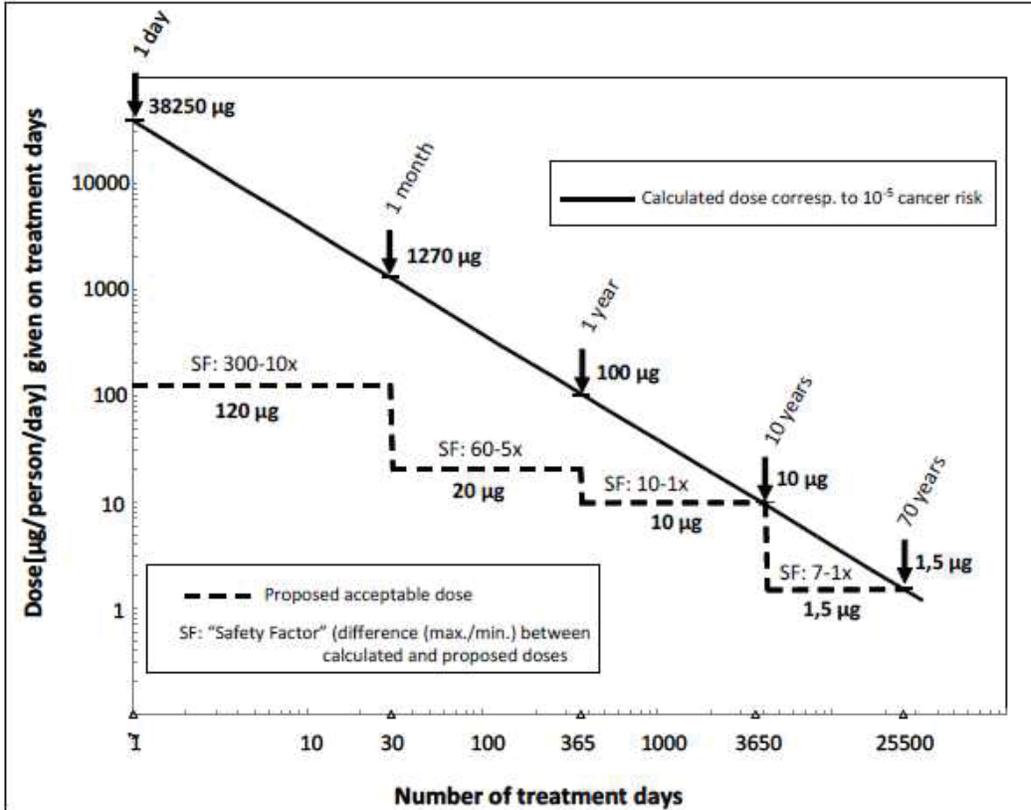


Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels as recommended in Section 7.3.

Based on the above approach, paliperidone palmitate administered once every 3 months will have 280 dosing days over 70 years (lifetime), (b) (4). The maximum recommended human dose of paliperidone palmitate 3-month is 819 mg therefore, the impurity limit will be:

(b) (4)

Dr. Chalecka-Franaszek did not take into consideration the once every 3 month administration but rather (b) (4) “daily” administration over a lifetime dosing therefore, the impurity limit she calculates is:

(b) (4)

Dr. Chalecka-Franaszek made the above calculation assuming that the 819 mg is administered daily for 70 yrs hence applied the (b) (4) ug impurity limit (b) (4)

She also states in her review that M7 does not specifically discuss depot formulations; section 7.5 in M7 states: “The above risk approaches described in Section 7 are applicable to all routes of administration and no corrections to acceptable intakes are generally warranted..... These approaches are also applicable to all patient populations based upon the conservative nature of the risk approaches being applied.”

I asked Dr. Imran Khan a pharm/tox reviewer on my team to assist in the NDA review during the extended leave of Dr. Chalecka-Franaszek. His task was to evaluate the information on these 2 genotoxic impurities (see Dr. Khan review for detail, April 28, 2015). Following several communications (emails) with the reviewing chemist Dr. Monica Cooper, Dr. Khan calculated the limit to be the same as above of (b) (4) ppm for each of the genotoxic impurities based on LTL approach in M7*.

Moreover, it is noted that in a DMF Amendment dated April 23rd 2014, the DMF holder justified removal of genotoxic testing in the drug substance (at batch release) based on a total of 180 commercial lots showing (b) (4) ppm for the sum of genotoxic impurities. So they are currently not testing each drug substance batch for these genotoxic impurities (as stated in email from Dr. Cooper, dated February 26, 2015). The chemist communicated to the sponsor in an information request dated March 16, 2015 (DMF 20902), that if or when any change occurs in the manufacturing method where testing for these mutagenic impurities is required, their limit should be kept at not more than (b) (4) ppm*. Additionally, (b) (4) therefore, a single limit value may be used and the more conservative is the one calculated for the highest dose i.e. the 3-month formulation, which is (b) (4) ppm.

* Dr. Imran earlier used the MRHD expressed as 525 mg Eq in calculating the impurity limit. This resulted in a limit of (b) (4) ppm and this limit was included in the letter sent to the DMF holder. The more appropriate calculation should be based on the drug substance in mg dose therefore, his final review reflects the limit of (b) (4) ppm which is calculated based on 819 mg MRHD of paliperidone palmitate. Consequently, the letter sent to the DMF will need to be updated to reflect the (b) (4) ppm limit.

Conclusion and Recommendation:

This memo addresses the difference in the calculation and recommendation for the limit of the 2 genotoxic impurities, (b) (4) and (b) (4) in drug substance from those in Dr. Chalecka-Franaszek's review. My calculations are based on the recommendations in ICH M7 (June, 2014) using the LTL approach for paliperidone palmitate administered once every 3 months over the lifetime of a patient (70 yrs) with the same cancer risk of 1 in 100,000 cases. It is also noted that these 2 impurities have not been detected in the drug substance (combined impurities (b) (4) ppm), in a total of 180 lots tested to date. These 2 impurities have also been qualified previously in toxicology studies including the 2 yr carcinogenicity conducted with the 1-month paliperidone injectable suspension.

My recommendations are as follows:

- The limits for the 2 genotoxic impurities (b) (4) and (b) (4) in paliperidone palmitate drug substance are to be set at not more than (b) (4) ppm for each impurity based on LTL approach in ICH M7 guideline (2014).
- The DMF holder has set a limit of (b) (4) ppm for these impurities. The DMF holder has the option of maintaining this limit especially since the sponsor has been able to keep the combined impurity limit to (b) (4) ppm and this limit of (b) (4) ppm was recommended by the Division previously for the paliperidone palmitate 1-month injectable suspension based on the draft guidance of 2008 on genotoxic impurities. Alternatively, the DMF holder set the limit to the (b) (4) ppm which is calculated based on the LTL approach in ICH M7 (2014).
- I disagree with Dr. Chalecka-Franaszek's calculation that used the (b) (4) ug limit applicable to genotoxic impurities in pharmaceuticals administered daily over a lifetime. The correct approach based on M7 is to use the LTL approach for pharmaceuticals administered intermittently over lifetime. M7 assessment is very conservative since it considers the worst case scenario of dose dumping and tumor incidence in the most sensitive sex and species while maintaining the cancer risk of 1 in 100,000 cases.

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/s/

AISAR H ATRAKCHI
04/28/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207946
Supporting document/s: SDN 1, Sequence 0000
Applicant's letter date: November 18, 2014
CDER stamp date: November 18, 2014
Product: INVEGA TRINZA™ (paliperidone palmitate 3-month extended-release injectable suspension)
Indication: Treatment of schizophrenia in patients who have been adequately treated with the paliperidone palmitate 1-month extended-release injectable suspension for at least four months
Applicant: Janssen Pharmaceuticals, Inc.
Review Division: Division of Psychiatry Products
Reviewer: Imran M. Khan, Ph.D.
Supervisor/Team Leader: Aisar Atrakchi, Ph.D.
Division Director: Mitchell Mathis, M.D.
Project Manager: Ann Sohn, Pharm. D.

This reviewer was asked to review the levels of the two genotoxic impurities (GTIs) (b) (4) and (b) (4) that could be present in the synthetic batches of paliperidone palmitate as the assigned reviewer of the NDA 207946, Dr. Chalecka-Franaszek, was on extended leave. In the NDA 207946, paliperidone palmitate is formulated as an aqueous suspension (F015) for extended release of paliperidone for the once every 3 months IM injection. The dose of paliperidone palmitate for the IM depot injection is 819 mg (525 mg R076477 eq/3-month).

Dr. Chalecka-Franaszek already addressed these two GTIs ((b) (4) and (b) (4)) in the pharmacology/toxicology reviews of the NDA 22264 dated August 25, 2008 and its

resubmission dated June 18, 2009. In the review, the following recommendations were conveyed to the Sponsor: “Revise the drug substance specification to include a limit of NMT (b) (4) ppm for potential genotoxic impurities (b) (4) and (b) (4) and their respective palmitate (b) (4)”. Accordingly, recently sponsor indicated that they are able to limit amounts of (b) (4) and (b) (4) to essentially undetectable amounts ((b) (4) ppm) in the manufacturing of paliperidone palmitate.

In the recent submission, the sponsor indicated that using the (b) (4) procedure, the sponsor is able to limit the levels of genotoxic impurities (b) (4) and (b) (4) to (b) (4) ppm and (b) (4) ppm, respectively in “crude” batches of paliperidone palmitate. Also, in the present NDA submission, in light of the ICH M7 guideline published in 2014, the sponsor proposed a concentration limit for each of the two above GTIs in the final paliperidone palmitate drug substance for a maximum dose of 525 mg R076477 eq./3 months at (b) (4) ppm. Although this reviewer agrees with the sponsor that the once every 3 months IM injection of paliperidone palmitate could be considered as intermittent dosing regimen and accordingly the acceptable limit of 20 ug for GTIs in LTL (less than life time) exposures as recommended in Table 2 of ICH M7 guidance could be applied, this reviewer points out that the sponsor’s calculation of the concentration limit is not correct and accordingly the numbers they derived for the specific dose are inaccurate.

According to ICH M7, in the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses are administered and that number of dosing days should be related to the relevant duration category (as shown in Table 2 below). (b) (4)

(b) (4)

(b) (4)

(b) (4)

Based on the above information, this reviewer recommends a limit of (b) (4) ppm for each of the impurities for the 819 mg paliperidone palmitate (525 mg R076477 eq.)/3 months dose formulation.

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

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/s/

IMRAN M KHAN
04/28/2015

AISAR H ATRAKCHI
04/28/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Indication: Treatment of schizophrenia in patients who have been adequately treated with the paliperidone palmitate 1-month extended-release injectable suspension for at least four months
Applicant: Janssen Pharmaceuticals, Inc.
Review Division: Division of Psychiatry Products
Reviewer: Elzbieta Chalecka-Franaszek, Ph.D.
Supervisor/Team Leader: Aisar Atrakchi, Ph.D.
Division Director: Mitchell Mathis, M.D.
Project Manager: Ann Sohn, Pharm. D.

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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION	5
2.1	DRUG	5
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs	6
2.3	DRUG FORMULATION	6
2.4	COMMENTS ON NOVEL EXIPIENTS	7
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	8
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	13
2.7	REGULATORY BACKGROUND	14
3	STUDIES SUBMITTED.....	14
3.1	STUDIES REVIEWED.....	14
3.2	STUDIES NOT REVIEWED	14
3.3	PREVIOUS REVIEWS REFERENCED.....	14
4	PHARMACOLOGY	14
4.1	PRIMARY PHARMACOLOGY	14
4.2	SECONDARY PHARMACOLOGY	15
4.3	SAFETY PHARMACOLOGY	15
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	15
5.1	PK/ADME.....	15
5.2	TOXICOKINETICS	15
6	GENERAL TOXICOLOGY.....	15
6.1	SINGLE-DOSE TOXICITY	15
6.2	REPEAT-DOSE TOXICITY	16
7	GENETIC TOXICOLOGY	37
8	CARCINOGENICITY	37
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	37
10	SPECIAL TOXICOLOGY STUDIES.....	37
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	37
12	APPENDIX/ATTACHMENTS	41

1 Executive Summary

1.1 Introduction

NDA 207946 is submitted by Janssen Pharmaceuticals, Inc. (the Sponsor), to support the use of the paliperidone palmitate 3-month extended-release injectable suspension for the treatment of schizophrenia in adult patients who have been adequately treated with the paliperidone palmitate 1-month extended-release injectable suspension for at least four months. The drug product is developed in four dosage strengths: 273 mg, 410 mg, 546 mg, or the maximum recommended human dose (MRHD) of 819 mg. The Sponsor has requested and was granted a priority review of this NDA.

Paliperidone palmitate is the palmitate ester of paliperidone and is hydrolyzed to paliperidone. Paliperidone (9-hydroxy-risperidone) is an active metabolite of risperidone, which has been approved for the treatment of schizophrenia in 1993. The mechanism of action of paliperidone in schizophrenia is unknown. Paliperidone is a selective, monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D₂) and serotonin [5-hydroxytryptamine (5-HT)] type 2A (5HT_{2A}) antagonism of the “atypical” (second generation) antipsychotic drugs.

Paliperidone is marketed as a prolonged release oral formulation (INVEGA® extended-release tablets) and long-acting intramuscular (IM) injectable suspension of paliperidone palmitate for 1-month dosing interval [INVEGA SUSTENNA® (PP1M, formulation F013)]. The third formulation of paliperidone palmitate for 3-month dosing interval (PP3M, formulation F015) is currently under review.

Paliperidone palmitate dissolves slowly after IM injection due to its low water solubility before being hydrolyzed to paliperidone, which is absorbed into the systemic circulation. The release of paliperidone starts as early as day 1 and lasts for as long as 18 months. Systemic exposure to paliperidone palmitate in humans and laboratory animals is minimal. Therefore, paliperidone is considered to be responsible for systemic effects following the IM injection of paliperidone palmitate.

Given the extensive nonclinical data generated with the approved paliperidone palmitate for 1-month dosing interval, nonclinical program for the paliperidone palmitate 3-month extended-release injectable suspension consists of two comparative local tolerability studies in minipigs using both the PP3M (F015) and PP1M (F013) formulations, with a cross reference back to the previous nonclinical data generated with the PP1M (NDA 22264) and the oral paliperidone (NDA 21999 and NDA 22043), as agreed upon in the pre-IND meeting of August 20, 2007.

Doses of paliperidone palmitate in nonclinical studies are expressed as mg eq./kg, referring to mg paliperidone equivalents (eq.)/kg body weight (conversion factor paliperidone to paliperidone palmitate, f = 1.56).

1.2 Brief Discussion of Nonclinical Findings

The local tolerability of the new PP3M formulation F015 was assessed and compared with the approved PP1M formulation F013 in the minipig. Since the maximum clinical dose was increased during the clinical development, the first local tolerance study (study No. TOX8249) was repeated with higher dose levels (study No. TOX10172).

The toxicological profile of both formulations observed in minipigs in the two local tolerance studies was comparable. There were no noteworthy adverse test article-related effects on survival, body weight, weight gain, food consumption, hematological and clinical chemistry parameters in either of the two studies. Adverse CNS effects, gross pathology and histopathology findings were, in general, qualitatively similar for both formulations in two studies. Similar dose-related inflammatory reactions were observed across formulations, but the cellular reaction patterns and sizes of (b) (4) material in inflammatory cells were different. Overall, the injection site reaction to the F015 formulation was greater and more advanced than that to the F013 formulation in minipigs.

The systemic exposure of minipigs to paliperidone after a single dose injection of the PP3M formulation was similar to that after 3 consecutive (once a month) dose injections of the PP1M formulation. Moreover, the systemic exposure to paliperidone generated by the PP3M administration appears to be covered by the combined nonclinical safety data from the PP1M as well as from the oral paliperidone and risperidone toxicology programs.

1.3 Recommendations

1.3.1 Approvability

The nonclinical studies submitted and referenced in support of the NDA 207946 for the paliperidone palmitate 3-month extended-release injectable suspension are sufficient to recommend approval of the application from the pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

It is recommended that the DMF be updated to limit the dose of each of the mutagenic impurities (b) (4) and (b) (4) to not more than (b) (4) µg per injection ((b) (4) ppm per injection of the maximum recommended human dose of 819 mg of paliperidone palmitate 3-month extended-release injectable suspension). This is not an approvability issue, since control of these mutagenic impurities to lower levels has already been demonstrated by the Sponsor.

It is recommended that the difference in the injection site reactions to the paliperidone palmitate 3-month extended-release injectable suspension and previously approved paliperidone palmitate 1-month extended-release injectable suspension observed in animals be described in the section 13.2 of the INVEGA TRINZA™ labeling.

1.3.3 Labeling

Sections of the labeling supported by animal data are being discussed with the Sponsor at the time of completion of this review. This document will be amended with a final version of the labeling when it becomes available.

The following new section of the labeling for the paliperidone palmitate 3-month extended-release injectable suspension is recommended by this reviewer:

13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 3-month paliperidone palmitate extended release injectable suspension at doses up to 819 mg, which is equal to the MRHD. Injection site inflammatory reactions were greater and more advanced than reactions to the 1-month paliperidone palmitate extended release injectable suspension. Reversibility of these findings was not examined.

2 Drug Information

2.1 Drug

CAS Registry Number: 1999739-10-1

Generic Name: paliperidone palmitate 3-month extended-release injectable suspension

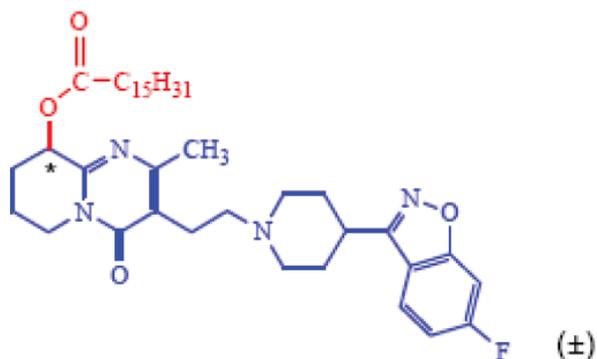
Code Name: R092670 (JNJ16977831)

Chemical Name: (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4Hpyridol[1,2-a]pyrimidin-9-ylhexadecanoate *

* hexadecanoate = palmitate.

Molecular Formula/Molecular Weight: C₃₈H₅₇N₄O₄F/664.89

Structure or Biochemical Description:



Pharmacologic Class: Atypical antipsychotic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 67356 and NDA 22264 for the paliperidone palmitate 1-month extended-release injectable suspension (INVEGA SUSTENNA[®]); IND 65850, NDA 21999 and NDA 22043 for the paliperidone extended release tablets (INVEGA[®]); DMF 20902

2.3 Drug Formulation

Paliperidone palmitate 3-month extended-release injectable suspension for repeated intramuscular injection once every three months (PP3M) contains the same API and excipients as the previously approved paliperidone palmitate 1-month extended-release injectable suspension (PP1M; INVEGA SUSTENNA[®]). (b) (4)

(b) (4)

Additionally, the maximum volume to be injected in patients is increased from 1.5 mL for the MRHD of 234 mg paliperidone palmitate (150 mg paliperidone eq.) for the PP1M formulation to 2.625 mL for the MRHD of 819 mg paliperidone palmitate (525 mg paliperidone eq.) for the PP3M formulation.

The composition of paliperidone palmitate F-015 formulation (b) (4) is provided in the following Sponsor's table:

Table 1: Composition of Paliperidone palmitate eq. (b) (4) Extended Release Suspension for Injection (F015)

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Paliperidone palmitate (R092670) (b) (4)	Company Specifications ^b	Active drug substance	(b) (4)
Polysorbate 20	NF	(b) (4)	10
Polyethylene glycol 4000	NF	(b) (4)	75
Citric acid monohydrate	USP	(b) (4)	7.5
Sodium dihydrogen phosphate monohydrate	USP	(b) (4)	(b) (4)
Sodium hydroxide	NF	(b) (4)	(b) (4)
Water for Injection	USP	(b) (4)	(b) (4)

^b Reference is made to Module 1 where the letter authorizing the FDA to access the DMF (20902) is included.

For commercial use, the paliperidone palmitate 3-month extended-release injectable suspension will be provided in a prefilled syringe. Dosage strengths ranging from 273 mg (175 mg paliperidone eq.) to the MRHD of 819 mg (525 mg paliperidone eq.) are obtained by filling the syringes with different volumes of the paliperidone palmitate (b) (4) bulk suspension.

2.4 Comments on Novel Excipients

There are no novel excipients in the paliperidone palmitate 3-month extended-release injectable suspension (F015 formulation). The same (b) (4) as used in the paliperidone palmitate 1-month extended-release injectable suspension (F013 formulation) were selected. The concentration of polysorbate 20 was lowered because (b) (4). However, the polyethylene glycol 4000 (PEG 4000) concentration was increased (b) (4)

In the F015 formulation, PEG 4000 level is 75 mg/mL (b) (4). However, the level of this excipient in the approved F013 formulation and other approved products for IM administration is less than that in the F015 formulation (30 mg/mL in the F013 formulation).

Since the maximum volume to be injected in patients is increased from 1.5 mL for the paliperidone palmitate 1-month extended-release injectable suspension to 2.625 mL for the paliperidone palmitate 3-month extended-release injectable suspension, this reviewer calculated that the highest dose of PEG 4000 administered to humans is 197 mg/dose (75 mg/mL x 2.625 mL) when the paliperidone palmitate 3-month extended-release injectable suspension is injected IM. This corresponds to a PEG 4000 dose of 3.3 mg/kg b.w. for a 60-kg person.

In the 12-week local tolerance study No. TOX10172, minipigs received 2.63 mL of F015 formulation vehicle containing 75 mg/mL PEG 4000 (i.e., 197 mg PEG 4000 or 13 mg/kg b.w. in a 15 kg minipig) by a single IM injection. Gross pathology and histopathology examinations were conducted only for the injection sites and did not show adverse findings in the vehicle control group animals injected IM with all components of the F015 formulation except the API. Based on this study, PEG 4000 is considered to be safe (qualified) for local toxicity (i.e. injection site reactions) at the proposed new levels but not for a systemic toxicity because study design did not include gross and histopathology investigations.

However, the systemic toxicity of PEG 4000 was evaluated in the 2-year rat carcinogenicity study conducted with the paliperidone palmitate 1-month extended-release injectable suspension (F013 formulation) injected IM once every 4 weeks. Animals in the vehicle control group received PEG 4000 at 18 mg/kg b.w./month (0.6 mL/kg b.w. of F013 vehicle containing 30 mg/mL PEG 4000). Both systemic and local tolerability was adequately investigated in this study, including full gross pathology and histopathology examinations. There were no relevant differences between the F013 vehicle control and saline control effects in animals. Therefore, the Sponsor's conclusion that in the rat carcinogenicity study, 0.6 mL of 30 mg/mL PEG 4000 was found to be safe both in terms of systemic and local tolerability following IM administration appears to be acceptable.

In conclusion, the level of PEG 4000 present in the paliperidone palmitate 3-month extended-release injectable suspension at concentration of 75 mg/mL is considered

tested for safety in animal studies and toxicologically qualified for systemic effects and local injection site reactions up to a dose of 18 mg/kg b.w./month when administered by an IM injection.

2.5 Comments on Impurities/Degradants of Concern

Non-mutagenic drug substance impurities:

The following six synthesis impurities are present in the paliperidone palmitate 3-month extended-release injectable suspension drug substance: (b) (4)

(b) (4) Chemical structures of paliperidone and these impurities are shown in the following Sponsor's figure:



(b) (4) These impurities have not been tested for mutagenic potential. However, they do not contain structural alerts indicative of mutagenic potential. Moreover, the fatty acid moieties are endogenous constituents of the body and normal substrates for fatty acid metabolism. Therefore, they are considered to be non-mutagenic compounds.

All five impurities are controlled in the final paliperidone palmitate 3-month extended-release injectable suspension drug substance as specified impurities with a limit of not more than (b) (4) % w/w ((b) (4) mg per impurity for the MRHD of 819 mg of the paliperidone palmitate 3-month extended release injectable suspension). These levels are higher than the impurity qualification threshold recommended by the ICH Guidance Q3A (0.15% or 1 mg per day intake, whichever is lower). The toxicological qualification of these impurities was described in the original NDA 22264 for the paliperidone palmitate 1-month extended-release injectable suspension. In this NDA 207946, the Sponsor calculated toxicological limits for these impurities for the once every 3 months dosing regimen of the paliperidone palmitate 3-month extended-release injectable suspension.

Two paliperidone palmitate batches No. ZR092670EXA002 and ZR092670EXA003 were tested in a 12-month repeat-dose IM toxicity study in Beagle dogs (study No. TOX4692) submitted to the NDA 22264. Formulation F004 was as the vehicle used in this study. Batches No. ZR092670EXA002 and ZR092670EXA003 contained the impurities (b) (4). For each impurity, the lowest concentration measured in either drug substance batch No. ZR092670EXA002 or ZR092670EXA003 was used by the Sponsor to calculate the dose levels of impurities tested at 40 mg eq./kg b.w./month, which was well tolerated dose in the 12-month dog study. Subsequently, these impurity doses were extrapolated by the Sponsor to a therapeutic dose of 525 mg eq./month or approximately 8.75 mg eq./kg b.w./month for a 60 kg patient.

The extrapolated dose levels (expressed as percentage of total drug intake) represent the concentration limits for the impurities in drug substance batches No. ZR092670EXA002 or ZR092670EXA003, as shown by the Sponsor in the following table:

Table 5: Calculations on Impurities in DS Batch nos. ZR092670EXA002 and ZR092670EXA003.

Component	Lowest concentration (% total)^a	Dose level (mg/kg/month)	Concentration limit (% total drug intake)
(b) (4)			

^aTable 3

In calculations described above, the once every 3 months rather than once monthly dosing regimen is not taken into account. According to the Sponsor, for the once every

3 months dosing regimen and the MRHD of 525 mg paliperidone eq., the toxicologically qualified concentrations of the impurities (b) (4)

This reviewer concluded that the paliperidone palmitate 3-month extended-release injectable suspension dose strength should be used for these calculations (instead of paliperidone equivalents) because tissues at the site of injection are exposed to a full dose of 819 mg of paliperidone palmitate (or approximately 13.65 mg paliperidone palmitate/kg b.w. for a 60 kg patient) for an extended period of time. When the MRHD of 819 mg paliperidone palmitate 3-month extended-release injectable suspension is considered, as recommended by this reviewer, the toxicologically qualified concentration limits, expressed as percentage of the total drug intake at the MRHD, are (b) (4)

For the once every three months dosing regimen, the toxicologically qualified concentrations of the impurities (b) (4)

These limits are less than the concentration limits for the once every three months dosing regimen calculated by the Sponsor. However, the concentration limit in the drug substance specification of not more than (b) (4) % proposed by the Sponsor is still acceptable for all five non-mutagenic impurities.

Mutagenic drug substance impurities:

Two DNA-reactive (mutagenic) impurities (b) (4) and (b) (4) are reasonably expected to reside in the paliperidone palmitate 3-month extended-release injectable suspension (PP3M) drug substance batches. Both impurities showed mutagenic activity in the in vitro Ames bacterial reverse mutation test and chromosomal aberration assay conducted in human lymphocytes. The impurities (b) (4) and (b) (4) on DNA, resulting in the formation of cross links within the DNA chain and thereby causing cytotoxic, mutagenic, and carcinogenic effects. Therefore, the levels of these impurities must be adequately controlled to limit potential carcinogenic risk.

This reviewer recommends that the DMF be updated to limit the concentration of each of the mutagenic impurities (b) (4) and (b) (4) to not more than (b) (4) µg per injection [(b) (4) ppm for the maximum recommended human dose (MRHD) of 819 mg of the paliperidone palmitate 3-month extended-release injectable suspension]. It is noted that the Sponsor is reproducibly capable of producing batches of paliperidone palmitate with undetectable ((b) (4) ppm) level of each mutagenic impurity, therefore there is no manufacturing feasibility issue.

[Reviewer's calculations are as follows: (b) (4)

Justification:

In this NDA 207946 for the paliperidone palmitate 3-month extended-release injectable suspension, based on the change in the MRHD of paliperidone palmitate to 525 mg paliperidone eq. and the once every 3 months dosing regimen, the Sponsor proposed the following limits for mutagenic impurities (b) (4) and (b) (4): (b) (4)

(b) (4)

(b) (4) see nonclinical overview of the NDA 207946). The limit of (b) (4) ppm cannot be accepted by this reviewer for the following reasons:

The Sponsor calculated acceptable intake of mutagenic impurity (b) (4)

(b) (4)

This Sponsor's approach cannot be justified. Although the ICH M7 guidance indicates that in the case of intermittent dosing the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses were administered and that number of dosing days should be related to the relevant duration category, (b) (4)

(b) (4)

Local exposure to the paliperidone palmitate and systemic exposure to paliperidone (real treatment) are constant and steady for a long period of time (three months or more).

(b) (4)

Per the ICH M7 guidance, the acceptable intake for an individual mutagenic impurity for the lifetime duration of treatment is 1.5 µg per day, (b) (4)

(b) (4)

(b) (4)

This reviewer concluded that in calculations of mutagenic impurity limits, the MRHD of 819 mg of the paliperidone palmitate 3-month suspension should be used since the tissues at the site of injection are exposed to this dose. The dose equivalents (525 mg paliperidone eq./injection), used by the Sponsor in calculation of acceptable limits, (b) (4)

(b) (4)

The risk evaluation approaches described in the ICH M7 guidance are applicable to all routes of administration. However, the guidance does not specifically discuss depot

formulations similar to that of the paliperidone palmitate 3-month extended-release injectable suspension. For clarification of the principles of the guidance, the authors provided several “*examples of clinical use scenarios with different treatment durations for applying acceptable intakes*”. According to the guidance, the intake of 20 µg/day is acceptable for treatments from 1 to 12 months in duration, for example for “*anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives)*”. All these treatments are clearly intermittent or shorter than the expected duration of treatment with the paliperidone palmitate 3-month extended-release injectable suspension. For the treatment of schizophrenia, the acceptable intake of mutagenic impurity proposed by the ICH M7 guidance is 1.5 µg/day. Therefore, the impurity intake limit of (b) (4) µg/day proposed by the Sponsor cannot be accepted by this reviewer.

Paliperidone palmitate for every three month dosing regimen is formulated as an aqueous suspension (F015 formulation) with low solubility, leading to an extended release of paliperidone into systemic circulation. Paliperidone has been detected in human plasma up to 18 months after a single-dose injection of this formulation.

The Sponsor did not provide any information regarding rate of release of mutagenic impurities from the paliperidone palmitate injection site or their potential degradation process. Slow rate of release of impurities from the injection site, similar to that of paliperidone, cannot be excluded. Since the release profile of the impurities in vivo is unknown, the Sponsor assumed “the worst case”, namely that the entire amount of impurities in the formulation is released in the first day after injection. However this reviewer concluded that the potential exposure should not be based on the rare chance that the impurity is absorbed at a faster rate than intended for the API, instead of being extrapolated over three months. It is the opinion of this reviewer that “the worst case”, from the safety perspective, is a prolonged exposure of tissues at or near injection sites to mutagenic impurities before their release into systemic circulation that leads to systemic exposure.

Mutagenic impurity (b) (4) and (b) (4) issues have been addressed by this reviewer in the pharmacology/toxicology reviews of the NDA 22264 dated August 25, 2008 and its resubmission dated June 18, 2009. During the review of this approved application for the paliperidone palmitate 1-month extended-release injectable suspension (PP1M), the following recommendations were conveyed to the Sponsor: “*Revise the drug substance specification to include a limit of NMT (b) (4) ppm for potential genotoxic impurities (b) (4) and (b) (4) and their respective palmitate (b) (4)* (see the CMC information request letter dated April 24, 2009). Moreover, the Division concluded the nonclinical studies submitted in support of the original NDA 22264 for paliperidone palmitate for the once a month IM injection were sufficient to recommend approval of the application from the pharmacology/toxicology perspective, provided the Sponsor sets a specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) µg per injection [(b) (4) ppm per

injection of the maximum recommended human dose (MRHD) of 150 mg paliperidone eq.]. These recommendations were based on the Division decision that the acceptance criteria for mutagenic impurities should be calculated based on 150 mg eq. monthly (not daily) dose and the CDER draft guidance on mutagenic impurities (“Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches and Acceptable Limits”) where (b) (4) µg/day is the acceptable limit for a mutagenic impurity administered for a period longer than 12 months.

It is important to note that the MRHD of the approved PP1M F013 formulation is 234 mg of paliperidone palmitate per injection. The MRHD proposed for the PP3M F015 formulation currently under review is 3.5 times greater (819 mg of paliperidone palmitate per injection). Since the potential dose of impurities can be higher per PP3M injection, the acceptable limits expressed in parts per million (ppm) are different for each formulation.

Based on this considerations and demonstrated in vitro adverse mutagenic effects of the impurities (b) (4) and (b) (4) as well as adverse reactions observed at/near injection sites in the local tolerance studies in minipigs, the ICH M7 guidance-based lifetime duration, instead of the LTL approach, is recommended by this reviewer for calculations of the acceptable mutagenic impurity limits. Therefore, mutagenic impurities (b) (4) and (b) (4) should be controlled to the acceptable intake limit of not more than (b) (4) µg/injection for each impurity.

From the safety perspective, proposing higher limits and administration of higher doses of mutagenic impurities cannot be justified when the levels less than (b) (4) ppm can be consistently maintained during the manufacturing process.

The paliperidone palmitate 1-month extended-release injectable suspension F013 formulation batches contained previously impurities (b) (4) and (b) (4) at levels up to (b) (4) and (b) (4) ppm, respectively. However, recently the Sponsor documented that the manufacturing process for paliperidone palmitate is sufficiently robust and reliable to produce essentially undetectable amounts of the mutagenic impurities (b) (4) ppm). The Sponsor proposed removal of the mutagenic impurity testing for (b) (4) from the final paliperidone palmitate drug substance specification. The approval for this proposal was granted by the Agency (see Dr. A.H. Fenselau DMF 20902 review dated August 8, 2014).

2.6 Proposed Clinical Population and Dosing Regimen

Data collected by the Sponsor in this NDA support the use of the paliperidone palmitate 3-month extended-release injectable suspension (PP3M) for the treatment of schizophrenia in adults who have been adequately treated and demonstrated a therapeutic effect and ability to tolerate the paliperidone palmitate 1-month extended-release injectable suspension (PP1M) over a treatment period of at least 4 months at the time of initiation of PP3M. Due to the slow release characteristics of PP3M, the product is not intended to be used for initiation of treatment in acutely symptomatic

patients or in patients who are immediately transitioning from oral to long-acting injectable antipsychotic therapy.

The PP3M formulation was developed for the once every 3 months dosing by intramuscular (deltoid or gluteal) injection. The proposed dose levels of the PP3M are 273, 410, 546, and 819 mg, which correspond to a 3.5-fold multiple of the marketed PP1M doses of 78, 117, 156, and 234 mg, respectively.

2.7 Regulatory Background

The Sponsor scheduled three meetings with the Division in order to discuss the development of the paliperidone palmitate 3-month extended-release injectable suspension (PP3M). A pre-IND meeting was held on 20 August 2007. An End-of-Phase 2 (EOP2)/pre-Phase 3 meeting was subsequently held on 4 November 2011. Based on the similarities between the PP3M and approved paliperidone palmitate 1-month extended-release injectable suspension (PP1M), a limited toxicological program for the PP3M was agreed upon at these meetings. A pre-NDA meeting, scheduled for 24 July 2014, was subsequently canceled after the Division indicated its overall agreement with the Sponsor's proposal regarding the content of the NDA submission. See minutes from these meetings for more information.

3 Studies Submitted

3.1 Studies Reviewed

- Study TOX8249: "12-Week local tolerance study of 2 paliperidone palmitate long acting injectable formulations in the minipig".
- Study TOX101172: "12-week local tolerance study of 2 paliperidone palmitate long acting injectable formulations in the minipig".

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

The pharmacology/toxicology review of the NDA 21999 for INVEGA® dated September 29, 2006 for studies supporting marketing approval of oral paliperidone administration and pharmacology/ toxicology reviews of the NDA 22264 for INVEGA SUSTENNA® dated August 25, 2008 and June 18, 2009 for studies supporting marketing approval of the paliperidone palmitate 1-month extended-release injectable suspension.

4 Pharmacology

4.1 Primary Pharmacology

No new primary pharmacology studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for primary pharmacology studies conducted with other formulations.

4.2 Secondary Pharmacology

No new secondary pharmacology studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for secondary pharmacology studies conducted with other formulations.

4.3 Safety Pharmacology

No new safety pharmacology studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for safety pharmacology studies conducted with other formulations.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new ADME studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for ADME studies conducted with other formulations.

5.2 Toxicokinetics

Toxicokinetics of the paliperidone palmitate 3-month extended-release injectable suspension was investigated in two local tolerance studies described in the Section 6.2.

6 General Toxicology

6.1 Single-Dose Toxicity

Studies conducted with the paliperidone palmitate administered to male minipigs by either a single intramuscular (IM) injection of the 3-month extended-release injectable suspension (PP3M, formulation F015) or by three IM injections once every 4 weeks of the 1-month extended-release injectable suspension (PP1M, formulation F013) are described in the Section 6.2.

6.2 Repeat-Dose Toxicity

Study title: “12-week local tolerance study of 2 paliperidone palmitate long acting injectable formulations in the minipig”

Study no.: TOX8249
Study report location: Archives of Janssen Research and Development
Conducting laboratory and location: Janssen Research and Development, Beerse, Belgium
Date of study initiation: March 03, 2007
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: paliperidone palmitate (R092670), lot 06J17/F015 (ZR092670PFA411 and ZR092670PFA452) for the formulation F015 (purity 98.8%) and lot 06K22/F013 (ZR092670PFA461 and ZR092670PFA471) for the formulation F013 (purity 98.4%)

Key Study Findings

Administration of paliperidone palmitate to male minipigs at a single time point of dosing by two IM injections in *musculus biceps femoris* (bilateral: left and right) of the paliperidone palmitate 3-month extended-release injectable suspension (PP3M, F015 formulation) at dose levels of 15 mg and 60 mg paliperidone equivalents (eq.)/kg b.w., or by three consecutive IM injections (each bilateral: left and right) once every 4 weeks of the paliperidone palmitate 1-month extended-release injectable suspension (PP1M, F013 formulation) at dose levels of 5 mg and 20 mg paliperidone eq./kg b.w./dose resulted in the following test article-related findings:

- The CNS-related adverse clinical signs of decreased general activity and tremors were observed at all dose levels, whereas excessive salivation and compulsive behavior were observed only in the high dose in animals administered both F013 and F015 formulations. In addition, following injection of the high dose of the F015 formulation, excitability, ataxia, hypotonia, and chewing were noted.
- White deposits of the test article were observed macroscopically in the subcutaneous tissue and/or fat and/or in the muscular tissue in a dose-dependent manner at the IM injection sites of both F013 and F015 formulations.
- Inflammatory reaction with granuloma formation, graded minimal to moderate, was observed microscopically mainly in the high dose groups administered the F015 and F013 formulations. Although no clear difference in (multi)focal chronic inflammation could be observed between the 2 formulations, the cellular reaction pattern and the size of (b)(4) material seen in the inflammatory cells were different and indicated more advanced granulomatous reaction at sites injected with the F015 formulation. (b)(4) material was larger than nucleus with the

F015 formulation and smaller than nucleus with the F013 formulation. Macrophages and giant cells with cholesterol-like clefts were present at both dose levels with the F015 but not with the F013 formulation. Inflammatory histiocytosis was observed at both dose levels with the F013 but not with the F015 formulation.

- A NOAEL could not be established in this study mainly due to the fact that the injection site lesions already occurred at the lowest dose level.
- The maximum plasma concentrations (C_{max}) were reached between 10-14 days after dosing of both formulation and were higher after dosing with the F015 formulation. Systemic exposure (AUC) was similar after dosing with the F015 or F013 formulations
- There were no adverse test article related effects on survival, body weight, weight gain, food consumption, hematological and clinical chemistry parameters.

Note: Reviewer's calculations: Doses of 15 mg and 60 mg paliperidone eq./kg b.w. of F015 formulation correspond to 23.4 mg/kg (351 mg/minipig*) and 93.6 mg/kg (1404 mg/minipig*; 702 mg/injection site) paliperidone palmitate, respectively. Doses of 5 mg and 20 mg paliperidone eq./kg of F013 formulation correspond to 7.8 mg/kg (117 mg/minipig*) and 31.2 mg/kg (468 mg/minipig*; 234 mg/injection site) paliperidone palmitate, respectively. (* mean weight of minipig: ~15 kg on Day 0).

Methods

- Doses: **0, 0, 15 and 60 mg** paliperidone equivalents (eq.)/kg of the F015 formulation or **0, 0, 5 and 20 mg** paliperidone eq./kg/dose of the F013 formulation; Remark: The dosages (mg eq./kg) are approximate and they are dosages for a minipig of 15 kg and 2 injection sites.
- Frequency of dosing: Single intramuscular (IM) injection (2 sites) of the F015 formulation or three IM injections (2 sites) once every 4 weeks of the F013 formulation
- Route of administration: IM injection in the hind leg (2 sites)
- Dose volume: For the F015 formulation: 2.3, 2.3, 0.56 and 2.3 mL/injection site for the control (saline), vehicle (F015), 15 and 60 mg paliperidone eq./kg groups, respectively
For the F013 formulation: 1.5, 1.5, 0.38, and 1.5 mL/injection site for the control (saline), vehicle (F015), 15 and 60 mg paliperidone eq./kg/dose groups, respectively
- Formulation/Vehicle: F015 formulation of paliperidone palmitate was used at one concentration: (b) (4) mg/mL (equivalent to (b) (4) mg paliperidone/mL). The ingredients of the suspensions were:
- paliperidone palmitate
 - polysorbate 20 parenteral, 10 mg
 - polyethylene glycol 4000 parenteral, 75 mg
 - citric acid monohydrate parenteral, 7.5 mg
 - sodium dihydrogen phosphate monohydrate parenteral (b) (4) mg
 - sodium hydroxide, (b) (4) mg
 - water for injections, (b) (4)
- F013 formulation of paliperidone palmitate was used at one concentration: (b) (4) mg/mL (equivalent to (b) (4) mg paliperidone/mL). The ingredients of the suspensions were:
- paliperidone palmitate
 - polysorbate 20 (b) (4) mg
 - polyethylene glycol 4000 (b) (4) mg
 - citric acid monohydrate (b) (4) mg
 - disodium hydrogen phosphate anhydrous (b) (4) mg
 - sodium dihydrogen phosphate monohydrate (b) (4) mg
 - sodium hydroxide, (b) (4) mg
 - water for injections, (b) (4)
- Vehicle groups: F015 and F013 formulations

without active ingredient

Species/Strain: Minipigs/ [REDACTED] (b)(4) (males only)

Number/Sex/Group: 3 males/group

Age: 7.5 to 9 month on Day 0

Weight: From 11.4 to 17.4 kg on Day 0 (mean value for the paliperidone palmitate treated groups: 14.7 to 15.1 kg on Day 0)

Satellite groups: None

Unique study design: Test article was administered by either a single IM injection of a 3-month depot formulation (F015) at dose levels of 15 and 60 mg paliperidone eq./kg, or by three consecutive IM injections once every 4 weeks of a 1-month depot formulation (F013) at dose levels of 5 and 20 mg eq./kg/dose. Two additional groups received F015 or F013 vehicle, respectively. Two control groups [saline] were also included.

Deviation from study protocol: In the opinion of this reviewer, none of the minor protocol deviations affected the quality or integrity of the study.

Observations and Results

Mortality

There was no test-article related mortality.

Clinical Signs

All animals were observed daily for clinical signs. On Days 0, 29 and 56, time-related observations were recorded in all minipigs at 30 minutes prior to dosing and at 1, 2, 4, 6 and 24 hours after daily dosing. The injections sites were observed on the day of treatment and daily thereafter in particular for hemorrhage, erythema, swelling (with indication of size) and sensitivity.

F015 formulation: Single IM injection of the F015 formulation of paliperidone palmitate at 15 mg eq./kg resulted in slightly decreased general activity in 3/3 animals and slight tremors in 1/3 animals. Single IM injection of the F015 formulation of paliperidone palmitate at 60 mg eq./kg produced slightly to moderately decreased general activity (3/3 animals), slight tremors (2/3 animals), excessive salivation (1/3 animals), compulsive behavior (3/3 animals), excitability (1/3 animals), ataxia (1/3 animals), hypotonia (2/3 animals) and chewing (3/3 animals). In general, observations of excitability, ataxia, hypotonia and chewing started approximately one week after the first dose and lasted maximally one week.

F013 formulation: IM injections of the F013 formulation of paliperidone palmitate at 5 mg eq./kg/dose resulted in slightly decreased general activity (3/3 animals) and slight tremors (2/3 animals). IM injections of the F013 formulation of paliperidone palmitate at

20 mg eq./kg/dose resulted in slightly to moderately decreased general activity (3/3 animals), slight tremors (1/3 animals), excessive salivation (1/3 animals), and compulsive behavior (3/3 animals).

Body Weights

Individual body weight was recorded prior to start of dosing (Day -7), on Day 0 and at weekly intervals. Single IM administration of the F015 formulation to minipigs at 15 and 60 mg eq./kg produced a slight increase in body weight (6 and 9%, respectively) and moderate increase in body weight gain (55 and 91%, respectively) at the end of dosing period compared with the control group. These findings have no clear toxicological significance. Intermittent IM injection of the F013 formulation did not result in adverse effects on body weights.

Food Consumption

Individual food consumption was recorded at weekly intervals during the dosing period. There were no test article-related adverse effects on food consumption in this study.

Ophthalmoscopy

Not examined

ECG

Not examined

Hematology

Hematology examination was performed in all minipigs, once before the start of dosing (to determine baseline values) from all minipigs, on Day 30 from the animals dosed with the F013 formulation and on Day 84 from all minipigs. The following parameters were determined:

- white blood cell count (1)	
- red blood cell count (1)	
- haemoglobin (1)	
- haematocrit (1)	
- red blood cell indices (1):	mean cell volume mean cell haemoglobin mean cell haemoglobin concentration
- reticulocytes (1)	
- thrombocyte count (1)	
- normoblasts (2)	
- differential white blood cell count (1, 2):	neutrophils lymphocytes monocytes eosinophils basophils - blast cells (2)* - promyelocytes (2)* - myelocytes (2)* - metamyelocytes (2)* - juvenile forms (2)*
(1): ADVIA 120 Haematology Analyser (Bayer Diagnostics)	
(2): microscopic	
*: reported in the annexes only.	

7

There was no test article-related adverse effects on hematology parameters in minipigs administered either F015 or F013 formulation. Sporadic differences were observed that were considered not meaningful due to the magnitude or direction of change, or the lack of dose relationship.

Clinical Chemistry

Clinical chemistry examination was performed in all minipigs, once before the start of dosing (to determine baseline values) from all minipigs, on Day 30 from the animals dosed with the F013 formulation and on Day 84 from all minipigs. The following parameters were determined:

- sodium	- triglycerides
- potassium	- blood urea nitrogen
- chloride	- creatinine
- calcium	- total bilirubin
- inorganic phosphorus	- alkaline phosphatase
- total protein	- aspartate aminotransferase
- albumin	- alanine aminotransferase
- glucose	- gamma glutamyl transferase
- cholesterol	

There were no test article-related adverse effects on clinical chemistry parameters in animals administered 15 and 60 mg eq./kg of the F015 formulation. In the F013-dosed animals, after 1 month of dosing, a minimal to slight decreases in alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, sodium, albumin,

triglycerides and potassium were observed in the high dose group. After 3 months, ALT, alkaline phosphatase, albumin and potassium were still slightly decreased.

Urinalysis

Not examined

Gross Pathology

Each intramuscular injection site with skin, underlying subcutaneous tissue and hind leg *musculus biceps femoris* was cut free as a block (approximately 4 x 4 x 4 cm) separated from skeletal muscle tissue. These blocks were excised with the injection sites in the center and fixed in neutral buffered 10% formaldehyde, and appropriate representative tissue sections were prepared for histological examination.

There were no gross lesions at the injection sites in the control saline and control F015 and F013 vehicle groups. IM injection of paliperidone palmitate formulations F013 and F015 in the hind leg muscle resulted in dose-related local adverse reactions. White deposit of test article formulation was observed in the subcutaneous tissue and/or fat and/or in the muscular tissue. In two high dosed animals dosed with the formulation F015, a more 'nodular' appearance of the deposit was noted. However, this reviewer agrees with the study pathologist conclusion that no clear difference in gross pathology reaction between the two formulations was observed. Number of animals per group with deposits is shown in the following Sponsor's table:

NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: KO								
Sex	Males							
Dose Group Animals Examined	C1 3	P1 3	L1 3	H1 3	C2 3	P2 3	L2 3	H2 3
GENERAL OBSERVATIONS - No gross correlation to clinical observation (NOSE)	-	-	-	-	1	1	-	-
INJ IM BICEPS FEM L1 - Deposit[s]	-	-	2	3	-	-	2	-
INJ IM BICEPS FEM L2 - Deposit[s]	-	-	2	2	-	-	2	3
INJ IM BICEPS FEM L3 - Deposit[s]	-	-	-	1	-	-	3	3
INJ IM BICEPS FEM R1 - Deposit[s]	-	-	2	3	-	-	-	1
INJ IM BICEPS FEM R2 - Deposit[s] - Discoloration	- -	- -	- -	2 -	- -	- -	- 1	3 -
INJ IM BICEPS FEM R3 - Deposit[s] - Discoloration	- -	- -	2 1	3 -	- -	- -	3 -	3 -
SKIN - Sore	-	-	-	-	-	-	1	-

Group C1, Control 1 (12 wk F015), males: R092670 (0 mg eq./kg)
 Group P1, Placebo 1 (12 wk F015), males: R092670 (0 mg eq./kg)
 Group L1, Low 1 (12 wk F015), males: R092670 (15 mg eq./kg)
 Group H1, High 1 (12 wk F015), males: R092670 (60 mg eq./kg)
 Group C2, Control 2 (4 wk F013), males: R092670 (0 mg eq./kg)
 Group P2, Placebo 2 (4 wk F013), males: R092670 (0 mg eq./kg)
 Group L2, Low 2 (4 wk F013), males: R092670 (5 mg eq./kg)
 Group H2, High 2 (4 wk F013), males: R092670 (20 mg eq./kg)

Organ Weights

Not examined

Histopathology

Adequate Battery: only injections sites were evaluated

Peer Review: Yes

Histological Findings:

For microscopic examination, collected tissues [injection site with skin, underlying subcutaneous tissue and hind leg muscle (*musculus biceps femoris*)] were processed using standard procedures and stained with H&E. Sections were also stained with Oil Red O and with Sudan Black to demonstrate the presence of lipids in the inflammatory tissue near injection sites. These sections were examined microscopically with polarized light for the presence of (b) (4) material. The microscopic findings were either graded 1: minimal histological change, 2: slight, 3: moderate, 4: marked and 5: severe histological change.

There were no relevant differences between the F015 and F013 vehicle control and saline control animals in the injection site histopathology findings indicating lack of vehicle-related adverse reactions. A dose-related inflammatory reaction with granuloma formation was observed mainly in the high dose groups administered the F015 and

F013 formulations but was more severe following administration of the F015 formulation. Histopathology findings in the test article groups included muscle granulomata, multifocal chronic muscle inflammation, subcutis granulomata, and multifocal chronic subcutis inflammation. They were graded minimal to moderate. No marked or severe reactions were observed. The histopathological findings of inflammatory fibro-granulomatous reactions in the skin (subcutis) near the administration site were likely due to backflow of the test article from the administration sites. According to the study pathologist, no clear difference in (multi)focal chronic inflammation could be observed between the 2 formulations. Sum of grading for (multi)focal chronic inflammation at the injection sites (muscle and/or subcutis) per test article dosed group is shown in the following Sponsor's table:

group	L1	L2	H1	H2
sum of grading/group	24	27	54	43
number of graded samples/group	9	15	15	13
number of injection-sites per group	6	18	6	18
inflammation with granulomata (positive injection sites/group)	2/6	5/18	5/6	7/18

L1: low dose F015, L2: low dose F013; H1: high dose F015, H2: high dose F013

However, the cellular reaction pattern and the size of (b) (4) material seen in the inflammatory cells were different between the two formulations. (b) (4) material was larger than nucleus with the F015 formulation and smaller than nucleus with the F013 formulation. Macrophages and giant cells with cholesterol-like clefts were noted at both dose levels with the F015 but not with the F013 formulation. Inflammatory histiocytosis was observed at both dose levels with the F013 but not with the F015 formulation. These data are summarized by the Sponsor in the following table:

2. FORMULATION	F015	F013
(fibro)histiocytosis	0	↑
macrophages + giant cells + cholesterol clefts	↑	0
(b) (4) material (frozen section) in millimetre (approximately)	larger than nucleus	smaller than nucleus

↑: more prominent; 0: minimal presence

This reviewer concluded that differences observed in the cellular reaction pattern indicate more advanced granulomatous reaction at sites injected with the F015 formulation compared to these injected with the F013 formulation. This difference is likely related to the higher concentration/amount of paliperidone palmitate in the F015 formulation designed for the longer release period (3 month) compared with the 1 month. Reversibility of the injection site adverse reactions was not examined.

Special Evaluation

None

Toxicokinetics

Blood samples were collected from all paliperidone palmitate-dosed minipigs at 24, 48 and 72 hours after dosing on Day 0 and at 10 AM on Days 7, 10, 14, 17, 21, 24, 29 (=pre-dose), 34, 38, 41, 43, 48, 52, 56 (= pre-dose), 59, 63, 66, 70, 73, 77, 80 and 84.

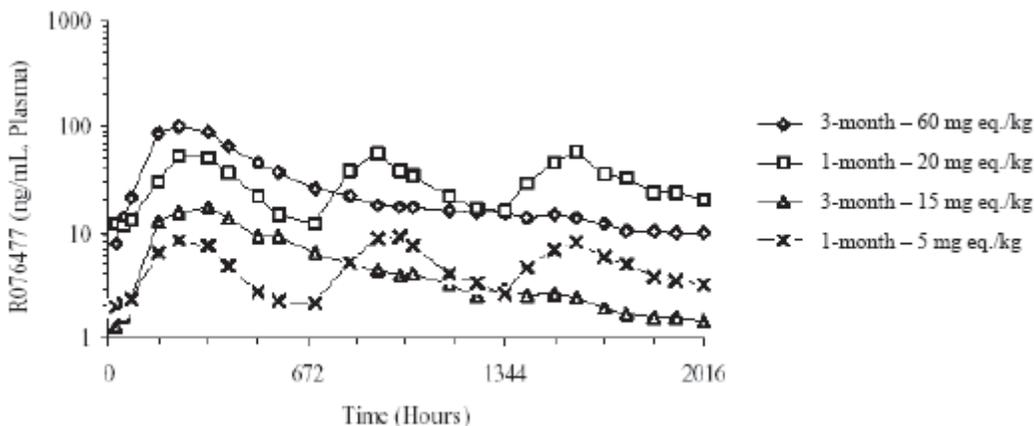
The maximum plasma paliperidone concentrations were observed in general around 9-13 days after dosing of both formulations. The maximum plasma concentrations (C_{max}) of paliperidone were slightly higher (by 64 to 71%) after dosing the F015 formulation (single dose) compared to the F013 formulation (3 doses). However, the exposure ($AUC_{0-84days}$) to paliperidone after dosing the F015 formulation was similar to that after three times dosing the F013 formulation. The exposure increased somewhat more than dose-proportionally for the studied dose levels of both formulations. TK data are shown in the following Sponsor's table:

Table 1: Mean Toxicokinetic Parameters after Dosing Minipigs with F015 or F013

TOX8249 Dose (mg eq./kg)	12-week depot formulation (F015)		4-week depot formulation (F013)	
	15	60	5	20
C_{max} (ng/mL)	18.5	105	10.8	64.1
AUC_{0-28d} (ng.d/mL)	297	1,649	127	823
AUC_{0-84d} (ng.d/mL)	462	2,482	413	2,551
$C_{av,\tau}$	5.5	30	4.4	28

$C_{av,\tau}$ = average plasma concentration over τ days; d =day

Mean plasma concentration versus time profiles of paliperidone after dosing with the F015 and F013 paliperidone palmitate formulations are shown in the following Sponsor's figure:



Dosing Solution Analysis

The following statement was provided by the Sponsor: “Bioburden of the placebo formulations was carried out. No other analysis was performed because the clinical vials were used in this study”.

Study title: “12-week local tolerance study of 2 paliperidone palmitate long acting injectable formulations in the minipig”

Study no.: TOX10172
Study report location: Archives of Janssen Research and Development
Conducting laboratory and location: Janssen Research and Development, Beerse, Belgium
Date of study initiation: August 9, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Paliperidone palmitate (R092670), lot 10A08/F015 for the formulation F015 (purity 98.6%) and lot AJB6R for the formulation F013 (purity 100.3%)

Key Study Findings

Administration of paliperidone palmitate to male minipigs at a single time point of dosing by two IM injections in *musculus biceps femoris* (bilateral: left and right) of the paliperidone palmitate 3-month extended-release injectable suspension (PP3M, F015 formulation) at dose levels of 17.5 and 70 mg paliperidone equivalents (eq.)/kg b.w. or by three consecutive IM injections (each bilateral: left and right) once every 4 weeks of the paliperidone palmitate 1-month extended-release injectable suspension (PP1M, F013 formulation) at dose levels of 5 and 20 mg paliperidone eq./kg b.w. resulted in the following test article-related findings:

- The CNS-related dose-dependent adverse clinical signs of decreased general activity, excessive salivation, compulsive behavior, tremors, and out of normal biting were observed at all dose levels of both formulation, except the low dose F013 animals, which had only decreased general activity.
- White/yellow deposits of the test article were observed macroscopically in the subcutaneous tissue and/or in the muscular tissue at the IM injection sites of both F013 and F015 formulations.
- Inflammatory reaction with granuloma formation was observed microscopically in groups administered both the F015 and F013 formulations. While no clear difference in (multi)focal chronic inflammation could be observed between the two formulations, the cellular reaction pattern and the size of crystalline material observed in inflammatory cells were different and indicated more advanced granulomatous reaction at sites injected with the F015 formulation. Crystalline material was larger than nucleus with the F015 formulation and smaller than nucleus with the F013 formulation. Macrophages and giant cells with cholesterol-

like clefts were present at both dose levels with the F015 but not with the F013 formulation. Inflammatory histiocytosis was observed at both dose levels with the F013 but not with the F015 formulation. Reversibility of these findings has not been examined.

- A NOAEL could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.
- Exposure to paliperidone (C_{max} and $AUC_{0-84days}$) after dosing the F015 formulation was similar to the exposure after 3 times dosing the F013 formulation.
- There were no significant adverse test article-related effects on survival, body weight, weight gain, food consumption, hematological and clinical chemistry parameters.

Note: Reviewer's calculations: Doses of 17.5 mg and 70 mg paliperidone eq./kg of F015 formulation correspond to 27.3 mg/kg (495.5 mg/minipig*) and 109.2 mg/kg (1638 mg/minipig*; 819 mg/injection site) paliperidone palmitate, respectively. Doses of 5 mg and 20 mg paliperidone eq./kg of F013 formulation correspond to 7.8 mg/kg (117 mg/minipig*) and 31.2 mg/kg (468 mg/minipig*; 234 mg/injection site) paliperidone palmitate, respectively. (* mean weight of minipig: ~15 kg on Day 0).

Methods

- Doses:** **0, 0, 17.5 and 70 mg** paliperidone equivalents (eq.)/kg of the F015 formulation or **0, 0, 5 and 20 mg** paliperidone eq./kg/dose of the F013 formulation. Remark: The dosages (mg eq./kg) are approximate and they are dosages for a minipig of 15 kg and 2 injection sites.
- Frequency of dosing:** Single intramuscular (IM) injection (2 sites) of the F015 formulation or three IM injections (2 sites) once every 4 weeks of the F013 formulation
- Route of administration:** IM injection in the hind leg (2 sites)
- Dose volume:** For the F015 formulation: 2.6, 2.63, 0.66 and 2.63 mL/injection site for the control (saline), vehicle (F015), 17.5 and 70 mg paliperidone eq./kg groups, respectively
For the F013 formulation: 1.5, 1.5, 0.38 and 1.5 mL/ injection site for the control (saline), vehicle (F013), 5 and 20 mg paliperidone eq./kg/dose groups, respectively
- Formulation/Vehicle:** F015 formulation of paliperidone palmitate was used at one concentration: (b) (4) mg/mL (equivalent to (b) (4) mg paliperidone/mL). The ingredients of the suspensions were:
- paliperidone palmitate
 - polysorbate 20 parenteral, 10 mg
 - polyethylene glycol 4000 parenteral, 75 mg
 - citric acid monohydrate parenteral, (b) (4) mg
 - sodium dihydrogen phosphate monohydrate parenteral, (b) (4) mg
 - sodium hydroxide, (b) (4) mg
 - water for injections, (b) (4)
- F013 formulation of paliperidone palmitate was used at one concentration: (b) (4) mg/mL (equivalent to (b) (4) mg paliperidone/mL). The ingredients of the suspensions were:
- paliperidone palmitate
 - polysorbate 20 (b) (4) mg
 - polyethylene glycol 4000 (b) (4) mg
 - citric acid monohydrate (b) (4) mg
 - disodium hydrogen phosphate anhydrous (b) (4) mg
 - sodium dihydrogen phosphate monohydrate (b) (4) mg
 - sodium hydroxide, (b) (4) mg
 - water for injections, (b) (4)
- Vehicle groups: F015 and F013 without active

ingredient
Species/Strain: Minipigs/ [REDACTED] (b)(4) (male only)
Number/Sex/Group: 3/group
Age: 240 days at first dose
Weight: From 12.1 to 18.1 kg (Day 0)
Satellite groups: None
Unique study design: Test article was administered by either a single IM injection of a 3-month depot formulation (F015) at dose levels of 17.5 and 70 mg paliperidone eq./kg, or by three consecutive IM injections once every 4 weeks of a 1-month depot formulation (F013) at dose levels of 5 and 20 mg eq./kg/dose. Two additional groups received the F015 or F013 vehicle, respectively. Two control groups [saline] were also included.
Deviation from study protocol: In the opinion of this reviewer, none of the minor protocol deviations affected the quality or integrity of the study.

This second study was conducted to bridge the new high dose of the PP3M (819 mg/injection) to the previously approved high dose of the PP1M and compare reaction to a single injection of the F015 formulation with three monthly injections of the F013 formulation. The design otherwise is similar to the first study.

Observations and Results

Mortality

There was no test-article related mortality.

Clinical Signs

All animals were observed daily for clinical signs. On Days 0, 28 and 56, time-related observations were recorded in all minipigs at 30 minutes prior to dosing and at 1, 2, 4, 6 and 24 hours after dosing. The injection sites were observed on the day of treatment and daily thereafter in particular for hemorrhage, erythema, swelling (with attention to size) and sensitivity.

F015 formulation: Single IM injection of 17.5 mg eq./kg produced slightly decreased general activity in 2/3 animals. In 1/3 animals, slight tremors, compulsive behavior (repetitive movements of the nose between the bars of the cage and/or food hopper), “out of normal biting”, excessive salivation and focal swelling and hardened injection site were observed. These clinical signs started approximately 1 week after dosing and lasted only a few days. Single IM injection of 70 mg eq./kg produced the same clinical signs with slightly increased severity and in more animals [slightly to moderately decreased general activity (3/3 animals), slight tremors (2/3 animals), excessive salivation (2/3 animals), compulsive behavior (3/3 animals), and “out of normal” biting

(2/3 animals)]. These signs started approximately 1 week after dosing. However, they lasted up to 1 month after dosing.

F013 formulation: IM injection of 5 mg eq./kg/dose produced only slightly decreased general activity in 3/3 animals. However, IM injection of 20 mg eq./kg/dose produced clinical signs similar to those observed after the F015 formulation injection: slight to moderate decrease in general activity (3/3 animals), slight tremors (1/3 animals), excessive salivation (3/3 animals), compulsive behavior (3/3 animals), and out of normal biting (3/3 animals). These signs started approximately 1 week after dosing and lasted up to 1 month after the first dose. After the second dose, decreased general activity and excessive salivation were recorded approximately 1 week after the second dose lasting for a few days.

Body Weights

Individual body weight was recorded prior to start of dosing (Day -22), on Day 0 and at weekly intervals. Single IM administration of the F015 formulation at 70 mg eq./kg produced a slight increase in body weight (10.7%) and moderate increase in body weight gain (24.6%) at the end of dosing period. IM injection of 20 mg eq./kg/dose of the F013 formulation also produced a slight increase in body weight (2.6%) and moderate increase in body weight gain (37.1%) at the same time. There were no changes in body weights in other groups. These findings have no clear toxicological significance.

Food Consumption

Individual food consumption was recorded at weekly intervals during the dosing period. Single IM administration of the F015 formulation at 70 mg eq./kg resulted a minimal decrease in food consumption (0.9-fold of the saline control) in Week 2; this finding is likely related to the decreased general activity recorded in that week. Similar decrease in food consumption (0.9-fold of the saline control) was also observed following IM injection of 20 mg eq./kg/dose of the F013 formulation. These findings are not considered adverse due to the low magnitude of change.

Ophthalmoscopy

Not examined

ECG

Not examined

Hematology

Hematology examination was performed in all minipigs, once before the start of dosing (to determine baseline values) from all minipigs, on Day 29 from the animals dosed with the F013 formulation and on Day 84 from all minipigs. The following parameters were determined:

- white blood cell count (1)
- red blood cell count (1)
- haemoglobin (1)
- haematocrit (1)
- red blood cell indices (1): mean cell volume
 mean cell haemoglobin
 mean cell haemoglobin concentration
- reticulocytes (1)
- thrombocyte count (1)
- normoblasts (2)
- differential white blood cell count: neutrophils (1, 2)
 lymphocytes (1, 2)
 monocytes (1, 2)
 eosinophils (1, 2)
 basophils (1, 2)
 blast cells (2)*
 promyelocytes (2)*
 myelocytes (2)*
 metamyelocytes (2)*
 juvenile forms (2)*

(1): ADVIA 2120 Haematology Analyser (Siemens Diagnostics)

(2): microscopic; microscopic differentiation was only performed in case of abnormalities indicated by the automated analysis on ADVIA-2120.

*: reported in the annexes only

IM injection of 20 mg eq./kg/dose of the F013 formulation produced a transient increase in white blood cells, neutrophils and eosinophils on Day 29 of treatment (1.3-, 1.5-, and 3.9-fold of the control value, respectively). No changes in hematology parameters were observed on Day 84 for both the F015 and F013 formulations.

Clinical Chemistry

Clinical chemistry examination was performed in all minipigs, once before the start of dosing (to determine baseline values) from all minipigs, on Day 29 from the animals dosed with the F013 formulation and on Day 84 from all minipigs. The following parameters were determined:

- | | |
|------------------------|------------------------------|
| - sodium | - triglycerides |
| - potassium | - blood urea nitrogen |
| - chloride | - creatinine |
| - calcium | - total bilirubin |
| - inorganic phosphorus | - alkaline phosphatase |
| - total protein | - aspartate aminotransferase |
| - albumin | - alanine aminotransferase |
| - glucose | - gamma glutamyl transferase |
| - cholesterol | |

IM injection of 20 mg eq./kg/dose of F013 formulation resulted in a slight increase in AST and ALT when measured on Days 29 (1.3- and 2.2-fold of the control value,

respectively) and 84 (2.0- and 3.9-fold of the control value, respectively). There were no relevant findings for the F015 formulation.

Urinalysis

Not examined

Gross Pathology of the injection site:

Each IM injection site with skin, underlying subcutaneous tissue and hind leg muscle (with *musculus biceps femoris*) was cut free as a block (approximately 4 x 4 x 4 cm) from skeletal muscle and fixed in 10% buffered formalin. The skin (with subcutis) at injection sites as well as the skeletal muscles were verified in the sections from each hind leg for macroscopic changes and appropriate representative tissue sections were prepared for histological examination.

IM injection of the formulations F013 and F015 in the hind leg muscle resulted in dose-related local discoloration at the injection sites, described as white or yellow deposits. Sometimes white deposit was also observed in the subcutis. Number of animals per group with deposits is shown in the following Sponsor's table:

NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0								
Sex	Males							
Dose Group Animals Examined	C1 3	P1 3	L1 3	H1 3	C2 3	P2 3	L2 3	H2 3
INJECTION SITE, IM(1) - Deposit[s]	-	-	3	3	-	-	-	1
INJ IM BICEPS FEM(2) - Deposit[s]	-	-	-	-	-	-	3	3
INJ IM BICEPS FEM(3) - Deposit[s]	-	-	-	-	-	-	3	3

Group C1, Control 1 (F015), males: R092670 (0 mg eq/kg)
 Group P1, Placebo 1 (F015), males: R092670 (0 mg eq/kg)
 Group L1, Low 1 (F015), males: R092670 (17.5 mg eq/kg)
 Group H1, High 1 (F015), males: R092670 (70 mg eq/kg)
 Group C2, Control 2 (F013), males: R092670 (0 mg eq/kg)
 Group P2, Placebo 2 (F013), males: R092670 (0 mg eq/kg)
 Group L2, Low 2 (F013), males: R092670 (5 mg eq/kg)
 Group H2, High 2 (F013), males: R092670 (20 mg eq/kg)

Organ Weights

Not examined

Histopathology

Adequate Battery: only injections sites were evaluated

Peer Review: Yes

Histological Findings:

For microscopic examination, collected tissues [injection site with skin, underlying subcutaneous tissue and hind leg muscle (*musculus biceps femoris*)] were processed using standard procedures and stained with H&E. Sections were also stained with Oil Red O and examined microscopically with polarized light for the presence of crystalline

material in the inflamed areas. The microscopic findings were either graded 1: minimal histological change, 2: slight, 3: moderate, 4: marked and 5: severe histological change. For bilateral occurring findings of different degrees of severity, an average score was calculated.

There were no relevant differences between the F015 and F013 vehicle control and saline control animals in the injection site histopathology findings indicating lack of vehicle-related adverse reactions. Histopathology examinations of the paliperidone palmitate formulations F015 and F013 injection sites showed dose-related local reactions. A dose-related inflammatory reaction, graded minimal to moderate, was observed for both formulations tested. This finding was associated with granuloma formation observed in 2/3 animals dosed at the low dose of 17.5 mg eq./kg of the F015 formulation and in 1/3 animals dosed at the high dose of 20 mg eq./kg/dose of the F013 formulation. No clear difference in (multi)focal chronic inflammation could be observed between the two formulations. There was no muscle degeneration at any injection area.

However, the cellular reaction pattern and the size of the crystalline material observed in the inflammatory cells were slightly different between the two formulations. Macrophages, giant cells, and cholesterol clefts were observed only in all animals injected with the F015 formulation at both dose levels tested, with an average score for two injection sites was minimal to moderate. Foamy histiocytes (histiocytosis) were observed only in all animals injected with the F013 formulation at both dose levels tested. An average score for two injection sites was minimal to slight. Moreover, crystalline material (frozen section) was larger than nucleus in preparations from the F015-treated animals while it was smaller than the nucleus in the F013-treated animals.

The incidence and mean grade* for test-article related histo-observations at the injection sites for the 2 formulations (F015 and F013) is shown in the following Sponsor's table. The microscopic findings were either graded 1: minimal histological change, 2: slight, 3: moderate, 4: marked and 5: severe histological change or indicated as present without a grade. For bilateral occurring findings of different degrees of severity, an average score was given (between brackets).

Formulation F015 with paliperidone palmitate								
Injection site		ADM 1						
Observation		Chronic inflammation	Granulomata	Macrophages - giant cells	Clefts			
Groups F015	Low dose	3 (2.67)	2 (3.00)	3 (1.33)	3 (1.00)			
	High dose	3 (2.67)	0	3 (2.67)	3 (3.00)			
Formulation F013 with paliperidone palmitate								
Injection site		ADM 1		ADM 2		ADM 3		
Observation		Chronic inflammation	Histiocytes	Chronic inflammation	Histiocytes	Chronic inflammation	Histiocytes	Granulomata
Groups F013	Low dose	2 (0.50)	2 (0.50)	3 (0.67)	3 (0.67)	3 (1.67)	3 (1.67)	
	High dose	3 (0.50)	3 (0.50)	3 (1.67)	3 (1.67)	3 (2.33)	3 (2.33)	1 (1.00)

*: unilateral grades were halved (mean between brackets).

ADM = administration

Number of animals with microscopic findings by organ/group at terminal sacrifice is shown in the following Sponsor's table:

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX Necropsy Status: TERMINAL SACRIFICE GROUP (K0)								
Sex	Males							
Dose Group No. Animals per Dose Group	C1 3	P1 3	L1 3	H1 3	C2 3	P2 3	L2 3	H2 3
INJECTION SITE,IM(1) No.Examined	3	3	3	3	3	3	3	3
- Chronic inflammation - OVERALL	1	1	3	3	-	-	2	3
Grade 1	1	1	-	-	-	-	2	3
Grade 2	-	-	1	1	-	-	-	-
Grade 3	-	-	2	2	-	-	-	-
- Clefts	-	-	3	3	-	-	-	-
Grade 1	-	-	3	-	-	-	-	-
Grade 3	-	-	-	3	-	-	-	-
- Degeneration	1	-	-	-	-	-	-	-
Grade 1	1	-	-	-	-	-	-	-
- Granulomata	-	-	2	-	-	-	-	-
Grade 3	-	-	2	-	-	-	-	-
- Macrophages/giant cells + cholesterol clefts	-	-	3	3	-	-	-	-
Grade 1	-	-	2	-	-	-	-	-
Grade 2	-	-	1	1	-	-	-	-
Grade 3	-	-	-	2	-	-	-	-
- Histiocytes foamy	-	-	-	-	-	-	2	3
Grade 1	-	-	-	-	-	-	2	3
INJ IM BICEPS FEM(2) No.Examined	-	-	-	-	3	3	3	3
- Chronic inflammation - OVERALL	-	-	-	-	-	-	3	3
Grade 1	-	-	-	-	-	-	3	1
Grade 2	-	-	-	-	-	-	-	2
- Histiocytes foamy	-	-	-	-	-	-	3	3
Grade 1	-	-	-	-	-	-	3	1
Grade 2	-	-	-	-	-	-	-	2
INJ IM BICEPS FEM(3) No.Examined	-	-	-	-	3	3	3	3
- Chronic inflammation - OVERALL	-	-	-	-	-	-	3	3
Grade 1	-	-	-	-	-	-	1	-
Grade 2	-	-	-	-	-	-	2	2
Grade 3	-	-	-	-	-	-	-	1
- Granulomata	-	-	-	-	-	-	-	1
Grade 2	-	-	-	-	-	-	-	1
- Histiocytes foamy	-	-	-	-	-	-	3	3
Grade 1	-	-	-	-	-	-	1	-
Grade 2	-	-	-	-	-	-	2	2
Grade 3	-	-	-	-	-	-	-	1

Group C1, Control 1 (F015), males: R092670 (0 mg eq/kg)
Group P1, Placebo 1 (F015), males: R092670 (0 mg eq/kg)
Group L1, Low 1 (F015), males: R092670 (17.5 mg eq/kg)
Group H1, High 1 (F015), males: R092670 (70 mg eq/kg)
Group C2, Control 2 (F013), males: R092670 (0 mg eq/kg)
Group P2, Placebo 2 (F013), males: R092670 (0 mg eq/kg)
Group L2, Low 2 (F013), males: R092670 (5 mg eq/kg)
Group H2, High 2 (F013), males: R092670 (20 mg eq/kg)

Special Evaluation

None

Toxicokinetics

Blood samples were collected from all paliperidone palmitate-dosed minipigs at 24, 48 and 72 h after dosing on Day 0 and at 10 AM on Day 7, 9, 13, 16, 20, 23, 28 (=pre-dose), 33, 37, 41, 43, 48, 51, 55 (= pre-dose), 58, 61, 65, 68, 71, 76, 79 and 84.

The maximum plasma paliperidone concentrations were generally reached between 7-16 days after dosing of both formulations. Exposure (to paliperidone (C_{max} and $AUC_{0-84days}$) after dosing the F015 formulation was similar to the exposure after 3 times dosing the F013 formulation and increased generally slightly more than in proportion to the dose for both formulations. TK data are shown in the following Sponsor’s table:

Table 2: Mean Toxicokinetic Parameters after Dosing Minipigs with F015 or F013

	12-week depot formulation (F015)		4-week depot formulation (F013)	
TOX10172				
Dose (mg eq./kg)	17.5	70	5	20
C_{max} (ng/mL)	17.6	68.3	9.77	68.1
AUC_{0-28d} (ng.d/mL)	278	1,067	111	682
AUC_{0-84d} (ng.d/mL)	378	1,888	314	1,740
$C_{av,\tau}$	4.5	23	4.0	24

$C_{av,\tau}$ = average plasma concentration over τ days

Mean plasma concentration versus time profiles of paliperidone after dosing with the F015 and F013 paliperidone palmitate formulations are shown in the following Sponsor’s figure:



Dosing Formulation Analysis

The following statement was provided by the Sponsor: “Bioburden of the placebo formulations was carried out. The result fell within the acceptance criteria (b) (4) No other analysis was performed because the clinical vials were used in this study”.

7 Genetic Toxicology

No genetic toxicology studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for genetic toxicology studies conducted with other formulations.

8 Carcinogenicity

No carcinogenicity studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for carcinogenicity studies conducted with other formulations.

9 Reproductive and Developmental Toxicology

No reproductive toxicology studies were conducted to support approval of the paliperidone palmitate 3-month extended-release injectable suspension. See reviews listed in the Section 3.3 for reproductive toxicology studies conducted with other formulations.

10 Special Toxicology Studies

No special toxicology studies were conducted to support the once every 3 months IM injection of paliperidone palmitate. See reviews listed in the Section 3.3 for special toxicology studies conducted with other formulations.

11 Integrated Summary and Safety Evaluation

The NDA 207946 submission concerns the use of paliperidone palmitate 3-month extended-release injectable suspension (PP3M; formulation F015) for the treatment of schizophrenia by repeated intramuscular (IM) injection into gluteal or deltoid muscle once every three months. (b) (4)

However, the tolerability of a single injection of the PP3M formulation F015 was compared with three injections of the PP1M formulation F013 in two GLP-compliant studies conducted in minipigs (No. TOX8249 and TOX10172). The minipig was selected as the test model because of its proven suitability in this type of studies.

In the first local tolerance study (TOX8249), the low dose tested in minipigs for the F013 (5 mg eq./kg b.w.; (b) (4) mg eq./mL) and F015 (15 mg eq./kg b.w.; (b) (4) mg eq./mL) formulations was equivalent to the highest clinical dose (that is 234 and 702 mg/subject, or 1.5 and 2.25 mL per unilateral injection, respectively) tested in clinical study R092670-PSY-1005, scaled on a per kilogram body weight basis (that is 0.38 and 0.56 mL per injection site, bilateral injection). The high dose tested in minipigs in this study (20 and 60 mg eq./kg b.w. for the F013 and F015 formulations, respectively) was achieved by bilateral injection of the same volume used clinically at the highest dose (1.5 and 2.25 mL, respectively).

Note: each injection site in minipigs got the volume and dose of the F015 formulation equal to that proposed for humans (450 mg paliperidone eq./injection equal to 702 mg paliperidone palmitate/injection) at the time this study was conducted.

At the End-of-Phase 2 meeting (see IND 76952 briefing document submitted Sept 13, 2011), the Sponsor proposed to repeat the local tolerability study with a similar design to support the 819 mg/injection dose as the highest clinical PP3M dose (MRHD). The Division agreed with this proposal. The second minipig study (TOX10172) was conducted to bridge the new high dose of the PP3M with the existing high dose of the PP1M and compare a single injection of the PP3M at 819 mg with three monthly injections of the PP1M at 234 mg/injection.

The maximum plasma paliperidone concentrations were generally reached between 7-16 days after dosing in both studies and were higher after dosing with the F015 formulation. Systemic exposure (AUC) was similar after dosing with each of the F015 or F013 formulations.

The toxicological profile of both formulations observed in the two local tolerance studies, was, in general, comparable. There were no noteworthy adverse test article related effects on survival, body weight, weight gain, food consumption, hematological and clinical chemistry parameters in either of the two studies in minipigs. Adverse CNS effects were, in general, qualitatively similar and were observed with both formulations. In the first minipig study, the CNS-related adverse clinical signs of decreased general activity and tremors were observed at all dose levels, whereas excessive salivation and compulsive behavior were observed only in the high dose in animals administered each of the F013 or F013 formulations. In addition, following injection of the high dose of the F015 formulation, excitability, ataxia, hypotonia, and chewing were noted. In the second minipig study, the CNS-related dose-dependent adverse clinical signs of decreased general activity, excessive salivation, compulsive behavior, tremors, and out of normal biting were observed at all dose levels of both formulations except the low dose F013 animals, which had only decreased general activity.

White/yellow deposits of the test articles were observed macroscopically in the subcutaneous tissue and/or in the muscular tissue at the IM injection sites of F013 and F015 formulations, with no relevant differences between the two formulations in both minipig studies.

The local injection site reactions were confirmed at the histological level in two studies. There were no clear microscopic differences in quantitative (multi)focal chronic inflammation between the two formulations. However, [REDACTED] (b) (4) [REDACTED] cellular reactions at the sites of injection differed. The animals injected with the F013 formulation responded with an increased histiocytosis with the sporadic presence of multinucleated giant cells. No cholesterol-like clefts were seen. The animals injected with F015 showed increased numbers of macrophages and multinucleated giant cells with cholesterol-like clefts. Examination with polarized light demonstrated the presence of large crystalline material

in the inflammatory cells (larger than nuclear diameter) with the F015 formulation and small crystalline material (smaller than nuclear diameter) with the F013 formulation. The “crystals” seen by the Sponsor’s pathologists are likely some form of the drug product. They have been phagocytized by macrophages and may eventually be transported away from the site and eliminated.

Detailed comparison of the minipig injection sites of paliperidone palmitate F013 with F015 formulations indicated that both caused an intramuscular granulomatous reaction of different degrees of severity and progression of the reaction. Injection site reaction to the F013 formulation was less advanced (foamy histiocytes is a synonym of foamy macrophages) than that to the F015 formulation (syncytial macrophages are a form of giant cells). The F015 injected sites seemed to have advanced to a more organized granuloma formation and cholesterol clefts were observed at cellular level. The clefts are empty spaces left when fat/lipid/cell-wall breakdown products are dissolved during processing in the histology laboratory. They are not seen following injection with the F013 formulation, nor were they mentioned in the reports of toxicology studies conducted during development of the paliperidone palmitate 1-month extended-release injectable suspension (see more detailed description below). Those breakdown products are not easily phagocytized. Importantly, no necrosis was reported among histopathology findings.

A no observed adverse effect level (NOAEL) could not be established in either of the two local tolerance studies in minipigs, mainly due to the fact that injection site lesions already occurred at the lowest dose level. However, these adverse findings do not preclude administration of the paliperidone palmitate 3-month extended-release injectable suspension to human subjects. Granuloma formation is an expected response and forms when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate. In pathology, a granuloma is an organized collection of macrophages (also known as histiocytes) that sometimes form multinucleated giant cells. Eventually these changes undergo vascularization (granulation tissue) and usually resolve to simple scar formation in the muscle. The Sponsor did not examine reversibility of the injection site reactions in minipigs.

Injection site reactions observed in the minipigs administered paliperidone palmitate 3-month extended-release injectable suspension (formulation F015) were, in general, similar to those reported for the paliperidone palmitate 1-month extended-release injectable suspension in studies conducted with the F004 vehicle (instead of F013 formulation).

In the previously conducted 12-month toxicology study, in which Beagle dogs received monthly injections of paliperidone palmitate at doses up to 40 mg eq./kg b.w. as F004 formulation, histological findings at the injection sites were described by the study pathologist as perimysially located chronic inflammatory fibrotic encapsulated histiocytic granulomas with necrotic center and granulocyte infiltration prominently present in all test article dosed groups. Volume- and dose-related differences could not be observed (NDA 22246, Study TOX4692).

In the previously conducted 6-month toxicology study, in which Wistar rats were dosed with monthly injections of paliperidone palmitate up to 160 mg eq./kg b.w. (F004 formulation), the injection site findings were similar to those observed in the dog and also included fibrogranulomatous reaction with histiocytes and giant cells seen in perimysium and epimysium in all drug groups of both sexes with dose dependent increase in severity; changes were more severe after 6 months (NDA 22246, Study TOX3848).

In conclusion, the injection site reaction in minipigs to the F015 formulation was greater and more advanced than that to the F013 formulation, but the reactions were qualitatively similar and the difference between the reactions to both formulations is a matter of degree. It is important to note that the severity of the reaction to the two formulations in minipigs is not necessarily species-specific, but may be species-related or breed-related. In conversation with LuAnn McKinney, DVM, DACVP, these conclusions were confirmed.

Although no new safety concerns were generated with the PP3M formulation F015 compared with what was already known for the oral paliperidone and PP1M formulations, this reviewer recommends that the difference in the injection site adverse reactions to the paliperidone palmitate 3-month extended-release injectable suspension and previously approved paliperidone palmitate 1-month extended-release injectable suspension observed in animals be described in the section 13.2 of the INVEGA TRINZA™ labeling.

Since the tolerance towards the PP3M formulation F015 is, in general, similar to that of the PP1M formulation F013 in the minipigs, the paliperidone palmitate 3-month extended-release injectable suspension formulation is anticipated to have similar effects in the clinic as the paliperidone palmitate 1-month extended-release injectable suspension formulation, although the degree of the response may be different. Several clinical studies have shown that overall local injection site tolerability, demonstrated with the paliperidone palmitate 3-month extended-release injectable suspension, is acceptable.

Excipient in the F015 formulation: The level of the excipient polyethylene glycol 4000 (PEG 4000) present in the paliperidone palmitate 3-month extended-release injectable suspension at concentration of 75 mg/mL, which is higher than that in the paliperidone palmitate 1-month extended-release injectable suspension, is considered toxicologically qualified for systemic effects and local injection site reactions up to a dose of 18 mg/kg b.w./month when administered by an intramuscular injection.

Non-mutagenic drug substance impurities: The following six synthesis impurities are present in the paliperidone palmitate 3-month extended-release injectable suspension drug substance and were also present in the 1-month formulation: (b) (4)

(b) (4) This limit is acceptable. The remaining five impurities were qualified in the 12-month repeat-dose IM toxicity study in Beagle dogs (study No. TOX4692) submitted to the NDA 22264 at levels higher than the concentrations limit in the drug substance of not more than (b) (4) % proposed by the Sponsor, which is acceptable for all five non-mutagenic impurities.

Mutagenic drug substance impurities: Two mutagenic impurities (b) (4) and (b) (4) (b) (4) can be present in the synthesis batches of paliperidone palmitate drug substance. Both impurities showed mutagenic activity in the in vitro Ames bacterial reverse mutation test and chromosomal aberration assay conducted in human lymphocytes. This reviewer recommends that the DMF be updated to limit the dose of each of the mutagenic impurities (b) (4) and (b) (4) to not more than (b) (4) µg per injection (or (b) (4) ppm per injection of the maximum recommended human dose of 819 mg of paliperidone palmitate 3-month extended-release injectable suspension). This is not an approvability issue, since the Sponsor is reproducibly capable of producing batches of paliperidone palmitate with undetectable (b) (4) ppm concentrations of these mutagenic impurities.

In conclusion, the nonclinical studies submitted and referenced in support of the NDA 207946 for the paliperidone palmitate 3-month extended-release injectable suspension are sufficient to recommend approval of the application from the pharmacology/toxicology perspective.

12 Appendix/Attachments

Nonclinical doses of paliperidone palmitate are presented in milligram equivalents of paliperidone throughout this review. The correspondence between milligram equivalents of paliperidone and milligrams of paliperidone palmitate is provided in the following Sponsor's table:

<i>Milligrams Paliperidone Palmitate</i>	<i>Milligram Equivalents Paliperidone</i>
	<i>PP1M</i>
<i>39 mg</i>	<i>25 mg eq</i>
<i>78 mg</i>	<i>50 mg eq</i>
<i>117 mg</i>	<i>75 mg eq</i>
<i>156 mg</i>	<i>100 mg eq</i>
<i>234 mg</i>	<i>150 mg eq</i>
	<i>PP3M</i>
<i>273 mg</i>	<i>175 mg eq</i>
<i>410 mg</i>	<i>263 mg eq</i>
<i>468 mg</i>	<i>300 mg eq</i>
<i>546 mg</i>	<i>350 mg eq</i>
<i>702 mg</i>	<i>450 mg eq</i>
<i>819 mg</i>	<i>525 mg eq</i>

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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.

/s/

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04/28/2015

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04/28/2015