

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203697Orig1s000

PHARMACOLOGY REVIEW(S)

**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: NDA 203697
Supporting Documents: S001
Applicant's letter date: 03/14/2010
CDER stamp date: 03/14/2010
Product: PL2200 (Formerly: Aspirin PC /PL2200)

Indication: For temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever

Applicant: PLx Pharma Inc.
Review Division: Division of Nonprescription Clinical Evaluation
Reviewer: Cindy Xinguang Li, Ph.D.
Secondary Reviewer: Paul Brown, Ph.D., ODE IV Associate Director for Pharmacology/Toxicology, OND
Division Director: Andrea Leonard-Segal, M.D.
Project Manager: Janice Adams-king, RN, BSN, MS

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA 203697) are owned by the applicant or are data for which the applicant has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

1 Executive Summary

1.1 Introduction

This New Drug Application (NDA) was submitted by PLx Pharma Inc. for the drug product, PL2200 (325 mg Aspirin) (Formerly: Aspirin PC /PL2200). PL2200 is a modified capsule formulation consisting of aspirin, a non-steroidal anti-inflammatory drug, formulated in a lipid suspension of soybean-derived lecithin. Each PL2200 capsule contains 325 mg of aspirin (active ingredient) plus (b) (4) (lecithin).

The proposed indication is for temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; and for temporarily reducing fever. The dosing regimen for adults and children 12 years and over will be 1 or 2 capsules every 4 hours or 3 capsules every 6 hours, not to exceed 12 capsules in 24 hours.

1.2 Brief Discussion of Nonclinical Findings

There are no nonclinical toxicology studies conducted with PL2200. The nonclinical section of the NDA includes a review of the literature with respect to the nonclinical safety of aspirin.

1.3 Recommendations

1.3.1 Approvability

Based on the previous human use experience for aspirin, the agency's previous review of aspirin in the Tentative Final Monograph, as well as the lack of novel significant nonclinical toxicity issues identified during the current review, there is no impediment to approval of this NDA from a Pharmacology/Toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

None

2 Drug Information

2.1 Drug

CAS Registry Numbers:
50-78-2

Generic Names:
Aspirin

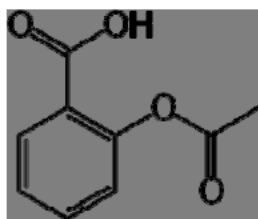
Trade Name:
Not Available

Code Names:
PL2200 Aspirin Capsules, 325 mg

Chemical Names:
Acetylsalicylic acid; 2-(acetyloxy) benzoic acid

Molecular Formulae/Molecular Weights:
 $C_9H_8O_4$ /180.16

Structure:



Pharmacologic Class:
Nonsteroidal anti-inflammatory drugs (NSAIDs)

2.2 Relevant INDs, NDAs, DMFs and other documents

Tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (53 Fed. Reg. 46204 on Nov. 16, 1988).

IND74290, AspirinPC / PL2200, PLx Pharma Inc.

The following list of DMFs is adapted from the submission:

Establishment	DMF	Component
(b) (4)		

2.3 Drug Formulation

The description of the product formulation is presented in the following table:

The quantitative composition and function of each component in the drug product is listed below.

Ingredient	Function	mg/capsule	Quality Standard
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Aspirin (b) (4)	Active Ingredient	325.0	USP
Lecithin (b) (4)	(b) (4)	(b) (4)	DMF (3)
Medium Chain Triglycerides	(b) (4)	(b) (4)	NF
Anhydrous Citric Acid	(b) (4)	(b) (4)	USP
Colloidal Silicon Dioxide	(b) (4)	(b) (4)	NF
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	DMF (3)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	USP
FD&C Blue #1	(b) (4)	(b) (4)	FDA/EC
(b) (4)	(b) (4)	N/A	USP
(b) (4)	(b) (4)	N/A	USP
Total Weight		881.6	
(b) (4)			

2.4 Comments on Novel Excipients

There are no novel excipients in PL2200. ONDQA review team (Office of New Drug Quality Assessment) assessed the formulation and confirmed that all excipients present in the drug product are either known or present in other approved drug products.

The proposed drug product contains (b) (4) in the formulation. The applicant claims that (b) (4) is lecithin and functions as an inactive ingredient in PL2200. A detailed evaluation of this issue is presented in Section 4.

2.5 Comments on Impurities/Degradants of Concern

There are no concerns of impurities/ degradants from nonclinical perspective.

The applicant has proposed separate specification for monitoring the levels of free salicylic acid (SA) in the product during release (b) (4) and stability (b) (4) and later revised to (b) (4). SA is a well-known active metabolite of aspirin, it is also found in many approved salicylate drugs in the market. The stability specification level of SA at (b) (4) in PL2200 does not raise safety concerns from a nonclinical perspective. Refer to Section 4 of this review for detailed evaluation.

2.6 Proposed Clinical Population and Dosing Regimen

The product is intended for temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; and for temporarily reducing fever. The dosing regimen for adults and children 12 years and over is 1 or 2 capsules every 4 hours or 3 capsules every 6 hours, not to exceed 12 capsules in 24 hours.

2.7 Regulatory Background

Aspirin products have been marketed worldwide for medicinal use since the 1800s. The non-prescription aspirin use for fever and pain is listed under FDA's Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (53 Fed.Reg. 46204 on Nov 16, 1988). Aspirin is also present in FDA-approved combination drug products for prescription use.

PLx first met with FDA on June 19, 2007 in a Pre-IND meeting to discuss their development plan for AspirinPC (b) (4)

On December 21, 2007, PLx submitted IND74290 for AspirinPC / PL2200. The IND was considered by the agency to be safe to proceed.

On June 30, 2009, PLx submitted an End-of-Phase 2 briefing package and the meeting with FDA was held on November 2, 2009. PLx stated that their development plan was to submit a 505(b)(2) NDA for PL2200 consistent with the OTC monograph for aspirin. (b) (4)

(b) (4) PLx also stated that (b) (4) is considered to be an excipient, not an active ingredient.

A second End-of-Phase 2 meeting was held on September 21, 2010. The meeting was focused on the role of (b) (4) and its potential impact on the efficacy and safety of aspirin. On June 17, 2011, PLx had a Type B meeting with FDA to discuss the nonclinical safety data package needed to support (b) (4). The Pre-NDA meeting for the current submission was held on December 16, 2011. In regards to the nonclinical questions at the pre-NDA meeting, PLx proposed to provide a review of the

literature with respect to the nonclinical safety of aspirin in the NDA submission. The agency considered the plan acceptable.

3 Studies Submitted

3. Studies Reviewed

There are no toxicology studies conducted with PL2200 to support the present NDA submission.

3.2 Studies Not Reviewed

There are no pivotal nonclinical studies conducted with PL2200.

(b) (4)

3.3 Previous Reviews Referenced

FDA's Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (53 Fed.Reg. 46204 (Nov 16, 1988).

Nonclinical review on AsprinPC / PL2200 under IND74290.

4 Integrated Summary and Safety Evaluation

Aspirin belongs to a family of compounds called the salicylates, the simplest of which is salicylic acid. Salicylic acid in willow bark and spiraea extracts had been known to help alleviate pains and fevers since ancient times. The success of salicylic acid prompted the pharmaceutical manufacturing house of Frederick Bayer to actively search for a derivative of comparable or better efficacy to salicylic acid. In 1897, Felix Hoffmann, a chemists working at Bayer AG produced a synthetically altered version of Salicin, acetylsalicylic acid (Aspirin), which caused less digestive upset than pure salicylic acid.

Aspirin is a non-narcotic analgesic with anti-inflammatory and anti-pyretic activity. Inhibition of prostaglandin biosynthesis appears to account for most of its anti-inflammatory and for at least part of its analgesic and antipyretic properties. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever. Aspirin can cause serious gastrointestinal injury possibly by inhibition of the production of prostaglandins, which plays a critical role in the defenses of the gastric mucosa, tissue repair and ulcer healing. Many of the salicylates share the same properties as aspirin, although its anti-platelet action is specific. Aspirin inhibits platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A₂.

Following absorption, aspirin is hydrolyzed to salicylic acid in the gut wall and during first-pass metabolism, with peak plasma levels of salicylic acid occurring within 1 to 2 hours of dosing. Salicylic acid is widely distributed to all tissues and fluids in the body

including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, kidneys, heart, and lungs. Following therapeutic doses of aspirin, approximately 75, 10, 10, and 5% is found excreted in the urine as salicylic acid, salicylic acid, a phenolic glucuronide of salicylic acid, and an acyl glucuronide of salicylic acid, respectively.

PL2200, the proposed drug product, is an immediate-release oral product consisting of aspirin formulated in a lipid suspension of soybean-derived lecithin. The proposed use of PL2200 refers to FDA's Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use.

No pivotal toxicology studies were conducted or submitted with PL2200 for the present NDA. The nonclinical safety of aspirin refers to the data and information supporting the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. The applicant, PLx Pharma Inc., has provided a review of the more recent published scientific literature on the nonclinical safety of aspirin. Overall there are no novel findings or unexplained toxicity observed. Based on the published information:

Mutagenicity and Carcinogenicity

In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Administration of aspirin for 68 weeks in the feed of rats was not carcinogenic. A carcinogenicity study conducted with current standards would generally involve 104 weeks of dosing so this previous study is of limited value.

Reproduction and Developmental Toxicities

Aspirin has been shown to inhibit ovulation in rats. Studies in rodents have shown salicylates to be teratogenic when given in early gestation, and embryocidal when given in later gestation in doses considerably greater than usual therapeutic doses in humans. Starting at 30 weeks gestation, aspirin should be avoided by pregnant women as premature closure of the fetal ductus arteriosus can occur, which may result in fetal pulmonary hypertension and fetal death. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, increased incidence of intracranial hemorrhage in premature infants, stillbirths, and neonatal death. Ingestion of aspirin within one week of delivery or during labor may prolong delivery or lead to excessive blood loss in the mother, fetus, or neonate. Prolonged labor due to prostaglandin inhibition has been reported with aspirin use. Nursing mothers should avoid the use of aspirin because salicylate is excreted in breast milk which may lead to bleeding in the infant.

The most common adverse reactions associated with the clinical use of aspirin have been gastrointestinal, including abdominal pain, anorexia, nausea, vomiting, gastritis, and occult bleeding. Other adverse reactions associated with the use of aspirin include elevated liver enzymes, rash, pruritus, purpura, intracranial hemorrhage, interstitial nephritis, acute renal failure, and tinnitus. Symptoms and

signs of severe salicylate poisoning, associated with plasma salicylic concentrations greater than 400 µg/mL, include hyperthermia, dehydration, delirium, GI hemorrhage, pulmonary edema, and CNS depression (e.g., coma). Death is usually due to respiratory failure or cardiovascular collapse.

(b) (4)

There are two issues noticed during the current nonclinical review with regards to the excipients and impurities/degradants of the drug product:

(1) The proposed drug product contains (b) (4) in the formulation. The applicant claims (b) (4) is lecithin and functions as an inactive ingredient.

A letter of authorization from (b) (4) manufacturer was included in the submission for the agency to access the information about (b) (4) contained in the corresponding DMF. (b) (4) is manufactured by (b) (4)

Lecithin is defined in the current USP/NF monograph as “a complex mixture of acetone-insoluble phosphatides, which consists chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. The evaluation by ONDQA review team and Botanical Review Team (BRT) confirmed that (b) (4) is consistent with the lecithin USP monograph (Refer to the NDA review and memorandum by ONDQA and BRT reviewers for the present NDA). Based on this information, the evaluation of (b) (4) (lecithin) in PL2200 is as follows:

- Lecithin is currently listed in FDA inactive ingredient (IIG) database at up to 15 mg/capsule for approved oral drug products and soybean-derived lecithin at up to 20 mg/capsule. The dose level of (b) (4) (lecithin) in PL2200 is (b) (4). The level of (b) (4) in PL2200 formulation is (b) (4) than amounts of lecithin currently used in approved drug products.

* For an adult at average body weight of 60kg

- However, lecithin is present in the human daily diet and is approved by FDA for human consumption as a direct food additive. The daily average intake of lecithin is approximately 1-5 grams/day (i.e. 17-83 mg/kg/day*). The levels of (b) (4) in PL2200 at (b) (4) are within the estimated daily dietary intake for lecithin. Per monograph 21CFR 184.1400, lecithin is generally recognized as safe (GRAS) as a direct food substance. "In accordance with 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice".
- The NDA contains a comprehensive literature review on the toxicity of lecithins, and two supplemental toxicity studies with (b) (4). Both studies were conducted in rats by oral gavage for 28 days. The first study was a GLP study conducted at (b) (4) on December 10, 2012. High mortality and morbidity occurred during the study. The applicant believed it was possibly associated with gavage-related trauma. The interpretation of the result of the study was therefore confounded. The applicant decided to conduct a second non-GLP study at (b) (4) on April 27, 2011. The results showed oral dosing of 2500 mg/kg/day (maximal feasible dose) of (b) (4) to rats for 28 days was not linked with any clinical or anatomic pathology. In a battery of genotoxicity studies, (b) (4) was not mutagenic or clastogenic.

Based on the above consideration in conjunction with a scientific literature review, there is no nonclinical concern related to the proposed use of lecithin under the condition specified in the proposed labeling in PL2200.

(2) The applicant has proposed separate specifications for monitoring the levels of free **salicylic acid (SA)** in the product during release (b) (4) and stability (b) (4).

The ONDQA review team considered the proposed stability specification for SA at (b) (4) is not consistent with the levels allowed for Aspirin USP tablets ($\leq 3.0\%$) and USP Aspirin capsules ($\leq 0.75\%$). An information request dated September 4, 2012 has been sent to the applicant from the agency. It was recommended that the applicant should:

- a. Revise your proposed acceptance criterion for free and total salicylic acid to NMT 3% limit to be consistent with the limits specified for reference listed drug and aspirin USP capsules and tablets

The applicant responded on October 9, 2012 and proposed a specification limit of Not More Than (NMT) (b) (4) SA and NMT (b) (4) Total Related Substances.

The stability specification level of SA at (b) (4) in PL2200 does not raise safety concerns from a nonclinical perspective because of the following factors:

- SA is present in daily food intake. Unripe fruits and vegetables are natural sources of SA, particularly strawberry, blackberries, blueberries, cantaloupes,

dates, raisins, kiwi fruits, guavas, apricots, green pepper, olives, tomatoes, radish, mushrooms and chicory. Some herbs and spices contain quite high amounts salicylates. Of the legumes, seeds, nuts, and cereals, only almonds, water chestnuts and peanuts also have significant amounts. SA is also used as a food preservative and as a bactericidal and an antiseptic.

- SA has extensive human use experiences as a medicinal product. The clinical uses, particularly fever relief, of SA have been known since ancient times. Some researchers believe that salicylate is an essential micronutrient in the human diet, potentially qualifying as a vitamin, namely Vitamin S.
- SA is a well-known active metabolite of aspirin and is responsible for the anti-inflammatory action of aspirin. It is also found in many approved salicylate drugs in the market (e.g., Pepto-Bismol). The SA limits defined in the USP monographs for Aspirin Tablets, Capsules, Coated Immediate-Release Tablets (PL2200 reference product), and Effervescent Tablets for Oral Solution are 0.3%, 0.75%, 3.0%, and 8.0%, respectively. The proposed specification of NMT (b) (4) [redacted]
- The applicant conducted a nonclinical pharmacokinetics study in male Beagle dogs. The objective of the study was to compare the bioavailability of acetylsalicylic acid or salicylic acid in PL2200 capsules under different stability conditions. Pharmacokinetic parameters of acetylsalicylic acid and free salicylic acid in the “aged” PL2200 (Bottle stored for 20 weeks at 40 °C/75% RH) were compared to those in the “fresh” PL2200 (Blister stored for 20 weeks at 25 °C/60% RH). Based on the results of this study, it was concluded that an increase in SA content in PL2200 to (b) (4) SA and a decrease in (b) (4) [redacted] to (b) (4) [redacted] do not affect the rate and extent of bioavailability. The reviewer does not consider that this nonclinical pharmacokinetics study adds any significant value to the evaluation of SA limits. Due to the extensive clinical experiences with SA, a clinical pharmacokinetics study might be more relevant or appropriate if the clinical team considers it necessary.

Overall, the stability specification level of SA at NMT (b) (4) in the PL2200 product does not raise any safety concerns from nonclinical perspective.

There are no pharmacology/ toxicology issues identified for other excipients and impurities/degradants of the drug product. ONDQA review confirms that the proposed limits for other individual related substances ((b) (4)) is acceptable and is consistent with ICH Q3B recommendations (Qualification threshold: 0.15%). No new impurities are observed during stability testing of primary and supportive batches of PL2200 above the reporting threshold of 0.05% (relative to aspirin peak area).

Based on the previous human use experience of aspirin products, the agency’s previous review of the nonclinical information, as well as the lack of novel significant

toxicity issues identified during the current review, there is no impediment to approval from a Pharmacology/Toxicology perspective.

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/s/

XINGUANG LI
12/07/2012

PAUL C BROWN
12/10/2012

I concur that the application can be approved from a pharmacology/toxicology perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203697 **Applicant:** PLx Pharma Inc. **Stamp Date:** 03/14/2012

Drug Name: Aspirin (PL2200 Aspirin Capsules, 325 mg)
Aspirin Capsules, 325 mg)

Background:

This New Drug Application (NDA) for Aspirin (PL2200 Aspirin Capsules, 325 mg) is submitted by PLx Pharma Inc. The proposed product is indicated for temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever. The proposed labeling is identical to that of other Over-The-Counter (OTC) aspirin products as per 21 CFR 343.

The descriptions of the product formulations are presented in the following tables:

The quantitative composition and function of each component in the drug product is listed below.

Ingredient	Function	mg/capsule	Quality Standard
	(b) (4)		
Aspirin (b) (4)	Active Ingredient	325.0	USP
Lecithin (b) (4)	(b) (4)	(b) (4)	DMF (3)
Medium Chain Triglycerides			NF
Anhydrous Citric Acid			USP
Colloidal Silicon Dioxide			NF
		(b) (4)	
(b) (4)		(b) (4)	DMF (3)
		(b) (4)	
(b) (4)	(b) (4)	(b) (4)	USP
FD&C Blue #1			FDA/EC
(b) (4)		N/A	USP
		N/A	USP
Total Weight		881.6	
(b) (4)			

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

PL2200 is an immediate-release oral drug product consisting of 325 mg of aspirin USP (active ingredient) and (b) (4) of soy lecithin ((b) (4), excipient). PL2200 was developed for OTC use and is being submitted as a 505(b)(2) NDA with reference to previous FDA approvals for OTC aspirin.

On initial overview of the NDA application: there are no other outstanding pharmacology/ toxicology filing issues identified at this time.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This is a 505(b)(2) application.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

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/s/

XINGUANG LI
05/15/2012

PAUL C BROWN
05/15/2012