# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203697Orig1s000

# MEDICAL REVIEW(S)

# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Application Number(s) | 203697 |
| Priority or Standard | Standard |
| Submit Date(s) | March 12, 2012 |
| Received Date(s) | March 14, 2012 |
| PDUFA Goal Date | January 14, 2013 |
| Division / Office | DNCE/ODE IV |
| Reviewer Name(s) | Linda Hu |
| Review Completion Date | December 10, 2012 |
| Established Name | Aspirin |
| (Proposed) Trade Name | (b) (4) |
| Therapeutic Class | Analgesic, antipyretic |
| Formulation(s) | Capsule, liquid filled |
| Dosing Regimen | 1 or 2 capsules every 4 hours or 3 capsules every 6 hours ;<br>do not exceed 12 capsules in 24 hours |
| Indication(s) | 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;<br>Temporarily reduces fever |
| Intended Population(s) | Adults;<br>Children 12 years and over |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Although there are issues with implementation and documentation of the PK bioequivalence study PL-ASA-001 yielded adequate data for review. For either of the two analyses presented (with or without the OSI-recommended subject exclusions), the product PL2200 is not bioequivalent to the reference drug. At the 325 mg dose, the PL2200 product may be slightly above bioequivalent dosing compared to reference drug (depending on inclusion or exclusion of specific subjects from analyses), so efficacy is not called into question, while safety is not an issue because 650 mg is also an allowed monograph dose. At the higher 650 mg dose, the PL2200 product is slightly below bioequivalent dosing compared to reference drug, so there is no safety issue, while the potential loss of efficacy is unlikely to be clinically significant. Hence the deficiencies of study PL-ASA-001 and the lack of bioequivalence for PL2200 are not such as to preclude approval. Thus, approval is recommended.

## 1.2 Risk Benefit Assessment

Aspirin (ASA) was developed in 1897 and is one of the most widely used drugs in the world, with an estimated 100 billion tablets taken per year. The Sponsor PLx Pharma (PLx) submitted the present NDA for the new aspirin formulation designated PL2200. The present submission is a 505(b)(2) application and uses a monograph aspirin as the reference drug. PL2200 is a novel immediate-release oral drug product consisting of aspirin formulated in a lipid suspension of soybean-derived lecithin. Each capsule contains 325 mg of aspirin USP (active ingredient) and (b) (4) of soy lecithin (b) (4) excipient). PLx is seeking the fever and pain indications for aspirin outlined in the Tentative Final Monograph (TFM) for over-the-counter (OTC) internal analgesic products (November 16, 1988). The Sponsor was required to submit an NDA for PL2200 because it contains (b) (4) soy lecithin which (b) (4) the quantity previously allowed as an excipient.

Two PK studies were submitted for PL2200, the cross-over aspirin bioequivalence study PL-ASA-001 and the cross-over food-effect trial PL-ASA-003. The submission also included a 7-day, endoscopic GI safety and tolerability trial. The Agency agreed that if bioequivalence was demonstrated to a monograph aspirin product, and if information was provided justifying the identification of soy lecithin as an acceptable excipient, the NDA could reference aspirin efficacy and safety from the literature and did not require pivotal efficacy or safety studies. The NDA also reviewed FDA's Adverse Event Reporting System (AERS) data from January1, 2001 through December 31, 2010. The BE study PL-ASA-001 additionally evaluated PD related to antiplatelet activity of PL2200 versus reference drug.

A consult from Dr. Marciniak (Division of Cardiorenal Products) concludes that the antiplatelet effects of PL2200 appear equivalent to reference aspirin at the 325 mg dosage.

An OSI review concluded that the clinical data generated for studies PL-ASA-001 and PL-ASA-003 are acceptable for further agency review, but not all analytical data are acceptable. The analytical data for four subjects from Study PL-ASA-001, and two subjects from Study PL-ASA-003, are not considered reliable pending review of revalidation data. Without exclusion of subjects that OSI has recommended, results of the bioequivalence study PL-ASA-001 show that test drug PL2200 is not bioequivalent to reference drug for salicylic acid, which is the aspirin metabolite primarily responsible for analgesic and antipyretic activity. PL2200 is marginally outside the BE limits of 80 to 125% to the reference drug at both dose levels (325 mg and 650 mg) evaluated in the study. With the exclusion of subjects that OSI has recommended, PL-2200 meets the BE criteria for salicylic acid at 325 mg dose, but not at 650 mg dose, where the lower limit of the 90% CI for salicylic acid AUC0-t was marginally lower than BE.

The three submitted trials provided favorable, but limited, safety experience using the new drug PL2200: a total of 151 subjects have been exposed, of whom 100 subjects received 325 mg for 7 consecutive days, 20 subjects received two doses of 650 mg each, and the remainder received single doses. There were no deaths or serious AEs in the three submitted trials. Most of the AEs were GI in nature, and there were no new or unexpected AEs. There were procedural errors in the endoscopic evaluations for study PL-ASA-002, which cast doubt on the results comparing gastric mucosal injury rates. A Central Reviewer was used but received in many cases the incorrect videos to review.

The published meta-analyses of the Bayer HealthCare database of randomized, controlled trials comparing aspirin with placebo for pain and fever relief (see Section 9.1) find AE rates with aspirin that are similar to those from placebo, although the rates of GI AEs with aspirin are slightly higher than those for placebo and statistically significant at an odds ratio (95% CI) of OR=1.3 (1.1, 1.5). Short-term use of aspirin for OTC indications is generally well tolerated. There is a higher incidence of adverse events with aspirin than with placebo, but aspirin side effects, most commonly nausea, vomiting, abdominal pain, headache, dizziness, and tinnitus, are mainly mild to moderate. When used for dysmenorrhea, aspirin does not increase menstrual blood loss.

Aspirin is also a commonly prescribed NSAID for treatment of pain and inflammation, and low-dose aspirin is prescribed routinely in primary and secondary prophylaxis of cardiovascular and cerebrovascular events. ASA is also combined with additional antiplatelet drugs such as clopidogrel, with increasing emphasis on extended use. Owing to this widespread use, the AERS database continues to accumulate serious adverse event reports for aspirin. AERS reports with oral dosage of aspirin as suspect drug amount to a total of 9704 case reports with 37,953 associated events over the ten-year interval covered from January 1, 2001 through December 31, 2010. Nearly all (98.3%) of these case reports were serious (as could be expected for a drug with such a long history of use). There were 8058 events from fatal cases including 472 completed suicides. The most common serious AEs were GI disorders, especially those related to GI

bleeding. The cases in which daily dose or dose regimen was reported account for about half of all serious events in AERS for oral, single ingredient aspirin. About 2/3 of AEs in the cases with known dose were experienced with daily doses of 100 mg or less, which are likely cases where aspirin was taken for a cardiovascular indication.

The aspirin literature (see Section 9.1) is notable for a 2008 consensus report, from the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, on GI risks from low-dose aspirin which is routinely used for primary and secondary prophylaxis of cardiovascular and cerebrovascular events. The use of low-dose ASA for cardio-prophylaxis is associated with a 2- to 4-fold increase in upper gastrointestinal event risk. The estimated average excess risk of upper gastrointestinal event related to cardio-prophylactic doses of ASA is 5 cases per 1000 ASA users per year. OTC use of low-dose ASA is implicated in over one-third of the patients admitted to hospitals for GI hemorrhage. Aspirin is also combined with additional antiplatelet drugs such as clopidogrel, e.g., after recent non-ST elevation acute coronary event, or after implantation of drug-eluting stents. The combined use of aspirin and clopidogrel may lead to further increased risk of GI bleeding.

The risk/benefit assessment notes that aspirin is included in the TFM for OTC internal analgesic products and has a well-established, favorable risk/benefit balance for short-term fever and pain relief. However, aspirin is also widely used for non-monograph indications like cardio-prophylaxis, which involve chronic use, often at low-dose. Here the risk of serious GI complications from such aspirin use is well-documented and must be balanced against the also well-documented cardiac benefits, but low-dose aspirin for cardio-prophylaxis is appropriately a prescription-only indication wherein the need for this treatment, with or without additional treatments such as anti-platelet therapy and/or proton pump inhibitor therapy, is judged by physicians for individual patients.

This review concludes that the safety and efficacy of PL2200 can still be bridged to safety and efficacy information from the aspirin literature and post-market experience from AERS. Major issues were noted with the implementation and/or documentation for the three submitted trials (see findings of the OSI audit listed in Section 5.2 and reviews of the individual studies in Section 5.3), and the pivotal BE trial did not demonstrate bioequivalence to monograph aspirin (see section 5.3). Nevertheless, the deviations from BE (PL2200 325 mg is slightly above BE dosing but PL2200 650 mg is slightly below BE) were unlikely to be clinically significant, and the available safety and efficacy information for aspirin are applicable to PL2200.

The Select Committee of GRAS Substances issued a 1979 evaluation of the safety of lecithin used in foods (see Section 9.1) which concluded that there is no evidence of a hazard from lecithin used at current levels. Patient exposure to the soy lecithin in each PL2200 capsule would be (b) (4) with a maximum daily exposure of (b) (4) (b) (4) which would be similar to the estimated natural dietary intake. It is concluded that there is no safety issue with the lecithin in PL2200.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

none

## 1.4 Recommendations for Postmarket Requirements and Commitments

none

# 2 Introduction and Regulatory Background

## 2.1 Product Information

The active ingredient in aspirin, acetylsalicylic acid, is a synthetic derivative of salicin which occurs naturally in plant, notably the willow tree. Extracts of willow have been used for centuries; as early as 400 BC, Hippocrates recommended a brew from willow leaves to treat labor pains. In 1897, Felix Hoffman of the Bayer pharmaceutical company developed the synthesizing process that produces acetylsalicylic acid, later named aspirin. Today aspirin is the best known and most widely used medication in the world with an estimated 100 billion tablets swallowed every year.

PL 2200 is a lipidic suspension containing the active ingredient aspirin (acetylsalicylic acid) in an opaque 2-piece (b) (4) hard capsule for oral administration. The capsule contains 325 mg aspirin and compendial inactive ingredients Soy Lecithin (b) (4) Medium Chain Triglycerides, Anhydrous Citric Acid, and Colloidal Silicon Dioxide. PL2200 is an immediate-release aspirin formulation, and PLx Pharma (PLx) is seeking the indications for aspirin outlined in the Tentative Final Monograph for over-the-counter (OTC) internal analgesic products (November 16, 1988):

- temporary relief of minor aches and pains associated with a cold, headache, backache, muscular aches, toothache, premenstrual and menstrual cramps, minor pain of arthritis
- temporarily reduces fever

(b) (4)

## 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1 Currently Available Drugs**

| Drug | Regulatory Status | Class |
|---|---|---|
| Ibuprofen | Prescription and OTC | NSAID |
| Naproxen | Prescription and OTC | NSAID |
| Ketoprofen | Prescription and OTC | NSAID |
| Aspirin | Monograph | NSAID |
| Acetaminophen | Prescription and Monograph | Analgesic, antipyretic |

## 2.3 Availability of Proposed Active Ingredient in the United States

Aspirin is widely available in the United States and worldwide. Aspirin is an accepted pain reliever and fever reducer in the OTC Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (Nov. 16, 1988).

## 2.4 Important Safety Issues with Consideration to Related Drugs

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) at higher than recommended OTC doses, or for longer than recommended, leads to increased risk of GI bleeds. In addition, cardiovascular risks of NSAIDs have also become a concern. Prescription labels for NSAIDs carry the following black box warnings:

**Cardiovascular Risk**

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- The NSAID is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

**Gastrointestinal Risk**

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Prescription class labeling of NSAIDs also includes warnings about anaphylactoid reactions and skin reactions including Stevens-Johnsons Syndrome and toxic epidermal necrolysis.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

PLx submitted a meeting request to the FDA for a Pre-IND meeting on June 19, 2007 to discuss developing an oil-based aspirin formulation (b) (4) As aspirin is chemically acetylsalicylic acid and is rapidly hydrolyzed to the primary metabolite salicylic acid after oral administration, it was agreed during the pre-IND stage to use salicylic acid as the analyte for demonstrating bioequivalence. Salicylic acid as a primary analyte for BE analysis was also used in the NDA review of Extra Strength Bayer Migraine drug product (NDA 21317; DARRTS dated 06/05/2001). From the mechanism of action point of view, salicylic acid is the active moiety responsible for most anti-inflammatory and analgesic effects whereas acetylsalicylic acid is the active moiety for the antiplatelet-aggregation effect. (b) (4)

(b) (4)

FDA had several concerns including:

- (b) (4)
- (b) (4)
- (b) (4)

The sponsor was also notified that (b) (4)

In a November 29, 2007 correspondence, PLx requested further clarification; a follow-up telephone conference was held. The IND was submitted on December 21, 2007 and felt to be safe to proceed. (b) (4)

- (b) (4)

PLx submitted an End-of-Phase 2 briefing package on June 30, 2009 and the meeting was held November 2, 2009. The sponsor stated their current development plan was to submit a 505(b)(2) NDA for PL2200 consistent with the OTC monograph for aspirin. (b) (4) PLx also stated that phosphatidylcholine is considered to be an excipient, not an active ingredient. Action items and discussion points from this meeting included:

- PLx will need to provide a scientifically justifiable function for the phosphatidylcholine as an excipient.
- The results of PL-ASA-001 (the pharmacokinetic study) did not demonstrate bioequivalence for PL2200 325 mg but did for 650 mg. PLx was asked to provide an explanation for this and to explain why the difference was not a clinical concern.
- FDA agreed that PLx may utilize well-conducted studies in the published literature to support the safety and efficacy of aspirin for the pain and fever indications.

- PLx will need to show that PL2200 is equivalent to aspirin in its pharmacodynamic profile; endpoints such as COX activity, prostaglandin concentration or platelet activity could be used to demonstrate this.

A second End-of-Phase 2 meeting was requested May 7, 2010 and the meeting was held September 21, 2010. The role of phosphatidylcholine and its potential effects on the human body and the action of aspirin were again discussed. FDA expressed concern regarding the extrapolation of data from PLx's *in vitro* study to *in vivo* settings, and recommended that PLx conduct an *in vivo* study with a control group to properly characterize the effects of (b) (4) on the PD and PK profile of aspirin. ( (b) (4) is the source of phosphatidylcholine for PL2200.) FDA reiterated that PLx's claim of (b) (4) as a GRAS ingredient in foods is not sufficient to prove that this ingredient is necessarily safe to be used in a drug product. PLx agreed to provide a comprehensive toxicity profile (including animal and human data) for (b) (4) PLx was also given specific advice regarding the CMC requirements and stability data needed for (b) (4) and PL2200.

Following this discussion, PLx submitted a meeting request January 15, 2011 to discuss the nonclinical safety data package needed to support (b) (4). This Type B meeting was held June 17, 2011. A primary point of discussion was the completed 28-day GLP toxicity study. The study had many complicating factors that made interpretation difficult. PLx planned to conduct a new GLP study with revised procedures to provide for more interpretable data. FDA agreed with this plan and requested that PLx submit the new study protocol for review. FDA also commented that although the analytical characterization of (b) (4) appeared to be (b) (4) they would prefer to know 100% of the components. PLx stated (b) (4) is a natural, soybean-derived product and that complete 100% characterization of all components would not be realistic. PLx planed to submit a formal request asking that DNCE seek input from the Botanical Review Team regarding the appropriate level of component characterization. PLx will also submit Type IV DMF standards for (b) (4)

A Pre-NDA meeting request was sent September 22, 2011. PLx submitted the briefing package on November 9, 2011 and the meeting was scheduled for December 16, 2011. The sponsor reported that their clinical, nonclinical, manufacturing, analytical, and contractor sites are ready for pre-approval inspections. PLx wished to review their application plan and provide an overview of the data to be presented in the NDA. The meeting package included a summary of the drug product, CMC information, a nonclinical data summary, and a clinical data summary. Discussion points and action items from this meeting included:

- PLx will submit primary data package to assess change in drug product over time
- PLx will provide a report of the dissolution method including paddle speeds along with justification in the NDA submission. PLx understands that (b) (4) paddle speeds may be acceptable if IVIVC and AUC data is also acceptable.
- PLx will provide particle size distribution of aspirin in the NDA submission.
- PLx will submit bioequivalence differences in the fed and fasted state to show that food effect is not clinically significant. PLx will need to provide a rationale for why

bioequivalence criteria were not met for the 325 mg dose and provide a rationale for why this difference is not of clinical concern.
- PLx will submit information regarding differences between the study drug and the final to-be-marketed drug product.
- PLx will submit IVIVC data prior to submission of the NDA.

The NDA was submitted by PLx Pharma on March 14, 2012. The sponsor believes their studies have demonstrated bioequivalence of PL2200 to Genuine Bayer® Aspirin 325 mg tablets. In addition, PLx is referencing FDA's prior findings of safety and efficacy of aspirin as set forth in the TFM as well as supporting literature references.

### 2.6 Other Relevant Background Information

NA

# 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

This was an electronic submission. It was deemed to be of acceptable quality and was filed. Debarment Certification, dated January 25, 2012, was submitted for this application.

### 3.2 Compliance with Good Clinical Practices

The clinical trials were carried out in accordance with the U.S. Code of Federal Regulations, Good Clinical Practice, 21 CFR Parts 50 and 312, the principles enunciated in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding Good Clinical Practice. All protocols, amendments, and informed consent forms were reviewed and approved by an Institutional Review Board (IRB). The studies did not start until the IRB had approved the protocol or a modification thereof. The IRB was constituted and operated in accordance with the principles and requirements described in the U.S. Code of Federal Regulations (21 CFR Part 56).

### 3.3 Financial Disclosures

In accordance with 21 CFR 54.4(a)(3) all clinical investigators that were involved in the conduct of a study as part of this new drug application were evaluated. Form FDA 3454 certifying and disclosing any financial interests and arrangements for studies was completed.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

[redacted] is manufacturer of the aspirin drug substance (active pharmaceutical ingredient, API). [redacted] were inspected by the FDA on [redacted] and were considered to be in compliance with the principles of Good Manufacturing Practice (GMP) for active substances (EU GMP Part II). PLx Pharma, Inc has been given the right of reference to [redacted] DMF [redacted].

Pharmaceutics International, Inc. (PII), Hunt Valley, MD 21031, is the manufacturer of the drug product, PL2200, Aspirin Capsules, 325 mg. The latest GMP inspection of PII took place on August 18, 2011 and the facility was found to be acceptable. All clinical batches (#13105.001, 13105.002, and 13105.003) and registration batches (#13105.004–13105.006) were manufactured, stored, and released at PII. All stability testing other than phospholipid testing was performed at PII.

[redacted] is a contract packager situated in two packaging facilities [redacted] facility has [redacted] of cGMP packaging space and conducted HDPE bottle packaging of PL2200 Aspirin Capsules, 325 mg for lots 13105.003, 13105.004, 13105.005, and 13105.006. The latest GMP inspection of [redacted]) took place on [redacted]. No Form FDA-483 was issued. The [redacted] facility has [redacted] of cGMP packaging space and conducted [redacted] blister packaging of PL2200 Aspirin Capsules, 325 mg for lots 13105.003, 13105.004, 13105.005, and 13105.006. The latest GMP inspection of the [redacted] took place on [redacted] No Form FDA-483 was issued.

PL2200 is a novel immediate-release oral drug product consisting of aspirin formulated in a lipid suspension of soybean-derived lecithin. Each capsule contains 325 mg of aspirin USP (active ingredient) and [redacted] of soy lecithin [redacted] excipient).

[redacted]

A listing of these excipients and their maximum approved unit amount in oral formulations, per the FDA Inactive Ingredients Database is shown in Table 2.

**Table 2: Inactive Ingredients in PL2200 Capsule**

| Excipients | CAS No. | Function | Amount/Capsule 325 mg API | Maximum Level in FDA Database for Oral Dosage Forms (mg/capsule or tablet) |
|---|---|---|---|---|
| (b) (4) | | | | |

API = aspirin; a: for oral solution
Source: NDA 203697, Module 2.4.2, Table 1

See the chemistry review for further information including discussion of stability/expiry issues.

## 4.2 Clinical Microbiology

NA

## 4.3 Preclinical Pharmacology/Toxicology

The primary source of lecithin in PL2200, (b) (4), is a soybean-derived lecithin excipient consisting of at least (b) (4) phosphatidylcholine, (b) (4) (b) (4). Soybean-derived lecithin is permitted for use by FDA as an inactive ingredient in drug products at oral dose amounts of up to 20 mg/soft gelatin capsule and up to 0.2% in oral suspensions. Phosphatidylcholine is permitted for use by FDA as an inactive ingredient at oral dose amounts of up to 15 mg/capsule, 53 mg/chewable bar, and as an oral powder for suspension at 3.34%. Lecithin is approved for human consumption as a food additive and generally recognized as safe (GRAS) by FDA Center for Food and Nutrition with no restrictions other than current GMPs. Lecithin is by definition a component of food (*e.g.* egg yolk, soybeans, grains, wheat germ, fish, legumes, yeast, and peanuts, to name a few). The average diet provides a daily intake of several grams of lecithin (approximately 1000-5000 mg) [15 – 77 mg/kg/day].

Patient exposure to (b) (4) in each PL2200 capsule would be (b) (4) with a maximum daily exposure of (b) (4) (325 mg/capsule x 12 capsules). For a patient with an average body weight of 65 kg, this would be equivalent to (b) (4) (1 capsule) and (b) (4) (12 capsules), respectively. Although patient exposure to Phosal® 35SB in the PL2200 formulation would be (b) (4) than amounts of soybean-derived lecithin or lecithin currently used in approved drug products, these exposure levels to (b) (4) are within the estimated daily dietary intakes for lecithin. Furthermore, a memo from chemistry notes that per CFR 184.1400, lecithin is generally recognized as safe (GRAS) material and is defined under chapter titled direct food substances affirmed as generally recognized as safe as follows:

(a) Commercial lecithin is a naturally occurring mixture of the phosphatides of choline, ethanolamine, and inositol, with smaller amounts of other lipids.
(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), pp. 166-167, which is incorporated by reference.
(c) In accordance with 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice.
(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

The chemists note that [redacted] meets the above definition for lecithin under the National Formulary (NF) monograph and 21CFR 184.1400. The botanical team has also evaluated Lecithin ([redacted]) and has not identified any safety nor quality issues concerning [redacted] they concluded that the use of [redacted] as an USP-NF equivalent lecithin is appropriate.

Medium chain triglycerides, anhydrous citric acid, and colloidal silicon dioxide are commonly used excipients in oral pharmaceutical formulations. The proposed levels in the PL2200 formulation do not present safety concerns.

See the pharmtox, botanical, and chemistry reviews for evaluation of the preclinical data and assessment of [redacted] as an inactive ingredient.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Acetylsalicylic acid (aspirin) is used to treat mild to moderate pain, including migraine headache pain; inflammatory conditions such as rheumatoid arthritis; and, in low doses, as an antiplatelet agent in cardiovascular disease. It is a gastrointestinal irritant, and may cause discomfort, ulcers and bleeding. It may also cause tinnitus at high dose, and it is no longer used in children and adolescents, in whom it may cause Reye's syndrome. The anti-inflammatory action for aspirin derives from inhibition of COX-1 and COX-2 proteins and the derived prostanoids. Aspirin also irreversibly inhibits formation of thromboxane A2 in platelets, thereby inhibiting platelet aggregation.

Phosphatidylcholine is important for normal cellular membrane composition and repair and is the major delivery form of the essential nutrient choline. Phosphatidylcholine is a normal, ubiquitous structural constituent of the mammalian cellular and subcellular membranes. High concentrations of phosphatidylcholine are normally present in bile, and it may be a component of the extracellular layer of the gastro-duodenal epithelia as well.

### 4.4.2 Pharmacodynamics

(b) (4)

[redacted]

### 4.4.3 Pharmacokinetics

Acetylsalicylic acid is poorly soluble in the acidic conditions of the stomach, which can delay absorption of high doses for eight to 24 hours but is rapidly absorbed in the small intestine with its increased pH and larger surface area. At low concentrations (< 100 μg/mL), approximately 90% of plasma salicylate is bound to albumin, while at higher concentrations (> 400 μg/mL), only about 75% is bound. Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide.

With large salicylate doses such that metabolic pathways in the liver become saturated, renal excretion becomes increasingly important. When small doses (less than 250 mg in an adult) are ingested, the elimination half-life is about 2.0 to 4.5 hours. When higher doses of salicylate are ingested (more than 4 g), the half-life becomes much longer (15–30 hours).

The pharmacokinetics of soy-derived phosphatidylcholine have not been extensively studied. Oral administration of purified soy phosphatidylcholine to humans has a $T_{max}$ of 6 hours, $C_{max}$ of 20% of the administered dose, and a plasma half-life of approximately 6 hours. A significant portion of the administered dose of phosphatidylcholine may be redistributed to the lipid compartment.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

**Table 3 Clinical Trials Submitted**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status |
|---|---|---|---|---|---|---|---|---|---|
| BE/ Phase 1 | PL-ASA-001 | Section 5.3.1.2 | Comparative PK study of 2 doses of PL2200 (ASA-PC) to assess BE, safety and to confirm anti-platelet activity after treatment | Randomized, open-label, single-dose, crossover<br><br>Active control | PL2200<br>325 mg (1 capsule)<br>650 mg (2 capsules)<br>[Lot# 13105.001B]<br><br>Genuine Bayer® Aspirin tablets<br>325 mg (1 tablet)<br>650 mg (2 tablets)<br>[Lot# 253217K]<br><br>Single oral dose with 240 mL of water<br>Treatments separated by 14-17 days washout | 32 randomized<br>30 completed | Healthy subjects | Single dose | Complete |
| GI Safety/ Phase 2 | PL-ASA-002 | Section 5.3.5.4 | Determine subchronic GI safety of PL2200 compared to immediate-release aspirin in healthy volunteers | Randomized, single-blind, parallel-group<br><br>Active control | PL2200<br>325 mg (1 capsule)<br>[Lot# 13105.001B]<br><br>Walgreens Aspirin<br>325 mg (1 tablet)<br>[Lot# P53405]<br><br>Oral dose, once daily for 7 days, 30 minutes prior to a meal with 240 mL of water. Day 1 dose no later than 7 days after baseline endoscopy. Final dose at Day 7, with 4-6 hours between final dose and Day 7 endoscopy. | 204 randomized<br>198 completed | Healthy subjects | 7 days | Complete |
| PK/ Phase 1 | PL-ASA-003 | Section 5.3.1.1 | Determine the effect of food on single-dose pharmaco-kinetics of PL2200 | Randomized, open-label, single-dose, crossover, food-effect<br><br>Active control (fed vs. fasted) | PL2200<br>650 mg (2 capsules)<br>[Lot# 13105.003A] | 20 randomized<br>20 completed | Healthy subjects | Single dose | Complete |

## 5.2 Review Strategy

The clinical program for PL2200 included two PK studies, the cross-over aspirin bioequivalence study PL-ASA-001, and the cross-over food-effect trial PL-ASA-003. The submission also included one GI safety and tolerability trial, PL-ASA-002 which was a multiple-dose, 7-day, endoscopic evaluation of upper GI mucosal damage induced by PL2200 versus aspirin in healthy volunteers. In agreement with the Agency, efficacy could be supported from the aspirin literature which is evaluated by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). Also in agreement with the Agency, safety of PL2200 was to be evaluated in the three studies noted above, and safety was further evaluated from the aspirin literature and from a review of aspirin adverse events in AERS and is covered in this review. The BE study PL-ASA-001 additionally evaluated PD related to antiplatelet activity of PL2200 versus reference aspirin, which was evaluated by DCRP.

The crossover BE study PL-ASA-001 comparing PL2200 with reference drug (Genuine Bayer® Aspirin tablets) and the food effect study PL-ASA-003 were reviewed by Dr. Naraharisetti (Clinical Pharmacology reviewer, OCP II) in regard to BE for salicylic acid PK. Audits of the clinical and analytical portions of both studies were performed by the Office of Scientific Investigations (OSI).

The OSI review concluded that the clinical data generated for studies PL-ASA-001 and PL-ASA-003 are acceptable for further agency review; however, not all analytical data are acceptable. The analytical data for subjects 102, 105, 126 and 116 (ASA and SA) from Study PL-ASA-001, and subjects 007 and 008 (SA only) from Study PL-ASA-003 are not considered reliable pending review of revalidation data by the Agency. OSI reported the following observations pertaining to studies PL-ASA-001 and the associated validation studies:

1. Failure to document all aspects of sample storage and handling (i.e. maintaining specimen tracking log) during conduct of Study PL-ASA 3-14-2008. for the following:
    a) Samples (plasma, serum and urine) received on 2-19-2008, 2-20-2008, 2-27-2008, 3-5-2008, 3-12-2008, and 3-14-2008.
    b) Plasma samples during analysis of plasma Acetylsalicylic Acid (ASA) and Salicylic Acid (SA) in runs AsaJ09, AsaJ10, AsaJ13, AsaJ16, and AsaJ17; serum samples during analysis of serum Thromboxane B2 in runs TBXG01, TBXGOla, TBXG02, TBXG03, TBXG04, and TBXG08.
    c) QC samples during analysis of plasma ASA, SA, and serum Thromboxane B2.
2. Failure to document all aspects of sample processing during validation study of ASA and SA: Specifically, adequate information was not documented for processing of calibration standards and QCs during evaluation of "Processed Batch Stability"/"Autosampler Reproducibility" (3 days at room temperature).
3. Failure to have a confirmatory step (e.g. by balance printer or witness initials) for the reference material weighing used in the preparation of calibration standard and QC stock solutions.

The OCP II Clinical Pharmacology reviewer evaluated the BE study PL-ASA-001 in two scenarios, with and without exclusion of the four subjects whose data was not considered to be reliable by OSI. The OCP II review is tentative pending resolution of data validity by OSI.

## 5.3 Discussion of Individual Studies/Clinical Trials

**PL-ASA-001**
**Study Title:** A Randomized, Actively Controlled, Cross-over Bioequivalence Study of Aspirin-PC (ASA-PC; PL2200) versus Aspirin in Healthy Volunteers.

**Methodology**:
This trial was a randomized, actively-controlled, cross-over bioequivalence study comparing single doses of PL2200 with the reference drug aspirin. A total of 32 healthy subjects were randomized to treatment with either immediate release reference aspirin tablets or PL2200 capsules. Subjects were further randomized to receive either 325 mg or 650 mg doses. After completion of the first treatment and a minimum of a 2-week washout period (14 - 17 days), all but 2 subjects were crossed over and received treatment with the alternative drug at the same dose level; i.e., subjects randomized to receive aspirin tablets in the first treatment received PL2200 as the second treatment, and vice-versa. Blood samples for evaluation of pharmacokinetic (PK) variables and anti-platelet activity were collected over a 24-hour period after drug administration. Laboratory assessments (hematology, blood chemistry) were performed at screening, just prior to each study drug administration (at Visits 1 and 3), and 24 hours after each study drug administration (at Visits 2 and 4). Adverse events and the use of concomitant medications were monitored throughout the study.

Thirty-two subjects were treated in this crossover study, such that 16 subjects were to receive both aspirin and PL2200 at 325 mg each and 16 subjects were to receive both aspirin and PL2200 at 650 mg each. Two subjects in the 325-mg treatment group were discontinued from the study before receiving their second study drug administration, resulting in 14 subjects receiving both aspirin and PL2200.

**Objectives:**
- To determine the safety of PL2200 at 325-mg and 650-mg dose levels.
- To assess the bioequivalence of single-dose pharmacokinetics of PL2200 to aspirin at 325-mg and 650-mg dose levels.
- To assess the anti-platelet pharmacodynamic (PD) bioequivalence of PL2200 to aspirin at 325-mg and 650-mg dose levels.

**Inclusion Criteria** were as follows:
Subject is at least 21 years of age.
- Subject is healthy.
- If female and of childbearing potential, subject has a negative pregnancy test and is not nursing.

- If female and of childbearing potential, subject is using adequate birth control for the duration of the study.
- Subject is able to understand and comply with study procedures.
- Subject is a non-smoker.
- Subject consumes no more than 1 alcoholic drink per day.
- Subject agrees to refrain from alcohol consumption for 48 hours prior to each drug administration and 48 hours after each drug administration.
- Subject is able and willing to provide written informed consent prior to any study procedures being performed.

**Exclusion criteria**:
- Subject has abnormal screening/baseline laboratory parameters deemed to be clinically significant by the Investigator.
- Subject has taken any prescription medications other than hormone replacement therapy or thyroid replacement hormones within 3 days prior to drug administration.
- Subject has taken any of the following medications within 2 weeks prior to study entry:
  - NSAIDs or other medications for pain, including aspirin or aspirin-containing products and acetaminophen
  - Proton pump inhibitors, including Prilosec®, Prevacid®, Aciphex®, Protonix®, or Nexium®
  - H-2 blockers, including Tagamet®, Zantac®, Axid®, or Pepcid®
  - Any anti-platelet agent, including Plavix®, Ticlid®, Pletal®, ReoPro®, Integrilin®, Aggrastat®, or Persantine®
  - Any anti-coagulant, including Coumadin®, Acenocoumarol, Phenprocoumon, Phenindione, Heparin, Exanta®, Argatroban, Lepirudin, Hirudin or Bivalirudin
- Subject has used an investigational agent within the past 30 days.
- Subject has hypersensitivity or contraindications to aspirin, ibuprofen, or other NSAID.
- Subject has sensitivity to lecithin.
- Subject has a history of gastrointestinal problems including ulcers, frequent indigestion, or heartburn.
- Subject has a history of stroke, myocardial infarction, or congestive heart failure.
- Subject has a history of asthma, other bronchospastic activity, nasal polyps, or angioedema other than resolved childhood asthma.
- Subject has a history of kidney or liver disease.
- Subject has a history of thrombocytopenia, neutropenia, or bleeding disorder.
- Subject has a history of coronary arterial bypass.
- Subject has a history of non-trauma related hemorrhage.
- Subject has a history of chronic hypertension.
- Subject is currently enrolled in another investigational trial.
- Subject's platelets are unresponsive to arachidonic acid.

**MO Comment:** *The inclusion and exclusion criteria to define healthy volunteer population were comprehensive and are acceptable for a PK study.*

Subjects were instructed to abstain from alcohol for 48 hours before each dose and for 48 hours after each dose. They were instructed not to eat anything for 10 hours prior to administration of the study drug, and they were required take the study medication with 240 mL water. Each subject was provided a standard meal 4 hours after drug administration, and dinner was allowed 10 hours after administration. After dinner, subjects refrained from eating until after their 24-hour blood draw, and they were allowed to consume a maximum of 8 ounces of water only until then. After the 24-hour blood draw, subjects were allowed to eat and drink immediately.

The study timeline is shown in Table 4

**Table 4 PL-ASA-001 Schedule**

| Procedure/Assessment | Screening[1] | Baseline Prior to First Treatment Day 0 | First Treatment Day 0 | 24 Hours After First Treatment (±1 hour) | Baseline Prior to Second Treatment (Treatment with Crossover Drug) Day 14-17 | Second Treatment (Treatment with Crossover Drug) Day 14-17 | 24 Hours After Second Treatment (±1 hour) |
|---|---|---|---|---|---|---|---|
| | | Visit 1 | Visit 1 | Visit 2 | Visit 3 | Visit 3 | Visit 4 |
| Informed Consent | X | | | | | | |
| Eligibility | X | X | | | X | | |
| Demographics | X | | | | | | |
| Medical History | X | | | | | | |
| Vital Signs | X | X | X | X | X | X | X |
| Physical Exam | X | | | X | X | | X |
| Hematology Labs[2] | X | | | X | X | | X |
| Blood Chemistry Labs[2] | X | | | X | X | | X |
| Pregnancy Test[3] | X | | | | X | | |
| Drug Administration | | | X | | | X | |
| Blood draw for PK tests[2] | | X | X | X | X | X | X |
| Platelet function tests[2] | X | X | X | X | X | X | X |
| Urinary 11-dehydro-$TxB_2$[4] | | X | | X | X | | X |
| Concomitant Medications | X | X | X | X | X | X | X |
| Adverse Events | | | X | X | X | X | X |

1 Performed within 10 days prior to Day 0.
2 Blood draws were performed according to the schedule in Table 2.
3 In females of childbearing potential only.
4 Subjects were given a sample container to collect the first urination of the day on the Day 0 and 14 prior to drug administration and Day 1 and 15 after drug administration.

The schedule of blood draws is shown in Table 5:

**Table 5 PL-ASA-001**

| Time Relative to Drug Administration (Per Treatment) | Blood Sampling Time Points for Intended Assays | | | | | |
|---|---|---|---|---|---|---|
| | PK | Platelet Aggregation | Hematology | Blood Chemistry | $TxB_2$ | Serum Pregnancy Test |
| Screening (within 10 days prior to treatment) | | X* | X | X | | X |
| Within three (3) hours pre-dose | X | X | | | X | |
| 5 minutes post | X | | | | | |
| 10 minutes post | X | | | | | |
| 15 minutes post | X | | | | | |
| 20 minutes post | X | | | | | |
| 25 minutes post | X | | | | | |
| 30 minutes post | X | | | | | |
| 40 minutes post | X | | | | | |
| 50 minutes post | X | | | | | |
| 60 minutes post | X | | | | | |
| 75 minutes post | X | | | | | |
| 90 minutes post | X | | | | | |
| 2 hours post | X | | | | X | |
| 3 hours post | X | | | | | |
| 4 hours post | X | | | | X | |
| 6 hours post | X | X | | | X | |
| 8 hours post | X | | | | X | |
| 10 hours post | X | | | | X | |
| 24 hours post (±1 hour) | X | X | X | X | X | |

*Applied to first treatment only

Safety Assessments included physical exam, vital signs, laboratory assessments (hematology, blood chemistry), and collection of adverse events.

Physical examinations were performed at Screening, and Visits 2, 3, and 4.

Vital signs were measured at Screening, prior to the dose administrations at Visit 1 (first treatment) and Visit 3 (second treatment), after the dose administrations at Visits 1 and 3, and at 24 hours after the dose administrations (Visits 2 and 4).

Laboratory assessments were performed at Screening, and after the 24-hour PK blood sample (Visit 2). Laboratory assessments were again performed prior to second treatment dose at Visit 3 and 24 hours after the second treatment (Visit 4). Additionally, platelet function was assessed at Screening, within 3 hours pre-dose, 6 hours post-dose and 24 hours post-dose. The following lab tests were assessed:

- Hematology: White blood cell count, red blood cell count, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, PT, and PTT.
- Blood Chemistry: Sodium, potassium, chloride, $CO_2$, BUN, creatinine, SGPT/ALT, SGOT/AST, total bilirubin, phosphorus, calcium, uric acid, total protein, albumin, cholesterol, triglycerides, glucose, and alkaline phosphatase.

**Salicylic acid PK results**

Mean plasma concentrations of salicylic acid were compared for PL2200 and aspirin at 325-mg and 650-mg doses. Salicylic acid levels are a measure of analgesic and anti-inflammatory activity. The PK analyses in the NDA as originally submitted by PLx Pharma on March 12, 2012 were incorrect, and the Sponsor submitted a revised dataset and analyses on Oct. 9, 2012. The Sponsor explained that programming errors were made in analyses of PK parameters, specifically Kel and AUC, and the incorrect statistical model was utilized (SAS ANOVA GLM fixed-effects model rather than SAS ANOVA mixed-effects model). The FDA Clinical Pharmacology reviewer, Dr. Naraharisetti, of the Division of Clinical Pharmacology II, re-evaluated bioequivalence, and results of his analyses are summarized below.

Also at issue is inclusion or exclusion of data from several subjects for salicylic acid bioequivalence analyses comparing ASA and PL2200 at 325 and 650-mg dose levels:

- For the 325-mg dose, out of 16 subjects, 14 subjects completed both treatment arms. Two subjects received only one of the treatments and were excluded from the BE analysis: #116 (received only reference drug) and #117 (received only PL2200).
- For the 650-mg dose, out of 16 subjects, 15 subjects completed both treatment arms. One subject, #115 was incorrectly dosed at 325-mg for PL2200 instead of 650-mg. Accordingly #115 was excluded from the BE analysis at 650 dose.
- In the Oct 9th submission, the Sponsor proposed to exclude subjects 126 (325- mg) and 123 (650-mg) as statistical outliers. The plasma concentration time profiles for these two subjects appeared not to match the reported doses: Subject 126 was dosed 325 mg but yielded a profile more like that of a 650 mg dose, whereas Subject 123 was dosed 650 mg with a profile more like that of a 325 mg dose. However per CRFs these two subjects were correctly dosed. The Clinical Pharmacology reviewer stated that these two subjects should be included in the BE analysis.
- The Office of Scientific Investigations (OSI) initial review recommended exclusion of subjects 102 (650 mg arm), 105 (320 mg), 126 (320 mg) and 116 (320 mg) from Study PL-ASA-001. They are awaiting further data from the Sponsor before making their final recommendation.

Table 6 summarizes results of the FDA Clinical Pharmacology BE analyses, without the exclusion of subjects as recommended by OSI ("Current Analysis"), and with these exclusions. According to the current BE analyses without OSI-recommended subject exclusions, the test drug PL2200 is not bioequivalent to reference drug for salicylic acid, as it is marginally outside the BE limits of 80% to 125% versus reference drug at both dose levels. At the 325-mg dose level, the 90% CI upper limits are marginally too high for (log transformed) Cmax, $AUC_{0-t}$, and $AUC_{0-inf}$ , since the upper confidence limit ratios for test product to reference product are 126.4%, 125.7% and 125.1% respectively. At the 650-mg dose level, the 90% CI lower limits for log transformed $AUC_{0-t}$ and $AUC_{0-inf}$ are marginally too low at 76.3% and 78.5%, respectively, for the test product versus the reference product.

With the exclusion of subjects that OSI has recommended, PL2200 meets the BE criteria for salicylic acid at the 325 mg dose, but not at the 650 mg dose. At the 325-mg dose level, the upper and lower 90% CI limits for log transformed Cmax, $AUC_{0-t}$, $AUC_{0-inf}$ ratios are within 80% to 125% of reference product. At the 650-mg dose level, the 90% CI lower limits for log transformed $AUC_{0-t}$ and $AUC_{0-inf}$ ratios are marginally too low at 75.8% and 78.0%, respectively, of reference drug.

**Table 6 Current BE analysis and analysis with OSI-recommended exclusion of subjects**

| DOSE | Salicylic acid PK | **Current analysis (without OSI exclusions)** | | **Analysis with OSI-recommended exclusions** | |
|---|---|---|---|---|---|
| | | Ratio | 90% CI (Lower - Upper) | Ratio | 90% CI (Lower - Upper) |
| 325 | Ln(Cmax) | 109.4 | 94.7 - **126.4** | 105.7 | 93.0 - 120.2 |
| 325 | Ln(AUClast) | 105.5 | 88.6 - **125.7** | 98.0 | 90.2 - 106.4 |
| 325 | Ln(AUCINF obs) | 106.3 | 90.3 - **125.1** | 99.8 | 92.5 - 107.7 |
| | | | | | |
| 650 | Ln(Cmax) | 99.4 | 87.8 - 112.6 | 101.3 | 89.0 - 115.2 |
| 650 | Ln(AUClast) | 89.3 | **76.3** - 104.5 | 89.8 | **75.8** - 106.4 |
| 650 | Ln(AUCINF_obs) | 90.8 | **78.5** - 105.1 | 91.3 | **78.0** - 106.9 |

**MO Comment** *Although there are significant issues with study implementation and with documentation of results, the PK bioequivalence study PL-ASA-001 yielded adequate data for review. For either of the two analyses presented (with or without the OSI-recommended subject exclusions), the product PL2200 is not bioequivalent to the reference drug. However, for approval of a 505(b)(2) application, it is not necessary to demonstrate bioequivalence, if the deviation from bioequivalence is not such as to affect the efficacy or safety of the product as compared to reference drug. In the present case, reference is made to aspirin 325 mg safety and efficacy from clinical experience and from the literature (see sections 6-9). At the 325 mg dose, the PL2200 product may be slightly above bioequivalent dosing compared to reference drug (depending on inclusion or exclusion of specific subjects from analyses), so efficacy is not called into question, while the deviation is too minor to affect safety. At the higher 650 mg dose, the PL2200 product is slightly below bioequivalent dosing compared to reference drug, so there is*

*no safety issue, while the potential loss of efficacy is unlikely to be clinically significant. Hence the deficiencies of study PL-ASA-001 and the lack of bioequivalence for PL2200 are not such as to preclude approval.*

See Dr Naraharisetti's review in DARRTS.

**Acetylsalicylic acid PK results**
Acetylsalicylic acid binds irreversibly to the enzyme COX-1 and inhibits its activity, thereby inhibiting platelet aggregation. The acetylsalicylic acid PK of PL2200 was measured and the PK analysis by Dr. Menon Anderson of the Division of Clinical Pharmacology I (DCPI) is summarized in Figure 1.

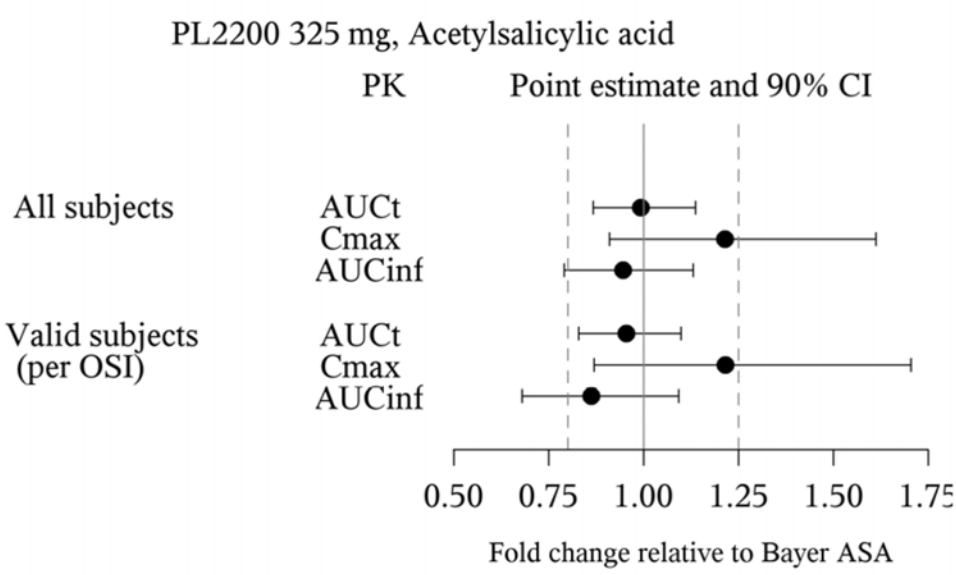


**Figure 1 PL2200 acetylsalicylic acid PK versus aspirin, for analysis of all subjects and for subjects with OSI exclusions. BE limits are dashed vertical lines.**

For either of the analyses shown, PL2200 was not BE to aspirin for acetylsalicylic acid, because the upper limit of the Cmax 90% CI was above the BE limit in either case. The lower limit of the AUCinf 90% CI was also below the BE limit in both cases (marginally in the "all subjects' case).

(b) (4)

**Safety**
Thirty subjects received either 325 mg each of PL2200 and aspirin, or 650 mg each of PL2200 and aspirin, and all thirty completed the study per protocol. Two additional subjects received only the first study drug. No severe or serious AEs were reported during this study.

**PL-ASA-002**
**Study Title: A RANDOMIZED, SINGLE-BLIND, ENDOSCOPIC EVALUATION OF UPPER GI MUCOSAL DAMAGE INDUCED BY ASPIRIN-PC (PL2200) VERSUS ASPIRIN (ASA) IN HEALTHY VOLUNTEERS**

**Methodology**:
PL-ASA-002 was a randomized, actively controlled, single-blind, parallel-group, multiple-dose, 7-day GI safety study. The study performed endoscopic evaluations of upper GI mucosal damage induced by once a day, 325 mg capsules of PL2200 versus Walgreens Aspirin tablets in healthy volunteers. The study enrolled 200 subjects in order to ensure a minimum of 82 evaluable subjects within each treatment group (ASA and PL2200).

After subjects gave informed consent and had been determined eligible (after a screening endoscopy), they were dispensed a subject diary and a supply of study medication. Subjects took 325 mg of study medication daily at home for a total of 7 days. The first dose was taken on Study Day 1, which was no more than 7 days after the baseline (screening) endoscopy. Subjects were contacted by telephone on Day 3 of the treatment period to review study procedures, assess compliance, and to inquire about adverse events (AEs) and concomitant medications.

At the outset of the study, subjects took their final dose of study medication on Day 7 at a time that allowed for a 90–120 minute window between the final dose and the Day 7 endoscopy. However, endoscopies performed in the first set of subjects revealed study medication residual remained in the GI tract. Therefore, the window was expanded to require subjects to take the final dose of study medication on Day 7 between 5:00 AM and 9:00 AM, with the final endoscopy to be performed on Day 7 between 9:00 AM and 3:00 PM. This schedule standardized the timing of the study drug dose relative to endoscopy, and ensured adequate time (4 to 6 hours) for dissolution of the last dose of study drug before the procedure.

Subjects who were diagnosed with a gastroduodenal ulcer during the Day 7 endoscopy began a 30-day treatment regimen with a PPI. The choice of PPI was made at the discretion of the Investigator according to the standard of care at the site. These subjects were contacted via telephone on Day 21 to monitor their status, and underwent a follow-up endoscopy on Study Day 37 to determine if the ulcer had healed.

**Objectives:**
The primary objective of this study was to determine the safety of PL2200 compared to ASA by evaluating the incidence rate of subjects with gastroduodenal composite scores of 3 or 4 for erosions or ulcers (> 5 erosions, or 1 or more ulcers 3 mm or greater in length with unequivocal depth).

Secondary objectives of the study were as follows:
- To determine the safety of PL2200 compared to ASA by assessing the incidence rate of subjects with ulcers (ulcers 3 mm or greater in length with unequivocal depth).

- To determine the safety of PL2200 versus ASA by comparing the mean number of erosions in the duodenum, in the stomach overall, and in the antrum, body, and fundus of the stomach.
- To determine the safety of PL2200 versus ASA by evaluating the change from baseline in mucosal injury grading based on the gastroduodenal composite score.

**Inclusion Criteria** were as follows:
- Subject was ≥ 50 to ≤ 75 years of age
- Subject was healthy
- Subject had a BMI between 20 and 32 inclusive
- If female and of child bearing potential, subject had a negative pregnancy test and was not nursing
- If female and of child bearing potential, subject agreed to use adequate birth control for the duration of the study
- Subject was able to understand and comply with study procedures.
- Subject was able and willing to provide written informed consent prior to any study procedures being performed
- Subject was free of any endoscopically observable erosions or ulcers, and had no more than 10 mucosal petechiae noted at the baseline endoscopy.

**Exclusion criteria**:
Candidate subjects were not enrolled in the study if they met any of the following criteria:
- Subject had a history of chronic alcohol consumption or abuse of narcotics or alcohol
- Subject had abnormal screening/baseline laboratory parameters or endoscopic observations deemed clinically significant by the Investigator
- Subject had an active *Helicobacter pylori* (*H. pylori)* infection
- Subject had taken an antimicrobial, PPI, or bismuth preparation within 2 weeks prior to study start
- Subject had been treated for an *H. pylori* infection within 4 weeks prior to the baseline endoscopy
- Subject had damage of 1 or more endoscopically observable erosions or an ulcer at baseline
- Subject had a prior GI ulcer, bleeding, obstruction or perforation
- Subject had taken aspirin or any aspirin-containing product within the last 4 weeks prior to the baseline endoscopy
- Subject was on low-dose aspirin under a physician's directive
- Subject had taken any prescription medication other than hormone replacement therapy, thyroid replacement hormones, hyperlipidemic agents, anti-hypertensive medications or contraceptives within 3 days prior to study drug administration
- Subject had taken any of the following medications within 3 weeks prior to the baseline endoscopy:
  - Ulcerogenic medications: NSAIDs or other medications for pain, including acetaminophen or acetaminophen-containing analgesic and cough and cold products; sumatriptan succinate; macrolide antibiotics (eg, erythromycin); supplements containing potassium or Vitamin C; salicylate-containing herbs (Betula lenta [Sweet Birch], Betula pendula [White birch], Filipendula ulmaria [Meadowsweet], Gaultheria procumbens

[Wintergreen], Populus balsamifera [Balsam Poplar], Populus nigra [Black Poplar], Populus candicans [Balm Of Gilead], Salix alba [White Willow] or Viburnum prunifolium [Black Haw])
  - Bisphosphonate medications: Fosamax®, Boniva®, Actonel®, and Actonel with Calcium®. Reclast® was permitted for this study; however, the subject must have had his/her yearly infusion at least 3 weeks prior to the baseline endoscopy
- Subject had taken any of the following medications within 2 weeks prior to the baseline endoscopy:
  - Any anti-platelet agents, including Plavix®, Ticlid®, Pletal®, ReoPro®, Integrilin®, Aggrastat®, or Persantine®; any anti-coagulant, including Coumadin®, Acenocoumarol, Phenprocoumon, Phenindione, Heparin, Exanta®, Argatroban, Lepirudin, Hirudin or Bivalirudin; or any antidepressants (eg, fluoxetine)
  - Gastroprotective agents including PPIs (eg, Prilosec®, Prevacid®, Aciphex®, Protonix®, Zegerid® or Nexium®), H-2 blockers (Tagamet®, Zantac®, Axid®, or Pepcid®) or other gastroprotective agents including misoprostol (Cytotec®, Arthrotec®), antacids, sucralfate, or bismuth-containing products o Prostaglandin derivatives such as lubiprostone (Amitiza®)
  - Supplements containing glucosamine
- Subject had used an investigational agent within the past 30 days
- Subjects who had taken Viagra or Levitra could have been entered into the study, however they could not have taken these medications 24 hours prior to the baseline endoscopy and while on study medication
- Subject had hypersensitivity or contraindications to aspirin, ibuprofen, or other NSAID
- Subject had a history of stroke, myocardial infarction, congestive heart failure, or diabetes
- Subject had sensitivity to soy
- Subject had a history of gastrointestinal symptoms such as frequent dyspepsia, indigestion, or heartburn
- Subject had a history of asthma, other bronchospastic activity, polyps, or angioedema other than resolved childhood asthma
- Subject had a history of thrombocytopenia, neutropenia, or bleeding disorder
- Subject had a previous coronary arterial bypass or current coronary artery stent
- Subject had a previous non-trauma related hemorrhage
- Subject had a history of kidney or liver disease
- Subject had uncontrolled hypertension defined as diastolic blood pressure of ≥ 90mm
- Subject had a diagnosis of cancer at time of screening or a history of malignancy of any organ system, treated or untreated, at any time, whether or not there was evidence of local recurrence or metastases.

NOTE – the following exception applied: Basal cell or squamous cell carcinoma of the skin or colonic polyps with non-invasive malignancy that had been removed and had not recurred, and carcinoma in situ (CIS) of either the breast, cervix or uterus that had been surgically removed and had not recurred.

- Subject had any other significant diagnosis or illness that the Investigator believed would interfere with the safety of the subject or the integrity of the data for the study.
- Subject was currently enrolled in another investigational trial.

**MO Comment**. *Study inclusion and exclusion criteria were so restrictive that results may not generalize to a consumer population.*

All subjects were randomized to treatment with either PL2200 or ASA, each at 325 mg once per day, for 7 days. Early morning dosing (between 5AM and 9AM beginning with Amendment 3) was implemented to mimic the low-dose ASA treatment regimen commonly followed to prevent cardio- and cerebrovascular events. As the rate of gastric acid secretion follows a circadian cycle, this timing standardized dosing with respect to nocturnal acid surge in order to minimize any effect of varying gastric acid levels during treatment and endoscopy windows due to time of day. The dose was also scheduled for 30 minutes before eating in order to standardize dose timing relative to food.

**Table 7 PL-ASA-002 Schedule**

| Procedure/Assessment | Within 21 Days of Day 1 | Within 14 Days of Day 1 | Within 7 Days of Day 1 | Day 1 | Day 3 (± 1 day) | Day 7 | Day 21[3] (± 3 days) | Day 37[3] (± 3 days) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent/ HIPAA | X | | | | | | | |
| Eligibility | X | | X[6] | | | | | |
| Demographics | | X | | | | | | |
| Medical History | | X | | | | | | |
| Electrocardiogram | | X | | | | | | |
| Vital Signs | | X | | | | X | | X |
| Physical Exam | | X | | | | X | | X |
| Breath Test for *H pylori* | X | | | | | | | |
| Hematology | | X | | | | X | | |
| Blood Chemistry | | X | | | | X | | |
| Urine Pregnancy Test[1] | | X | | | | | | |
| Endoscopy | | | X | | | X[2] | | X |
| Dispense Subject Diary | | | X | | | | | |
| Dispense Study Medication | | | X | | | | | |
| First Dose of Study Medication | | | | X | | | | |
| Telephone Call | | | | | X | | X | |
| Dispense PPI | | | | | | X[4] | | |
| Collect Subject Diary | | | | | | X | | |
| Collect Study Medication | | | | | | X | | |
| Concomitant Medications | X | X | X | | X | X | X | X |
| Adverse Events | | | | | X[5] | X | X | X |

[1] In females of child-bearing potential only.
[2] Day 7 study medication to be taken between 5:00 AM and 9:00 AM with a 4- to 6-hour window prior to the final endoscopy.
[3] Only to be completed if an endoscopic ulcer is found at the Day 7 endoscopy.
[4] Only if subject has an endoscopic ulcer found during Day 7 endoscopy procedure.
[5] AEs which occur prior to the first dose of study medication should not be recorded.
[6] Reconfirm subject eligibility.

As indicated in the study timeline (Table 7), screening/baseline assessments were performed within 21 days prior to the start of study medication, screening/baseline assessments were performed, including a breath test for active infection by H. pylori. The following screening assessments were performed: history and physical exam, concomitant medications, ECG, hematology, blood chemistry and urine pregnancy test (for females of child bearing potential).

**Endoscopic Assessment of GI Mucosal Damage**

| | *Number of Petechiae** | *Number of Erosions*** | *Number of Ulcers ≥ 3mm**** | *Number of Ulcers ≥ 5mm**** |
|---|---|---|---|---|
| Stomach | | | | |
| Fundus | | | | |
| Body | | | | |
| Antrum | | | | |
| Total Stomach | | | | |
| Duodenum | | | | |

Mucosal Lesion Score*****

| | |
|---|---|
| Stomach | |
| Duodenum | |

* Petechiae are submucosal microhemorrhages.

** Erosions are defined as a definite discontinuity in the mucosa without depth.
Note: If the microhemorrhage is superficial and is consistent with a mucosal break, this lesion should be characterized as erosion.

*** Ulcers are defined as any mucosal break in the mucosa ≥ 3 mm with unequivocal depth. If an ulcer is found, record size of ulcer as ≥ 3 mm or ≥ 5 mm with depth.

**** *Mucosal Injury Grading System*

| Score: | |
|---|---|
| 0 | No Injury |
| 1 | 1 to 10 petechiae |
| 2 | >10 petechiae or 1-5 erosions |
| 3 | 6-10 erosions |
| 4 | >10 erosions and/or an ulcer |

**Figure 2 Mucosal Injury Grading System**

Within 7 days before start of study medication, the subject's eligibility for the study was reconfirmed. Subjects who were negative for active infection with *H. pylori* underwent endoscopic examination of gastric mucosa. The appearance of the gastric mucosa was recorded to DVD-R and graded (see Figure 2). Subjects with any number of erosions or ulcers detected during this screening endoscopy in specified regions were not enrolled in the study. Subjects with petechiae were enrolled at the Investigator's discretion, but did not qualify if the number of petechiae was greater than 10. Esophageal damage was also evaluated and considered in

assessing subject eligibility. Mild asymptomatic esophagitis at baseline endoscopy was not a criterion for study exclusion.

The final dose of study drug was given on Study Day 7. Prior to endoscopy on Study Day 7, the following assessments were completed: physical exam, concomitant medications, hematology, blood chemistry, and adverse events. After these assessments and the final dose was administered, endoscopic examination was performed with visual recordings of gastric mucosa of subjects was performed. The number of petechiae, erosions, and ulcers in the fundus, body and antrum of the stomach, and the proximal duodenum, were recorded on the CRF separately. The condition of the mucosa was graded for the stomach overall and proximal duodenum, using the same mucosal injury scale used at baseline (see Figure 2). If an ulcer was found, its size ($\geq$ 3 mm and < 5 mm, or $\leq$ 5 mm or greater) and location were recorded in the CRF. Video recordings of the mucosa at each endoscopy were made and the original DVD was sent to the sponsor.

On Study Day 7, any remaining study drug was collected and counted for compliance. The subject diaries were also collected at this visit.

Subjects who were diagnosed with a gastroduodenal ulcer during the Study Day 7 endoscopy began treatment with a PPI for 30 days and had a follow-up endoscopy on Study Day 37 to determine if the ulcer had healed. The subjects were interviewed by telephone on Study day 21 and were asked about any ongoing AEs and any additional concomitant medications. The subject's tolerability of the PPI was also assessed.

All endoscopy procedures were evaluated and assessed by the site PI and later by a Central Independent Reviewer who was blinded to subject identity, study treatment, endoscopic sequence order, and endoscopic site. If a significant discrepancy was noted between endoscopy scoring results of the PI and the Central Reviewer (CR), scores were adjudicated by a panel of 3 blinded gastroenterologists who scored each endoscopy by viewing the high-resolution video recorded during the procedure, using the same process as the Central Reviewer. If all 3 endoscopists recorded the same gastroduodenal composite injury score (with the exception of an injury score of 0 or 1) and number of erosions and/or ulcers, then the endoscopy would not require discussion and would be entered into the database. If the 3 endoscopists differed on scoring, the number of erosions and/or ulcers was discussed until a consensus was reached by 2 out of the 3 endoscopists.

**MO Comment** *The adjudication process was critical for efficacy results dealing with reduction in gastroduodenal mucosal injury rates. The submission relates the following procedural error in analysis: "The video imaging company* (b) (4) *compiled the endoscopy videos for scoring by the Central Reviewer, divided them among 4 data folders, and placed one on each of 4 hard drives for viewing on a laptop computer. Each hard drive was delivered to the CR in a separate shipment. When the first drive arrived, the videos in the folder were reviewed and scored, and the drive was returned to* (b) (4) *When the second drive arrived, it contained a folder with new videos for review, in addition to a second folder with videos from the first drive (for answering queries). Due to a technical error, the videos from the first batch were reviewed and scored*

*again, and those in the second folder were never accessed. Comparison of the 2 sets of scores for the first batch of videos revealed discrepancies. To resolve this issue, both scores for each endoscopy video were entered into the database. Videos for which at least 1 of the Central Reviewer scores matched the score assigned by the site PI were not entered into adjudicat*ion."

A total of 370 healthy volunteers were screened, and 204 subjects were enrolled in the study; of these, 100 subjects were randomized to PL2200 and 104 were randomized to ASA. A total of 198 subjects completed the study, with 97 subjects completing treatment with PL2200 and 101 subjects completing treatment with ASA. There were no discontinuations for adverse events.

**MO Commen**t *The study was originally intended to screen 235 subjects in order to obtain 180 subjects randomized for treatment, expecting 164 completing the study evaluation. However, as study began early experience showed that as many as 20% of treated subjects were considered non-evaluable (no reason stated in submission), and moreover the screening failure rate exceeded 30%. The target enrollment was increased to 200 subjects, and the number of subjects screened was increased to 370.*

*This was a highly selected study population in order to demonstrate a reduction of GI mucosal injury. Close to half of screened subjects failed to qualify for enrollment. Of the subjects who were enrolled, almost 10% were subsequently excluded from efficacy analyses because of endoscopy findings at baseline. Results of this endoscopy study may not generalize to the general consumer population who might use the OTC product.*

The 204 subjects enrolled were divided into 3 groups for analysis: the Safety Population, the Full Analysis Set (FAS), and the Per Protocol Population (PPP). The Safety Population consists of all subjects who received at least one dose of study drug, regardless of treatment assignment, and it included all 204 enrolled subjects: 100 were treated with PL2200 Aspirin Capsules, 325 mg and 104 with ASA. All safety analyses were performed using the Safety Population.

The FAS consists of the subset of the Safety Population with post-baseline endoscopy assessments on Day 7. A total of 201 subjects met these criteria: 99 treated with PL2200 and 102 treated with ASA. Three subjects in the Safety Population did not undergo the Day 7 endoscopy due to withdrawal (loss to follow-up).

The PPP consists of the subset of the FAS with: at least 85% compliance taking the assigned study medication; final dose of study medication taken on the day of the second endoscopy; and no major protocol violations (i.e., medications prohibited by the protocol or significantly deviation from meal and dosing times). The PPP used in all primary and secondary analyses included 181 subjects: 91 subjects who received PL2200 and 90 subjects treated with ASA. A total of 20 subjects in the FAS were excluded from the PPP: Of these, 18 were excluded due to an adjudicated baseline gastroduodenal mucosal score >1. Another two were excluded due to prohibited medications, one for Vitamin C, and one for Tylenol.

Efficacy Results
The incidence of GI injury in the 2 study groups was comparable at baseline in both study populations (Table 8). However, the Sponsor notes endoscopy results at Study Day 7 indicated a higher incidence of Grade 3 and 4 injury in those treated with ASA than in those receiving PL2200.

**Table 8 Incidence of GI injury by Mucosal Injury Composite Score**

| Visit | Gastroduodenal CompositeScore | Treatment Group (Per Protocol Population) | | Treatment Group (Full Analysis Set) | |
|---|---|---|---|---|---|
| | | PL2200 N=91 n (%) | ASA N=90 n (%) | PL2200 N=99[a] n (%) | ASA N=102[b] n (%) |
| Baseline/Screening | 0 | 62 (68.1) | 64 (71.1) | 62 ( 62.6) | 64 ( 62.7) |
| | 1 | 29 ( 31.9) | 26 (28.9) | 30 ( 30.3) | 27 (26.5) |
| | 2 | 0 (0.0) | 0 (0.0) | 4 ( 4.0) | 9 ( 8.8) |
| | 3 | 0 (0.0) | 0 (0.0) | 2 ( 2.0) | 2 (2.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 1 ( 1.0) | 0 ( 0.0) |
| Day 7 | 0 | 7 (7.7) | 7 (7.8) | 7 ( 7.1) | 7 ( 6.9) |
| | 1 | 13 (14.3) | 9 (10.0) | 15 ( 15.2) | 9 ( 8.8) |
| | 2 | 52 (57.1) | 38 (42.2) | 55 ( 55.6) | 43 ( 42.2) |
| | 3 | 9 (9.9) | 12 (13.3) | 11 ( 11.1) | 15 ( 14.7) |
| | 4 | 10 ( 11.0) | 24 ( 26.7) | 11 ( 11.1) | 28 ( 27.5) |

Reference Tables 14.2.1.1 and 14.2.1.2
[a] The FAS consisted of 99 subjects at Day 7 due to 1 subject withdrawal/lost to follow-up after baseline endoscopy.
[b] The FAS consisted of 102 subjects at Day 7 due to 2 subjects withdrawal/lost to follow-up after baseline endoscopy.

The Sponsor's analysis (Table 8) found that subjects treated with PL2200 demonstrated a significantly lower incidence of grade 3 or 4 erosions/ulcers compared to those treated with ASA, as indicated by the gastroduodenal composite scores at Day 7. In the PPP, the incidence was 20.9% in subjects receiving PL2200, and 40.0% in those receiving ASA (p=0.0061). In the FAS, a 22.2% incidence of Grade 3 or 4 erosions/ulcers was noted in subjects treated with PL2200, and a 42.2% incidence in those treated with ASA (p=0.0027).

**MO Comment** *The impact of the procedural error on analysis of endoscopy videos is unclear. Study was single blind such that investigators were blinded to the treatment, but subjects could be aware of their treatment identity. Although the study assessments used endoscopy findings, the evaluations of the endoscopy were subjective. The benefit of the CR review and adjudication process planned by the Sponsor to assure objectivity of the assessments was largely negated by the procedural error. A major proportion of the assessments (not further explained in the submission) was apparently obtained from the site investigator reports without further review.*

(b) (4)

(b) (4)

**PL-ASA-003**
**Study Title: A RANDOMIZED, ACTIVELY CONTROLLED, CROSS-OVER FOOD-EFFECT STUDY OF PL2200 IN HEALTHY VOLUNTEERS**

**Methodology**:
PL-ASA-003 was a randomized, actively-controlled, open-label, single-site, cross-over food-effect study of PL2200 capsules in 20 healthy volunteers. The study assessed fed versus fasted PK of a single 650 mg dose of PL2200, administered as two 325-mg capsules. After completion of the first treatment period and a washout period of at least 7 days, subjects were crossed over to receive PL2200 in the alternative fed or fasted state. Subjects had 6-mL blood samples drawn for PK analysis at the following time points for each of the 2 treatments (fed and fasted): within 1 hour prior to study drug administration, at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, and 90 minutes post study drug administration; and at 2, 3, 4, 6, 8, 10, 12, and 24 hours post study drug administration.

**Objectives:**
The objectives of this study were to:
- Determine the effect of food on the single-dose pharmacokinetics of 650 mg PL2200.
- Compare the single-dose PK profiles of PL2200 administered in the fed state versus the fasted state.

**Inclusion Criteria** were as follows:
- Subject was between 21 and 65 years of age, inclusive.
- Subject had a normal physical examination.
- Subject had normal, or abnormal but not clinically significant, clinical laboratory test results during the screening visit, as assessed by the Investigator.
- Subject had a BMI between 20 and 32 $kg/m^2$, inclusive.
- If female and of childbearing potential, the subject must have had a negative serum pregnancy test and not be nursing.
- If female and of child-bearing potential, the subject must have agreed to use adequate birth control for the duration of the study.
- Subject was able to understand and comply with study procedures.
- Subject was able and willing to provide written informed consent prior to any study procedures being performed.
- Subject must have been able to refrain from alcohol within 48 hours prior to and 24 hours after study drug administration.

**Exclusion criteria**:

- Subject had abnormal screening/baseline laboratory parameters deemed clinically significant by the Investigator.
- Subject had taken any prescription medication within 14 days prior to study drug administration, other than hormone replacement therapy, thyroid replacement hormones, hyperlipidemic agents, anti-hypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, or contraceptives.
- Subject had taken any of the following medications within 14 days prior to study entry:
  - NSAIDs or other medications for pain, including aspirin or aspirin-containing products
  - Proton pump inhibitors including Prilosec®, Prevacid®, Aciphex®, Protonix®, Nexium® , or Zegerid®
  - H-2 blockers including Tagamet®, Zantac®, Axid®, or Pepcid®
  - Any anti-platelet agent, including Plavix®, Ticlid®, Pletal®, ReoPro®, Integrilin®, Aggrastat®, or Persantine®
  - Any anti-coagulant, including Coumadin®, Acenocoumarol, Phenprocoumon, Phenindione, Heparin, Exanta®, Argatroban, Lepirudin, Hirudin, or Bivalirudin
- Subject had used an investigational agent within the 30 days previous to study entry.
- Subject with hypersensitivity or contraindications to aspirin, ibuprofen, or other NSAID.
- Subject with a history of stroke, myocardial infarction, or congestive heart failure.
- Subject with sensitivity to lecithin.
- Subject with a history of gastrointestinal problems, including ulcers, frequent indigestion, or heartburn.
- Subject with a history of asthma, other bronchospastic activity, polyps, or angioedema, other than resolved childhood asthma.
- Subject with a history of thrombocytopenia, neutropenia, or bleeding disorder.
- Subject with a previous coronary arterial bypass.
- Subject with a previous non-trauma related hemorrhage.
- Subject with a history of kidney or liver disease.
- Subject diagnosed with chronic hypertension.
- Subject was a smoker at the time of screening.
- Subject had a history of alcoholism or was drinking more than 1 alcoholic beverage per day at the time of screening.
- Subject had any other significant diagnosis or illness that the Investigator believed would interfere with the safety of the subject or the integrity of the data for the study.
- Subject was enrolled in another investigational trial at the time of screening.

**MO Comment.** *These comprehensive inclusion and exclusion criteria to define healthy volunteer population are acceptable for PK study.*

Subjects were administered PL2200 at the study site in the morning for each of the 2 treatment periods (fed and fasted) with a minimum 7 day washout period between treatments. Whether randomized to the fed or fasted state, all subjects were instructed to refrain from eating or drinking anything but water for at least 10 hours prior to arrival at the study site. Additionally, except for 240 mL water provided with the meal for subjects in the fed state and 240 mL water

provided for PL2200 administration, water was prohibited for 1 hour before and 1 hour after administration of PL2200. A standard meal was provided 4 hours after administration of PL2200, and dinner was permitted immediately following the 10-hour blood draw for all subjects (fed or fasted).

Subjects randomized to the fed state were given a standard high-fat meal approximately 30 minutes prior to administration of PL2200, as recommended by the FDA/CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. Subjects were to be instructed to eat this meal in 30 minutes or less, and PL2200 was to be administered 30 minutes following the start of the meal.

The study timeline was

**Table 9 PL-ASA-003 Schedule**

| Procedure/Assessment | Screening[1] | Baseline Prior to 1st Treatment (Day 0) Visit 1 | 1st Treatment (Day 0) Visit 1 | 24 Hours Post 1st Treatment (±1 hour) Visit 2 | Baseline Prior to 2nd Treatment (Minimum 7 days after 1st Treatment) Visit 3 | 2nd Treatment (Cross-over) Visit 3 | 24 Hours Post 2nd Treatment (±1 hour) Visit 4 |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Eligibility | X | X | | | X | | |
| Demographics | X | | | | | | |
| Medical History | X | | | | | | |
| Vital Signs | X | X | X | X | X | X | X |
| Physical Examination[2] | X | | | X | X | | X |
| ECG | X | | | | | | |
| Hematology Labs[3] | X | | | X | X | | X |
| Blood Chemistry Labs[3] | X | | | X | X | | X |
| Serum Pregnancy Test[4] | X | | | | | | |
| Urine Pregnancy Test[4] | | | | | X | | |
| Standard High-Fat Meal | | | X[5] | | | X[5] | |
| Study Drug Administration | | | X | | | X | |
| Blood Draw for PK Analysis[3] | | X | X | X | X | X | X |
| Concomitant Medications | X | X | | X | X | | X |
| Adverse Events[6] | | | X | X | X[7] | X | X |

1 Performed within 10 days prior to Day 0.
2 Weight and height were to be measured at the screening physical examination in order to calculate the BMI.
3 Blood draws for salicylic acid and acetylsalicylic acid were to be performed at the following time intervals: within 1 hour prior to study drug administration; at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, and 90 minutes post study drug administration; and at 2, 3, 4, 6, 8, 10, 12, and 24 hours post study drug administration.
4 For females of childbearing potential only.
5 Standard meal was to be given approximately 30 minutes prior to administration of the study drug for subjects being treated in the fed state only.
6 AEs were to be collected during the time periods from immediately following each administration of study drug through 24 hours after each administration of study drug. SAEs were to be collected from the first administration of study drug through 24 hours post the second administration of study drug, including the washout period.
7 At Visit 3/baseline prior to second treatment, the Investigator was to question subjects about all AEs that occurred during the 7-day washout period, determine if any were SAEs, and record and report them as required (see Section 9.5.2).

Physical examinations were performed at: Screening, Visit 2 (24 hours post the first treatment, ±1 hour), Visit 3 (Baseline prior to the second treatment/minimum of 7 days after the first treatment), and Visit 4 (24 hours post the second treatment, ±1 hour).

Vital signs were assessed at least at the following times/visits: Screening (within 10 days prior to the first administration of PL2200), twice at Visit 1 (baseline prior to, and immediately following first administration of PL2200), Visit 2 (24 hours post first administration of PL2200, ±1 hour), twice at Visit 3 (baseline prior to, and immediately following second administration of PL2200), and at Visit 4 (24 hours post second administration of PL2200).

Laboratory assessments (hematology and blood chemistry) were performed at Screening (baseline assessment within 10 days prior to the first administration of PL2200), Visit 2 (24 hours post first administration of PL2200, ±1 hour), Visit 3 (baseline prior to second administration of PL2200), and Visit 4 (24 hours post second administration of PL2200, ±1 hour). Hematology assessments required 4.0 mL of blood to be drawn at each sampling time; chemistry assessments required 8.5 mL of blood to be drawn at each sampling time.

Blood chemistry assessments included: aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, albumin, calcium, uric acid, glucose, phosphorus, total protein, sodium, potassium, chloride, carbon dioxide, cholesterol, triglycerides. Hematology assessments included: complete blood count, differential, platelets, prothrombin time, and partial thromboplastin time.

**Salicylic acid PK results**

Results of PL-ASA-003 salicylic acid PK analyses in fed vs. fasted states were evaluated by the Clinical Pharmacology reviewer (see Table 10). The study PL-ASA-003 determined the food effect on single dose, 650-mg PL2200 (administered as two 325-mg capsules) using FDA-recommended high fat food. Of the 20 subjects treated, all completed both fasted and fed treatments. Administration of PL2200 with food resulted in 10%, 11% and 22% reductions of salicylic acid AUC0-t, AUCinf and Cmax, respectively. In addition, there was an approximately 1.73-hour delay in salicylic acid Tmax (4.73 hours vs. 3.00 hours) compared to that under fasted conditions.

**Table 10 Salicylic acid PK, fed vs. fasted, for PL2200 650 mg**

| **Parameter** | **Fed** (n=20) | | **Fasted** (n=20) | | **Mean Ratio (Fed /Fasted)** |
|---|---|---|---|---|---|
| | Mean | %CV | Mean | %CV | |
| Cmax (µg/mL) | 30 | 29 | 38 | 26 | 0.78 |
| AUC0-t (min*µg/mL) | 14946 | 43 | 16522 | 36 | 0.90 |
| AUCinf (min*µg/mL) | 15203 | 44 | 16791 | 37 | 0.91 |
| T1/2 (min) | 153 | 28 | 153 | 28 | |
| Tlag (min) | 30 | | 15 | | |
| Tmax (min) Median (min, max) | 360 (90 – 360) | | 180 (90- 240) | | |

**MO Comment.** *Administration of PL2200 with food leads to a delay in absorption and to reductions in Cmax and AUC. The observed food effect for PL2200 is similar to that of currently marketed immediate release aspirin products. The 21 CFR 343.80 Subpart C– Labeling notes that the rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents) and other physiologic factors. The proposed OTC labeling recommends that the product should be taken with a full glass of water but does not include a recommendation to take with food. This is appropriate.*

**Acetylsalicylic acid PK results**
Study PL-ASA-003 measured the food effect on acetylsalicylic acid PK of PL2200. According to Dr. Menon Anderson's review, the food effect is summarized in Figure 3.

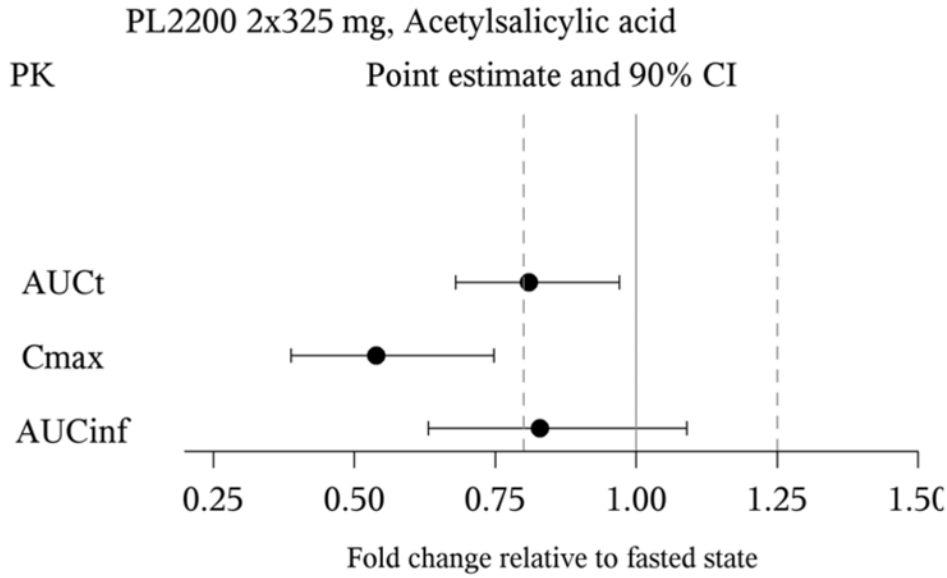


**Figure 3. Food effect on PL2200 acetylsalicylic acid PK. BE limits are dashed vertical lines.**

Study PL-ASA-003 showed that administration of PL2200 with food decreased Cmax of acetylsalicylic acid such that the full 90% CI lay below the lower limit for BE, and the lower limits for AUC also fell below the BE limit.

**MO Comment.** *Close to the maximal effect on TxB2 inhibition is attained following administration of 100 mg of aspirin. Therefore the food effect on PL2200 325 mg is unlikely to affect the anti-platelet activity.*

# 6 Review of Efficacy

## ***Efficacy Summary***

No efficacy trials were submitted with this application. See DAAAP's review of the literature submitted to support the efficacy of aspirin.

# 7 Review of Safety

## ***Safety Summary***

The 3 submitted trials were a pivotal bioequivalence (BE) study, a food effects study, and a seven-day, endoscopic GI tolerability trial. These provided favorable, but limited, safety experience using the new drug PL2200: a total of 151 subjects have been exposed, of whom 100 subjects received 325 mg for 7 consecutive days, 20 subjects received two doses of 650 mg each, and the remainder received single doses. There were no deaths or serious AEs in the 3 submitted trials. Most of the AEs were GI in nature, and there were no new or unexpected AEs.

Although the clinical experience specifically with PL2200 is limited, the experience with its active ingredient aspirin is extensive, as aspirin was developed in 1897 and is the most widely used drug in the world, with an estimated 100 billion tablets taken per year. PL2200 is a new formulation of aspirin in a lipidic suspension with soy lecithin and other excipients, contained in (b) (4) capsule for oral consumption. The Sponsor was required to submit an NDA under 505(b)(2) for PL2200 because it contains (b) (4) soy lecithin in addition to 325 mg aspirin.

The reference drug for the 505(b)(2) application was Genuine Bayer Aspirin 325 mg tablets. With bioequivalence demonstrated to a monograph aspirin product, and with information justifying the identification of soy lecithin as an excipient, the NDA could reference aspirin efficacy and safety from the literature and did not require pivotal efficacy or safety studies. The NDA also reviewed AERS data from January 1, 2001 through December 31, 2010.

There were major issues with the implementation and/or documentation for the three submitted trials (see findings of the OSI audit listed in Section 5.2 and reviews of the individual studies in Section 5.3). Pending final reviews from OSI and OCP, it is concluded that 1. the clinical data from the pivotal BE trial and from the food effects trial are adequate for Agency review, although data from several individual subjects were evaluated as unreliable pending review of revalidation data to be submitted to the Agency; and 2. the pivotal BE trial did not demonstrate bioequivalence to reference drug (see section 5.3). Nevertheless, the deviations from BE were such that the safety and efficacy of PL2200 could still be bridged to safety and efficacy from the aspirin literature and post-market experience (because PL2200 325 mg is slightly above BE dosing but PL2200 650 mg is slightly below BE).

AERS reports with oral dosage of aspirin as suspect drug amount to a total of 9704 case reports with 37,953 associated events over the ten-year interval covered. Nearly all (98.3%) of these case reports were serious (as could be expected for a drug with such a long history of use). There were 8058 events from fatal cases including 472 completed suicides. The most common serious AEs were GI disorders, especially those related to GI bleeding. There were 939 gastrointestinal hemorrhage, 523 melena, 515 hematemesis, and 432 gastric ulcer events. The cases in which daily dose or dose regimen was reported account for about half of all serious events in AERS for oral, single ingredient aspirin. About 2/3 of AEs in the cases with known dose were experienced with daily doses of 100 mg or less, which are likely cases where aspirin was taken for a cardiovascular indication.

The aspirin literature (see Section 9.1) is notable for a 2008 consensus report, from the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, on GI risks from low-dose aspirin which is routinely used for primary and secondary prophylaxis of cardiovascular and cerebrovascular events. The use of low-dose ASA for cardio-prophylaxis is associated with a 2- to 4-fold increase in upper gastrointestinal event risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. The estimated average excess risk of upper gastrointestinal event related to cardio-prophylactic doses of ASA is 5 cases per 1000 ASA users per year. OTC use of low-dose ASA is implicated in over one-third of the patients admitted to hospitals for GI hemorrhage. Aspirin is also combined with additional antiplatelet drugs such as clopidogrel, e.g., after recent non-ST elevation acute coronary event, or after implantation of drug-eluting stents. The combined use of aspirin and clopidogrel leads to further increased risk of GI complications.

The aspirin literature also includes meta-analyses of a large database of clinical trials supported by Bayer HealthCare evaluating short-term use of aspirin for OTC indications, as opposed to the chronic use for cardio-prophylaxis. These studies (see Section 9.1) find AE rates with aspirin that are similar to those from placebo, although the rates of GI AEs with aspirin are slightly higher than those for placebo and statistically significant at an odds ratio (95% CI) of OR=1.3 (1.1, 1.5).

The Select Committee of GRAS Substances issued a 1979 evaluation of the safety of lecithin used in foods (see Section 9.1) which concluded that there is no evidence of a hazard from lecithin used at current levels. Patient exposure to the soy lecithin in each PL2200 capsule would be (b) (4) with a maximum daily exposure of (b) (4) which would be similar to the estimated natural dietary intake.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety evaluations were performed for the three clinical trials listed in Table 3, namely, the bioequivalence study PL-ASA-001, the endoscopic GI mucosal injury study PL-ASA-002, and the food effect study PL-ASA-003.

### 7.1.2 Categorization of Adverse Events

The adverse events were mostly GI in nature. There were no deaths or serious AEs.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling was done across the studies. See results for individual trials above.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 151 subjects were exposed to PL2200. Combined exposure to PL2200 in the three studies listed in Table 3 by number of patients exposed and dose is summarized in Table 11.

**Table 11 Overall Exposure to PL2200 by Dose**

| Total Doses, mg Quantities, Ingested | Number of Subjects | |
|---|---|---|
| | PL2200 | Comparator ASA |
| 325 mg (single dose) | 15 | 15 |
| 650 mg (single dose) | 16 | 16 |
| 1,300 mg (two doses)[a] | 20 | NA |
| 2,275 mg (multiple doses)[b] | 100 | 104 |
| **Total** | 151 | 135 |

[a] Note that subjects received two independent doses of 650 mg given 2 weeks apart
[b] Note that each subject received 7 consecutive daily doses of 325mg/day

### 7.2.2 Explorations for Dose Response

NA

### 7.2.3 Special Animal and/or In Vitro Testing

See pharmtox review.

### 7.2.4 Routine Clinical Testing

Hematology and chemistry labs were obtained. See section 7.4.2.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

NA

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths in the studies submitted.

### 7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious events in the studies submitted.

### 7.3.3 Dropouts and/or Discontinuations

There were no AEs leading to discontinuation in the studies submitted.

### 7.3.4 Significant Adverse Events

There were no adverse events in the food effect Study PL-ASA-003, and only a single adverse event in the bioequivalence Study PL-ASA-001 (flu, Subject 130 who received 650 mg PL2200), which was judged to be unrelated to study medication.

In the GI mucosal injury study PL-ASA-002, there were 20 subjects (20% of 100 subjects treated) who reported drug-related AEs, compared to 27 subjects (26%) given aspirin tablets. The vast majority of AEs definitely, probably, or possibly related to study drug fell within the Digestive SOC for both PL2200 and aspirin tablets: 17 subjects (17%) reported such AEs for PL2200, and 23 subjects (22%) did so for aspirin tablets. The Sponsor concluded that there were no clinically or statistically significant differences between treatment groups in the incidence of AEs,

**MO Comment.** *In general, events were similar between the 2 treatment groups. We are unable to tell whether there is a difference in GI lesions as there was not agreement and some mix-up of materials for the central reviewers to examine.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Only one adverse event was recorded during PL-ASA-001 and none in PL-ASA-003. In study PL-ASA-001, one subject experienced mild flu-like symptoms following ingestion of PL2200, which were evaluated by the Sponsor as unlikely related to study drug. In study PL-ASA-002, there were 23 subjects who reported mild or moderate adverse events with PL2200 vs. 31 subjects who reported events with aspirin. Most of the common AEs were gastrointestinal, in particular, nausea, dyspepsia and heartburn. These events all resolved spontaneously without specific treatment within a few days. The general distribution of adverse events between PL2200 and ASA arms was similar, with no suggestion of any toxicity specific to PL2200.

The AEs for PL-ASA-002 that were Possibly, Probably, or Definitely treatment-related are listed by SOC and Preferred Term in Table 12.

**Table 12 Subjects Reporting ≥ 1 AEs Possibly, Probably, or Definitely Related to Study Drug**

| System Organ Class<br>Preferred Term | Treatment Group<br>PL2200<br>N=100<br>n (%) | Treatment Group<br>ASA<br>N=104<br>n (%) | p-Value[b] |
|---|---|---|---|
| **Reported ≥ 1 Adverse Event Related to Study Drug*** | 17 (17.0) | 13 (12.5) | 0.4308 |
| **Body as a Whole** | | | |
| Abdominal Pain | 2 (2.0) | 1 (1.0) | 0.6158 |
| **Digestive (GI)** | | | |
| Abnormal Stools | 1 (1.0) | 1 (1.0) | 1.0000 |
| Constipation | 1 (1.0) | 1 (1.0) | 1.0000 |
| Diarrhea | 0 (0.0) | 1 (1.0) | 1.0000 |
| Dyspepsia | 4 (4.0) | 2 (1.9) | 0.4383 |
| Eructation | 1 (1.0) | 1 (1.0) | 1.0000 |
| Esophagitis | 0 (0.0) | 1 (1.0) | 1.0000 |
| Flatulence | 2 (2.0) | 0 (0.0) | 0.2391 |
| Gastric Reflux | 1 (1.0) | 0 (0.0) | 0.4902 |
| Heartburn | 3 (3.0) | 1 (1.0) | 0.3616 |
| Nausea | 5 (5.0) | 3 (2.9) | 0.4918 |
| Vomiting | 1 (1.0) | 0 (0.0) | 0.4902 |
| **Hemic and Lymphatic** | | | |
| Ecchymosis | 0 (0.0) | 2 (1.9) | 0.4977 |
| **Musculoskeletal** | | | |
| Muscle Spasm | 2 (2.0) | 1 (1.0) | 0.6158 |
| **Nervous** | | | |
| Dizziness | 0 (0.0) | 1 (1.0) | 1.0000 |
| **Special Senses** | | | |
| Tinnitus | 1 (1.0) | 1 (1.0) | 1.0000 |

Reference Table 14.3.8.1

[a] Note – excludes asymptomatic duodenal ulcers and stomach ulcers.

[b] Fisher's Exact test.

**MO Comment.** *There were no serious AEs or deaths in this trial. No statistically significant difference was observed in the frequency of treatment-related GI adverse events between subjects treated with ASA and those treated with PL2200. The procedural errors with the evaluations of endoscopy videos cast doubt on the results comparing gastric mucosal injury rates.*

### 7.4.2 Laboratory Findings

Abnormal laboratory findings in PL-ASA-001 and in PL-ASA-002 were similar between ASA and PL2200 subjects (no significant differences by treatment group). For instance, in Study PL-ASA-002 there were elevated serum potassium levels (over 6 meq/L) found for subjects in both the ASA and PL2200 treatment groups, that were attributed by the investigator to prolonged exposure of serum to cells and that were neither repeated nor followed up. Each treatment group had one reported potassium level over 7 meq/L.

Study PL-ASA-001 also assessed the hematology parameters CBC, differential and platelets, PT, and PTT. Statistically significant, but not clinically significant, decreases in hemoglobin and hematocrit were observed for both PL2200 and ASA. For 325 mg PL2200, hematocrit decreased from 39.7±3.7 to 38.4±4.2 (p=0.0008) and hemoglobin decreased from 13.5±1.5 to 13.1±1.6 (p=0.0022). For 650 mg PL2200, hematocrit decreased from 39.5±4.1 to 38.4±4.3 (p=0.041). For 325 mg aspirin, there were no statistically significant changes in hematocrit or hemoglobin. For 650 mg aspirin, hematocrit decreased from 39.5±4.3 to 38.1±4.0 (p=0.0002) and hemoglobin decreased from 13.5±1.6 to 13.0±1.4 (p=0.0004).

Additional hematology changes were reported as statistically significant but were not clinically significant: decreases in PTT for PL2200 650 mg and ASA 650 mg; decreases in RBC for PL2200 325 mg and ASA 650 mg.

**MO Comment.** *Subject 105 in PL-ASA-001 was a 48 yo female who had an apparent bleeding episode after one dose of PL2200 325 mg. The PTT increased to 57sec. from baseline 32sec., while HR increased from 49 to 85 bpm and HGB decreased from 11.3 to 10.4. The events experienced by this subject were not reported as an AE and were not followed up by the investigator. However, they should have been.*

### 7.4.3 Vital Signs

No clinically significant differences were noted between ASA and PL2200 groups in the three submitted trials. Study PL-ASA-001 assessed blood pressure, heart rate, respiration and temperature pre-dose and post-dose for PL2200 and ASA at 325mg and 650 mg doses. For PL2200 650 mg, statistically significant increases in systolic BP were found (from 114.2±8.8 to 120.8±9 mmHg, p=0.0069) and for respiration (from 15.6±0.8 to 16.2±.7, p=0.02); neither change is clinically significant. No statistically significant changes were found for PL2200 at 325 mg. For ASA 325 mg there were statistically significant, but not clinically significant, increases

in systolic BP and heart rate. For ASA at 650 mg, there was a statistically significant, but not clinically significant, increase in temperature.

### 7.4.4 Electrocardiograms (ECGs)

Baseline ECGs were obtained in studies PL-ASA-002 and PL-ASA-003 as a screening exam.

### 7.4.5 Special Safety Studies/Clinical Trials

NA

### 7.4.6 Immunogenicity

NA

## 7.5 Other Safety Explorations

NA

## 7.6 Additional Safety Evaluations

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The Sponsor has requested that a full waiver be granted since aspirin does not represent a meaningful therapeutic benefit over existing therapies such as acetaminophen and ibuprofen, and is not likely to be used for fever treatment in a substantial number of children because of the association with Reyes Syndrome.

Compliance and DNRD have opined that a capsule is not considered a new dosage form under the monograph. Thus, PREA should not be triggered. PMHS has also agreed that should PREA be triggered a full waiver would be appropriate for the following reasons:

- For the indication, "temporary relief of minor aches and pains associated with cold, headache, backache, muscular aches, toothache, premenstrual and menstrual cramps, and minor pain of arthritis", a full waiver would be appropriate because the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

- For the indication, "to temporarily reduce fever", a full waiver would be appropriate because there is evidence suggesting that the drug would be ineffective or unsafe in all pediatric age groups, in this case, due to the Reye Syndrome risk.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In aspirin overdoses, symptoms of mild to moderate toxicity include GI upset, tinnitus, tachypnea, and respiratory alkalosis. In severe toxicity, metabolic acidosis, hyperpnea, diaphoresis, fever, altered mental status, seizures, coma, cerebral edema, pulmonary edema and death can occur. Chronic overdoses may be subtle, especially in the elderly, and may consist primarily of neurologic manifestations such as confusion, delirium, and agitation. Coagulopathy, hepatic injury, and dysrhythmias are rare complications of severe overdose.

Over the 10 year period January 1, 2001 through December 31, 2010, AERS reports included 472 completed suicides with aspirin. See section 8.

### 7.7 Additional Submissions / Safety Issues

NA

# 8 Postmarket Experience

The Sponsor searched the AERS database for current safety reports with suspect mentions of single ingredient aspirin products. The search was limited to reports with an initial FDA receive date between January 1, 2001 and December 31, 2010, inclusive. This date range was chosen to provide adverse events from a safety update period approximately since the time that the NDA for the most recent aspirin product (Extra Strength Bayer Plus Aspirin) was submitted to the Agency. Query results were further limited to reports where the suspect aspirin product was believed to have an oral formulation, based on one or more of the following conditions having been met: Route was reported as ORAL; Reported drug name contains TABLET or CAPLET; or Dosage text contains ORAL, PO, or BY MOUTH.

A total of 9,704 individual case reports were identified, with a total of 37,953 associated events. Of these, 98.3% (37,324) were serious adverse events. A total of 8,058 adverse events were from fatal cases. A total of 629 adverse events were from cases coded as nonserious; these are not further discussed in the safety assessment.

The Sponsor tabulated AERS adverse events for preferred terms organized by primary system organ class. The most common serious adverse events (see Table 13), those with a frequency >2% [number of events divided by all events], were gastrointestinal disorders, especially those related to hemorrhage (gastrointestinal hemorrhage, melena, hematemesis, rectal hemorrhage, feces discolored, upper gastrointestinal hemorrhage, gastric hemorrhage and hematochezia).

Less commonly reported but still with frequency >2%, and also associated with hemorrhage, were events listed within investigations related to blood loss (hemoglobin decreased, and hematocrit decreased) and hemorrhagic events listed within vascular disorders (hemorrhage), respiratory disorders (epistaxis), and nervous system disorders (cerebral hemorrhage). Hemorrhagic events, gastric and duodenal ulcers are expected events for aspirin.

**Table 13 Aspirin SAEs with Frequency >2% from AERS, January 1, 2001-December 31, 2010**

| System Organ Class / Preferred Term | Number of Events |
|---|---|
| Gastrointestinal haemorrhage | 939 |
| Anaemia | 648 |
| Melaena | 523 |
| Haematemesis | 515 |
| Haemoglobin decreased | 511 |
| Completed suicide | 472 |
| Gastric ulcer | 432 |
| Dizziness | 388 |
| Dyspnoea | 350 |
| Drug interaction | 337 |
| Vomiting | 336 |
| Nausea | 326 |
| Asthenia | 324 |
| Hypotension | 313 |
| Myocardial infarction | 301 |
| Rectal haemorrhage | 289 |
| Haemorrhage | 270 |
| Duodenal ulcer | 256 |
| Epistaxis | 255 |
| Fall | 248 |
| Renal failure acute | 246 |
| Cerebral haemorrhage | 240 |
| Drug toxicity | 236 |
| Chest pain | 219 |
| Faeces discoloured | 218 |
| Upper gastrointestinal haemorrhage | 218 |
| Diarrhoea | 216 |
| Gastric haemorrhage | 204 |
| International normalised ratio increased | 204 |
| Haematochezia | 197 |
| Haematocrit decreased | 196 |

Other commonly reported adverse events such as nausea, vomiting, dizziness and diarrhea are known side effects of aspirin, and although seen with use of standard therapeutic doses of salicylates are also potentially related to overdosage. Events commonly characteristically associated with aspirin chronic toxicity such as tinnitus/hearing loss were also reported. (83 reports).

**MO Comment** *Notable in Table 13 are common events that are not associated with GI system or hemorrhage. The sixth most common event was completed suicide, with 472 cases reported in the ten year period. Also notable in this compilation are acute renal failure, with 246 cases in the same period, and INR increased with 204 cases. Aspirin in very high and toxic doses also exerts a direct inhibitory effect on vitamin K dependent hemostasis by inhibiting the synthesis of vitamin K dependent clotting factors. Prothrombin synthesis is impaired, resulting in hypoprothrombinemia which can result in increase INRs. Aspirin induced reduction in renal function may occur in diseases where prostaglandin synthesis contributes to the maintenance of renal function. Also listed were 301 myocardial infarctions (MI) which would not be totally unexpected given aspirin is taken by many millions of individuals for primary or secondary prevention or treatment of an MI.*

*Also of note were 87 events of Stevens-Johnson syndrome and 93 cases of toxic epidermal necrolysis, which were not included in the table because they were <2% frequency. Details of the cases were not provided. This review will be shared with the Division of Nonprescription Regulation Development (DNRD) to consider making the aspirin allergy alert warning consistent with that for OTC NSAIDs.*

The daily aspirin dose or regimen is known for 49.2% of the AERS events. For all adverse events, the four most common daily doses were: 75 mg, 11.7% of 18,656 known-dose reports; 81 mg, 25.6% of 18,656 known-dose reports; 100 mg, 28.6% of 18,656 known-dose reports; and 325 mg, 15.8% of 18,656 known-dose reports. Similar findings were found with the adverse events from serious cases.

**MO Comments.** *The cases in which daily dose or regimen was reported account for about half of all AERS events for single ingredient aspirin, the vast majority of which were serious. The AERS data did not show any new or unexpected events. About 2/3 of AEs in the cases with known dose were experienced with daily doses of 100 mg or less, which are likely cases where aspirin was taken for a cardiac indication. This is a prescription indication for long term use of aspirin at a low dose.*

There were 337 AERS reports with "DRUG INTERACTION" listing 1,008 total suspect medications. The drugs appearing as suspect drug interaction in more than 5 reports were: Plavix (43 reports), Vioxx (18), Norvasc (17), Simvastatin (17), Voltaren (15), warfarin sodium (15), clopidogrel bisulfate (12), heparin (10), clopidogrel (9), enalapril maleate (9), furosemide (9), citalopram hydrochloride (8), ibuprofen (8), hydrochlorozide (7), nifedipine (7), phenprocoumon (7), Zocor (7), allopurinol (6), amlodipine (6), atorvastatin calcium (6), bisoprolol fumarate (6), Celebrex (6), glucophage (6), metoprolol succinate (6), spironolactone (6), theophylline (6),

torsemide (6), and xipamide (6). The Tentative Final Monograph includes a section recommending that patients speak to a doctor before using aspirin if also taking medications for anticoagulation, diabetes, gout and arthritis. There is no suggestion that the recent AERS evaluation has identified any new drug interactions.

*A list of aspirin drug interactions was provided by the Sponsor:*

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.
Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.
Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.
Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.
Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.
Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAID's should be avoided because this may increase bleeding or lead to decreased renal function.
Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.
Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

The FDA has issued an advisory that 400 mg of ibuprofen can interfere with the antiplatelet effects of low dose aspirin (81 mg per day) and recommends administering ibuprofen at least 8 hours before or at least 30 minutes after aspirin if concurrent therapy is needed (*Clinical Pharmacology Online*).

**MO Comments.** *Current aspirin labeling warns consumers to ask a doctor before use if they have high blood pressure, heart disease, liver cirrhosis, or kidney disease, if they are taking a*

*diuretic, or if they are taking a drug for gout, diabetes, or arthritis. The stomach bleeding warning on aspirin labeling informs consumers that taking additional NSAIDs may increase their chance of GI bleeding. These warnings generally cover the listed interactions, except for the increased risk of GI bleeding when used with anti-platelet agents, and for the loss of cardio-protective effect when aspirin is used with ibuprofen and possibly naproxen.* (b) (4)

[redacted]

# 9 Appendices

## 9.1 Literature Review/References

The section is a review of safety information on aspirin trials reported in the published literature as submitted by the Sponsor. Selected trials were randomized, blinded, and placebo controlled. Studies were included if they focused on aspirin indications from the TFM, such as fever, headache and minor aches and pain. Some studies and meta-studies focusing on GI risk are reviewed. Additional safety studies including some consensus statements on aspirin use from professional societies are also reviewed below. The efficacy information from these trials is being evaluated by DAAAP.

**Fever and Pain Studies**
Three papers were identified by the Sponsor in which placebo-controlled trials have characterized aspirin antipyretic activity to be significantly better than placebo (Cashman et al. 1979, Bachert et al. 2005, Seed 1965). The magnitude of aspirin's antipyretic effects was in the range of approximately 2-2.5ºF with the duration of effect up to 6 hours.

The three fever studies reported that aspirin was well-tolerated. Bachert et al. compared aspirin (500 mg and 1000 mg), acetaminophen and placebo in 392 adults, and they found that the proportion of patients with treatment-related AEs was higher for aspirin than for placebo: ASA 500 mg (n=78): 10.3%; ASA 1000 mg (n=78): 29.5%; Placebo (n=78): 5.1%; $p<0.001$ vs placebo. The frequency of gastrointestinal adverse events was identical with aspirin 500 mg and placebo, higher with aspirin 1000 mg. All AEs were of mild or moderate intensity. The Cashman et al fever study compared aspirin, naproxen and placebo in 109 pediatric patients (3 to 12 years of age) and found no significant differences among treatment groups in the incidence of total complaints (there were 25 pts treated with aspirin). No safety data was provided by the Seed study.

Pain from headaches, including tension and migraine headaches, was evaluated in seven placebo-controlled studies (MacGregor et al. 2002, Martinez-Martin et al. 2001, Murray 1964, Pfaffenrath et al. 2009, Steiner et al. 2003, Von Graffenried et al. 1980, Frey 1961). Headache relief was evaluated using a variety of endpoints including visual analog scale (VAS), categorical pain intensity or pain relief, and responder analysis. Each study demonstrated statistical benefit compared to placebo.

The headache studies of MacGregor et al. 2002, Martinez-Martin et al. 2001, and Steiner et al. 2003 reported that aspirin was generally well tolerated. McGregor et al. studied 101 adult pts with migraine and compared ASA 900 mg (three doses of 300 mg) with placebo in a crossover study. The most commonly reported adverse events, were involved with the gastrointestinal system. Adverse events were reported in 22 (22%) of patients. There were 8 (8%) patients with GI AEs, all possibly or probably related to ASA which occurred on the day of ASA treatment: Dyspepsia N = 4, Nausea N = 3, Vomiting N = 1 and 4 (4%) patients reported 4 events after placebo (abdominal pain, N=2, dyspepsia, N=3; vomiting, N=1). Three events were considered severe: abdominal pain following treatment with aspirin, nausea following treatment with aspirin leading to withdrawal, and vomiting following placebo. Other possibly or probably related AEs leading to withdrawal following aspirin treatment: Tinnitus N= 1, Coughing N = 1, Taste perversion N = 1. Two non-gastrointestinal reported adverse events were considered 'serious' (both of which were considered unrelated to study medication): 1 case of headache after aspirin treatment and 1 case of endometriosis following placebo. In the headache study of Martinez-Martin et al of 417 adult patients with moderate episodic tension headache, of the group treated with aspirin 1 g (102 patients), there were 8 reported AEs, one of which was a case of drug-related nausea. Dyspepsia was the most frequently drug-related adverse event with 6 occurring in the aspirin group and 7 in the placebo group. In the study of Steiner et al. comparing aspirin (500 mg and 1000 mg) to acetaminophen and placebo in 638 adults with tension headache, the rates of drug-related GI AEs were 3.9% to 7.2% in aspirin-treated patients and were higher for aspirin than for acetaminophen or for placebo, but the AE rates were not related to dose.

Kirthi et al. 2010 was a Cochrane Collaboration review of the migraine literature. Thirteen studies (4222 participants) compared aspirin 900 mg or 1000 mg, alone or in combination with metoclopramide 10 mg, with placebo or other active comparators, mainly sumatriptan 50 mg or 100 mg. Aspirin 1000 mg is an effective treatment for acute migraine headaches, with participants in these studies experiencing reduction in both pain and associated symptoms, such as nausea and photophobia. Addition of metoclopramide 10 mg improved relief of nausea. Adverse events were mainly mild and transient (digestive and nervous systems were most commonly affected), and were slightly more common with aspirin than placebo, but less common than with sumatriptan 100 mg. Serious adverse events were uncommon and were reported in only 5 studies. In one study a case of phlebitis following use of aspirin plus metoclopramide was considered to be drug-related, while another 4 events with aspirin plus metoclopramide and six with zolmitriptan were considered unrelated. The review noted that participants with any contraindications to study medication were excluded, so the study population may differ from the general population and noted that while short-term use of aspirin

probably does not pose a large problem, the potential for gastrointestinal harm with long-term use is well documented.

The headache study of Murray 1964 was a randomized, placebo-controlled chronic headache pain study, comparing several aspirin doses to placebo, conducted in 100 subjects over 12 weeks. The study supported aspirin use in therapy as long as an adequate dose was employed (650 mg of aspirin was significantly more effective than lower doses). Dizziness or nausea was noted by 3 subjects receiving an aspirin containing dosage and were the only effects reported. The remaining headache studies did not present safety information.

Pain with common cold identified two studies in which aspirin efficacy for throat pain associated with the common cold was evaluated (Eccles et al. 2003, Schachtel et al. 1991). Each study investigated an aspirin dose of 800 mg, slightly greater than the range included in the OTC Tentative Final Monograph dosing directions. Eccles et al. compared aspirin 800 mg to placebo in 272 adults with sore throat pain in a multiple dose study. No serious adverse events were reported. Fifty adverse events were reported in 34 patients, and the most commonly reported events were headache (5 ASA, 5 placebo), abdominal pain (3 ASA, 2 placebo), nausea (2 ASA, 1 placebo), and epistaxis (2 ASA, 1 placebo). Overall, adverse events occurred in 17 patients in each treatment group. There was no change in the frequency and severity of adverse events for repeated doses of the study medications. The Schactel et al. trial compared single doses of aspirin 800 mg, aspirin 800 mg combined with 64 mg caffeine, and placebo, in 210 adults with sore throat pain; one subject given aspirin discontinued due to nausea and vomiting.

Dysmenorrhea pain and cramping was evaluated in five placebo-controlled studies (DeLia et al. 1982, Janbu et al. 1979, Kajanoja 1978, Klein et al. 1981, Pendergrass et al. 1985). Aspirin is not effective (Janbu) in severe dysmenorrhea or is marginally superior (DeLia) to placebo for treatment of dysmenorrhea, while indomethacin was superior to aspirin (Kajanoja). Aspirin and acetaminophen do not affect menstrual blood loss (Pendergrass).

The DeLia et al. 1982 study compared aspirin (650 mg q 6 hr) with flurbiprofen and placebo in a multiple dose, crossover trial over three consecutive menstrual periods in 87 women. Of these, 5 patients reported AEs during the aspirin cycle (diarrhea, nausea, headache, dizziness), all of which were mild to moderate, and one patient discontinued due to diarrhea. The similar Kajanoja study compared aspirin (500 mg tid) with indomethacin and placebo in a crossover study of 47 women during 6 consecutive menstrual periods; there were 7 reports of gastric pain, 6 reports of dizziness/drowsiness, and 1 report of headache for aspirin. Also similar was the Klein et al study of aspirin (600 mg qid) versus placebo, where each subject alternated monthly between aspirin and placebo over 4 months; there were three reports of tinnitus and one “mild GI bleed”.

Janbu et al. 1979 described a double-blind cross-over comparison of aspirin 500 mg, placebo and a comparator analgesic for the dysmenorrhea treatment. Thirteen women reported side effects during 16 total menstrual periods, including 4 with aspirin, and 6 with placebo, and 6 with comparator (paracetamol). The authors reported side effects of nausea, lower abdominal pain, headache, dizziness, tiredness and general discomfort attributable to underlying dysmenorrhea. It

was noted that one subject reported cardialgia after treatment with aspirin. The authors also provided data of measured blood loss into tampons, showing no effect of test drugs compared to placebo to promote bleeding.

Klein et al. 1981 performed a randomized, double-blind, placebo-controlled cross-over study of aspirin 600 mg for the treatment of dysmenorrhea. Test medications were taken 4 times daily during a monthly cycle. Forty-seven adolescent women entered and 29 completed the study. Side effects reported during aspirin therapy were tinnitus in 3 subjects and one report of mild gastrointestinal bleeding. It was also noted that menstrual bleeding was heavier in 6 patients when taking aspirin and 3 patients when taking placebo.

From meta-analysis of dysmenorrhea trials, Zhang and Li Wan Po 1998 found at least moderate pain relief for aspirin to be better than placebo (rate ratio 1.60, 95% CI, 1.12, 3.63), but also found that women taking aspirin required rescue analgesics as often as those receiving placebo (rate ratio = 0.79, 95% CI: 0.58, 1.08). The proportion of women experiencing any side effect when taking aspirin was no different than that of women taking placebo (rate ratio=1.31, 95% CI: 0.79-2.17). Likewise, there were no significant differences in rates of nausea, dizziness or headache between aspirin and placebo.

Aspirin is often used as an analgesic to which other agents are compared, in clinical trials of treatments for general non-surgical pain including musculoskeletal pain and postpartum pain secondary to uterine contractions and trauma to the perineal musculoskeletal structures (Bruni and Holt 1964, Boyle et al. 1960, DeKornfeld et al. 1962, Olson et al. 1997, Silberman 1983, Sunshine et al. 1983, Cass and Frederik 1965, Gruber et al. 1955, Sevelius et al. 1980).

Sunshine et al. 1983 compared single oral doses of ibuprofen, zomepirac, aspirin (600 mg), and placebo in 120 patients with severe post-episiotomy pain in a 4-hour trial. No adverse events were reported or observed.

Silberman 1983 compared aspirin (650 mg qid for three days, 12 doses in total) with suprofen in 75 adults with musculoskeletal pain (moderate to severe pain due to strains or sprains) and reported AEs in 4 aspirin patients (2 nausea and two vertigo reports). Bruni and Holt 1964 studied 757 postpartum women to determine feasibility of omitting a narcotic (562 received aspirin alone or with other drugs); no AEs “of any importance” were reported. Events of nausea and dizziness were noted after aspirin combination products. DeKornfeld et al. 1962 compared the incidence of GI AEs for five aspirin or aspirin-containing formulations in 298 postpartum women; GI AEs were more frequent after administration of Excedrin and Anacin (both also containing acetaminophen and caffeine) than after administration of the other 3 forms (two plain aspirin, one buffered aspirin). Olsen et al. compared diclofenac with aspirin (650 mg, single dose) for post-episiotomy pain in 255 females. Among 51 women given aspirin, there was a subject who reported tachycardia (heart rate not provided) which resolved spontaneously without treatment. Gruber et al. 1955 compared propoxyphene with aspirin (325 mg q 4 hr), codeine and placebo in a crossover study in 14 patients with a variety of conditions, each patient receiving every treatment for one day; no differences in frequency of AEs were observed.

Cass and Frederick 1965 compared immediate release (IR) and sustained release (SR) aspirin regimens (all of which provided 40 grains aspirin per day over 6 days) with placebo in moderate chronic pain for various reasons including back, leg or shoulder injuries, arthritis and other conditions; the incidence of AEs was similar between placebo and active drug. The side effects included nausea/vomiting, constipation, excitement, and drowsiness.

Sevelius et al. 1980 compared single doses of naproxen with aspirin (650 mg) and placebo in 194 adults for pain relief (mainly musculoskeletal or headache). Of 61 patients given aspirin, there were 25 AEs, significantly more than the 15 AEs from 63 patients given placebo (p=0.04). The aspirin AEs were mostly GI-related (14/25), with 5 additional reports of drowsiness and 3 of dizziness or light-headedness; there was one report of tinnitus.

**Other Non-Monograph Indications**
Mewa et al. 1987 studied aspirin given in high doses (1300 mg) in 10 patients with rheumatoid arthritis. Use in rheumatoid arthritis and osteoarthritis typically involves single dose exposures up to twice that of the monograph but with lesser frequency such that total daily doses of aspirin fall within the upper limit recommended by the monograph. No safety findings were presented.

Aspirin is commonly used for pain following dental extractions (Cooper et al. 1992 Desjardins et al. 1984 Forbes et al. 1980, Mehlisch et al. 1990), and for general postoperative or posttraumatic pain control (Okun et al. 1979, Parkhouse et al. 1968). In each of these studies, except for the Parkhouse et al. study, aspirin was used as an active comparitor for another drug.

Cooper et al. 1992 compared oxaprozin with aspirin 650 mg in 112 patients after 3$^{rd}$ molar extractions; there were 28 patients given aspirin of whom 3 reported AEs (not specified). Desjardins et al. 1984 compared single dose propiram fumarate to aspirin (650 mg) and codeine in 159 patients with post-op dental pain; 14 aspirin patients reported 19 AEs [drowsy (12), headache (3), dizzy (2), nausea (1), feverish (warm)]. Forbes et al. 1980 compared single dose proquazone with aspirin (650 mg) in 247 patients with post-op dental pain. Of 42 patients given aspirin, there were 4 AEs reported (vomiting, headache, drowsy, tired). Mehlisch et al. 1990 compared single dose FS 205-397 with aspirin (650 mg) and placebo in 161 patients with post-op dental pain. Seven of 40 patients given aspirin reported AEs (3 nausea, 3 drowsiness, 1 vomiting). Winter et al. 1983 compared a single dose combination acetaminophen/phenyltoloxamine with aspirin (650 mg) and placebo in 161 patients with post-op dental pain; 'seven minor AEs' were reported across all arms in the study. Okun et al. 1979 compared single dose indoprofen with aspirin (650 mg) and placebo in 208 patients with severe post-op, post-fracture or musculoskeletal pain; of 51 patients given aspirin, there were 17 patients who reported 20 AEs: Drowsiness (N=12), Dizziness (N=3), Lightheadedness (N=2), Depression (N=1), Tinnitus (N=1), Dry mouth (N=1).

Parkhouse et al. 1968 studied 500 patients given single dose aspirin at 0 mg (placebo), 300 mg, 600 mg, and 1200 mg doses, in order to determine whether a dose-response could be established with subjective ratings of pain relief. Data were acquired as five separate studies of 100 patients

each (~25 patients at each of four dose levels) in three hospitals. One nurse-investigator led three of the studies and saw 300 patients, two other nurse-investigators led one study each. A dose response was found in each of the five studies, although there was significant variation in the dose-response by investigator and by hospital. In four of the five studies, the incidence of AEs was very low, but the AE rate was much higher in the fifth study led by a different nurse-investigator than the other studies. Specifically, in the fifth study with 100 patients, there were 9 AEs for placebo, 15 AEs for 300 mg, 29 AEs for 600 mg, and 21 AEs for 1200 mg doses. For the other four studies combined (400 patients), there were only 9 AEs for placebo, 1 AE for 300 mg, 3 AEs for 600 mg, and 7 AEs for 1200 mg doses. The authors conclude that reported incidence of side effects may be expected to vary strongly with investigator.

**MO Comment.** *According to the literature submitted by the Sponsor, aspirin used for pain and fever relief is generally well tolerated. There is a higher incidence of adverse events with aspirin than with placebo, but aspirin side effects, most commonly nausea, vomiting, abdominal pain, headache, dizziness, and tinnitus, are mainly mild to moderate. When used for dysmenorrhea, aspirin does not increase menstrual blood loss.*

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**Consensus Report on GI risks**

The American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents issued a consensus report on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use (Bhatt et al. 2008). NSAIDs, both through prescription and OTC use, are the most widely used class of medications in the United States, especially among the elderly. In people 65 years of age and older, 70% used NSAIDs at least once weekly, and 34% used them at least daily. The prevalence of at least weekly ASA usage was 60%. More than 111 million NSAID prescriptions were written in 2004. NSAIDs, including ASA, are commonly used for treatment of pain, inflammation, and fever. Additionally, low-dose ASA is used routinely in primary and secondary prophylaxis of cardiovascular and cerebrovascular events. ASA is also combined with additional antiplatelet drugs such as clopidogrel, with increasing emphasis on extended use (e.g., after recent non-ST elevation acute coronary event, use for at least a month), and especially use after implantation of drug-eluting stents (at least 12 months continuous, dual antiplatelet therapy with ASA and clopidogrel).

The consensus report makes the following findings and recommendations:

- The use of any NSAID, including COX-2–selective agents and OTC doses of traditional NSAIDs, in conjunction with cardiac-dose ASA, substantially increases the risk of ulcer complications, and gastro-protective therapy is recommended for at-risk patients.
- The use of low-dose ASA for cardio-prophylaxis is associated with a 2- to 4-fold increase in upper gastrointestinal event risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of adverse events, gastro-protection should be prescribed. The risk of upper gastrointestinal event increases with ASA dose escalation, and doses greater than 81 mg should not be routinely prescribed for the chronic phase of therapy.
- The combination of ASA and anticoagulant therapy (including unfractionated heparin, low molecular weight heparin, and warfarin) is associated with a clinically meaningful and significantly increased risk of major extracranial bleeding events, a large proportion from the upper GI tract. This combination should be used with established vascular, arrhythmic, or valvular indications; patients should receive concomitant PPIs as well. When warfarin is added to ASA plus clopidogrel, an international normalized ratio (INR) of 2.0 to 2.5 is recommended.
- Substitution of clopidogrel for ASA is not a recommended strategy to reduce the risk of recurrent ulcer bleeding in high-risk patients and is inferior to the combination of ASA plus PPI
- PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury

**MO Comment.** *The estimated average excess risk of upper gastrointestinal event related to cardio-prophylactic doses of ASA is 5 cases per 1000 ASA users per year (Hernandez-Diaz et al. 2006), and the risk may increase with higher doses, without providing additional anti-thrombotic benefit (Weil et al. 1995, Sorenson et al. 2000, Serebruany et al. 2005, Antithrombotic Trialists' Collaboration 2002). Case series implicate OTC use of low-dose ASA in over one-third of the patients admitted for GI hemorrhage (Wilcox et al. 1994), suggesting*

*that patients who self-medicate may be unaware of the significant increase in their risk of upper gastrointestinal event.*

*The ACCF/ACG/AHA consensus report also cited several trials confirming that combined ASA and clopidogrel therapy is associated with significantly increased risk of upper gastrointestinal events (UGIE) complications when compared with either agent alone (Bhatt et al. 2008). In addition, the Plavix label includes a precaution that states that Plavix prolongs bleeding time, and warns that drugs which may induce lesions which may bleed (such as ulcers), explicitly noting aspirin and other NSAIDs, should be used with caution in patients using Plavix. The aspirin label should be strengthened to clarify that the "ask a doctor before use" warning regarding blood-thinning agents specifically includes anti-platelet as well as anticoagulant therapies.*

**Consensus Assessments of Lecithin Safety**

The Cosmetic Ingredient Review Expert Panel issued a 2001 consensus report on safety of lecithin and hydrogenated lecithin for use in skin conditioning agents and as surfactant-emulsifying agents. Lecithin is virtually nontoxic in acute oral studies, short-term oral studies, and sub-chronic dermal studies in animals. Lecithin is not a reproductive toxicant, nor is it mutagenic in several assays. Lecithin and hydrogenated lecithin were generally nonirritating and non-sensitizing in animal and human skin, and they are safe as used in rinse-off cosmetic products and in leave-on products at concentrations up to 15%.

The Select Committee of GRAS Substances issued a 1979 evaluation of the safety of lecithin used in foods, based on literature through 1974. Phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol are the major constituents of oil-free soybean lecithin but are not discrete chemical entities. The Committee concluded that there is no evidence in the available information on lecithin that demonstrates or suggests reasonable grounds to suspect a hazard to the public when used at (then) current levels. The average daily consumption of lecithin added to foods in 1970, based on the total amount reported to be used, was 92 mg, amounting to about 1.5 mg per kg body weight for adults. The lecithin added to foods amounts to only 2 to 10 percent of the 1 to 5 g of phosphoglycerides consumed daily as natural constituents of the diet (e.g., in eggs, liver, soybeans, peanuts).

**MO Comment.** *Patient exposure to* (b) (4) *soy lecithin in each PL2200 capsule would be* (b) (4) *a maximum daily exposure of* (b) (4)*). This maximum lecithin exposure level would be similar to the estimated natural dietary intake.*

**Bayer HealthCare Database**

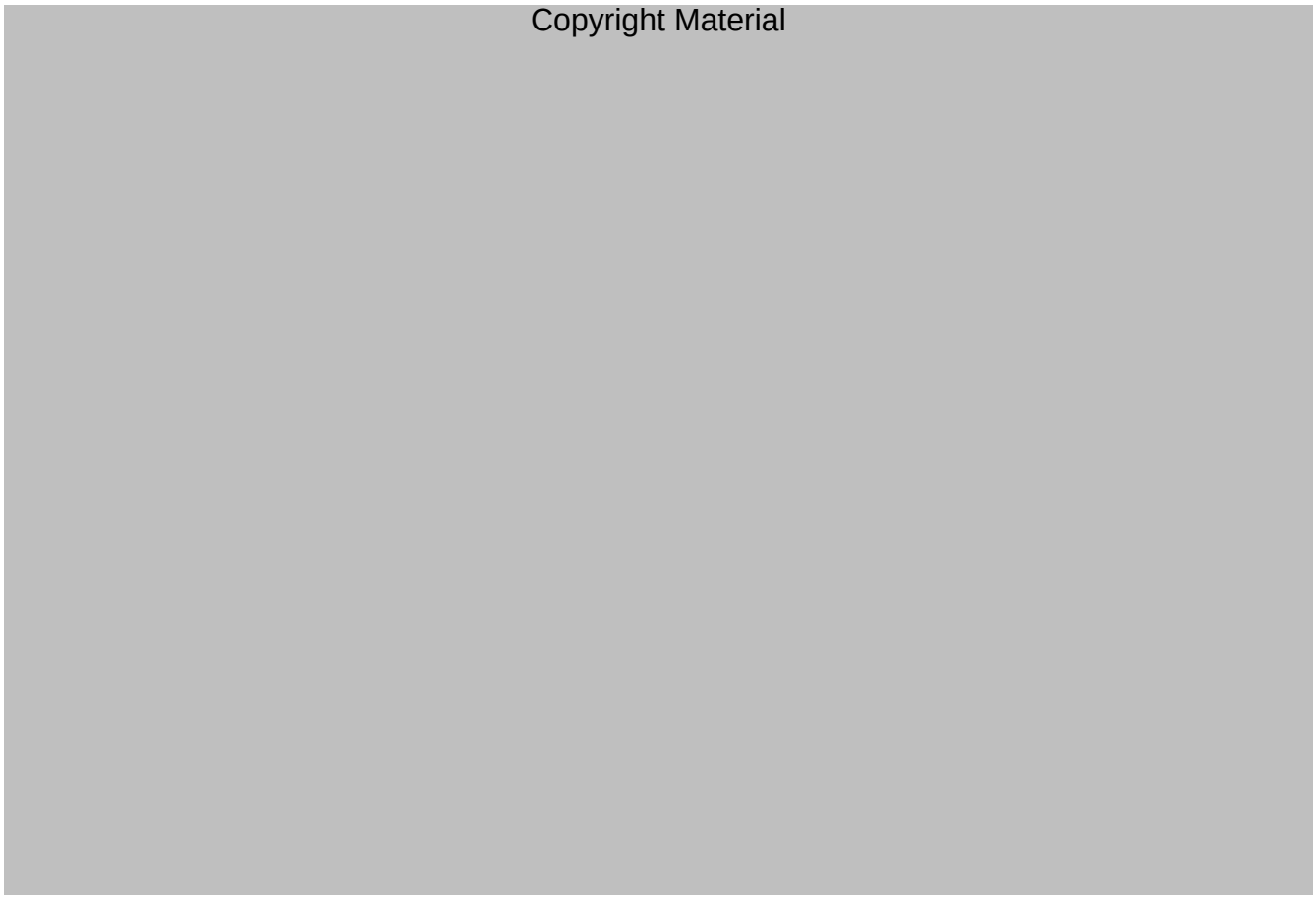
Lanas et al. 2011 performed a meta-analysis of data from aspirin clinical trials conducted by Bayer HealthCare prior to March 31, 2008. This database included 87 studies, 67 of which met the inclusion criteria for the meta-analysis. Most of the aspirin studies evaluated efficacy for pain, fever, or colds; a small number evaluated pharmacokinetics. The primary endpoints were patient-reported gastrointestinal (GI) adverse events (AEs); the secondary endpoints were the incidence of patient-reported non-GI AEs. In total, 6181 patients were treated with ASA, 3515 with placebo, 1145 with acetaminophen (paracetamol), and 754 with ibuprofen. Exposure to

ASA was short term. In the aspirin groups, 5,099 subjects (82.5%) received a single dose, 1,082 (17.5%) received a multiple-dose regimen, and 188 (3.0%) were treated for more than 5 days. Over half (54%; 3,337 patients) of the aspirin study population took a daily dose between 500 and 1,000 mg.

GI AEs were more frequent with ASA (9.9%) than with placebo (9.0%); the OR was 1.3 (95% CI 1.1, 1.5). Dyspeptic symptoms were reported by 5.3% of aspirin subjects versus 4.6% of placebo subjects. The rate of dyspeptic symptoms was slightly but significantly elevated for ASA vs placebo, but was similar for ASA, ibuprofen and acetaminophen. The ORs for ASA were 1.3 (95% CI 1.1, 1.6) versus placebo; 1.55 (95% CI 0.7, 3.3) versus ibuprofen; and 1.04 (95% CI 0.8, 1.4) versus acetaminophen. There was one serious GI AE case for ASA and three placebo cases. No cases of cerebral hemorrhage were reported.

The overall incidence of AEs was similar between subjects treated with aspirin (741/4,884; 15.2%) and those treated with placebo (580/3,731; 15.5%). GI AEs and non-GI AEs are shown in Table 14 for aspirin and placebo.

**Table 14 AEs with aspirin or placebo (Lanas et al. 2011)**



Steiner and Voelker 2009 reported similar results from pooled analyses of individual patient data from all nine randomized controlled clinical trials in acute pain disorders that have been supported by Bayer HealthCare and that compared single-dose aspirin 1000 mg with placebo. These trials enrolled 1581 patients treated with aspirin 1000 mg and 1271 with placebo. The fraction of aspirin subjects reporting any AE was 14.9% versus 11.1% of placebo subjects which was a statistically significant difference (RR = 1.3; 95% CI 1.1-1.6). GI AEs were reported by 5.9% of aspirin subjects and 3.5% of placebo subjects which was also statistically significant (RR = 1.7; 95% CI 1.2-2.4).

**MO Comment.** *It is unclear why the higher dose studied (ASA 1000mg) had lower rates of AEs than the doses studied under the Lanas article which also included lower doses of aspirin.*

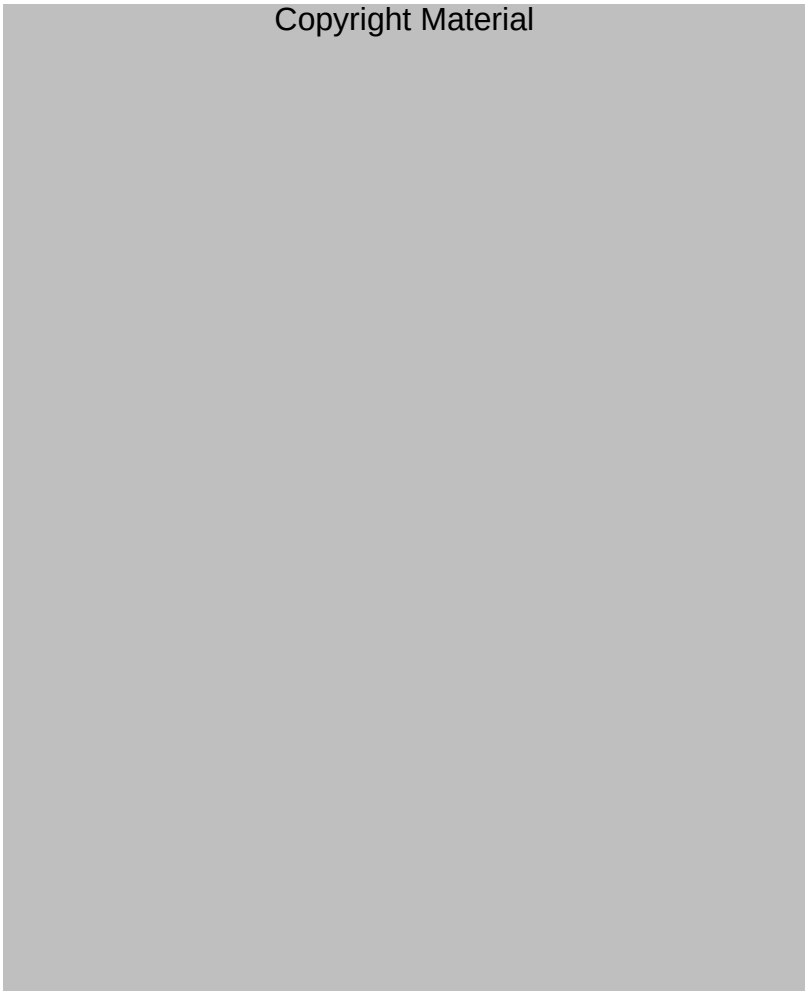



**Figure 4. Advanced age and ulcer history as risk factors for GI complications in low-dose ASA users (Hernandez-Diaz et al. 2006)**

**Other Aspirin Literature**

Cryer 2009 reviewed the increasing use of antiplatelet therapies for the prevention of coronary artery and coronary stent occlusion as well as prevention of cerebrovascular occlusion. Oral

antiplatelet therapies, aspirin and thienopyridines (clopidogrel and prasugrel), are of clinical benefit but are associated with increased rates of ulcer and Gl complications. Observational studies indicate a seven-fold increase in upper Gl bleeding with the combination therapy when compared with aspirin, with GI risk increasing in patients who are at higher risk. In treating cardiovascular disease, clinicians are caught between competing considerations of cardiovascular benefit and gastrointestinal (GI) risks. Hernandez-Diaz et al. 2006 assessed risk factors for GI complications in users of low dose ASA (Figure 4).

Gerard Thiefin et al. 2008 reported results of a postal survey with 8106 respondents looking at the prevalence of upper GI symptoms in 986 users of low-dose ASA. Prevalence of upper-GI symptoms was 15%. Overall, 60% of these patients suffered from symptoms at least once a week. The fractions of these patients reporting moderate and severe impairments of their daily lives were 53% and 20%, respectively. Twelve percent did not take their treatment every day because of bothersome upper GI symptoms.

Lanas et al. 2005 studied mortality associated with hospital admission due to major gastrointestinal (GI) events and NSAID/aspirin use, using data from two studies counting deaths after hospitalizations in 2001. Study 1 was carried out in 26 Spanish general hospitals serving 7,901,198 people. Study 2 used a database from 197 general hospitals in the Spanish National Health System, including 77% of the total hospitalizations during 2001. Information regarding gastrointestinal complications and deaths was provided by participating hospitals. Deaths attributed to NSAID/aspirin use were estimated on the basis of prospectively collected hospital data from study 1. The incidence of hospital admission due to major GI events of the entire (upper and lower) gastrointestinal tract was 121.9 events/100,000 persons/year, but those related to the upper GI tract were six times more frequent than lower GI events. Mortality rate was 5.57% (95% CI = 4.9–6.7), and 5.62% (95% CI = 4.8–6.8) in study 1 and study 2, respectively. Death rate attributed to NSAID/aspirin use was between 21.0 and 24.8 cases/million people, respectively, or 15.3 deaths/100,000 NSAID/aspirin users. Up to one-third of all NSAID/aspirin deaths can be attributed to low-dose aspirin use.

**MO Comment.** *The estimated number of individuals who died as a result of their NSAID-related GI complications is similar to that for deaths associated with occupational activities according to the Spanish Ministry of Labour and Social Affairs in 2001. Low dose aspirin use accounts for a significant fraction (up to one third) of this mortality from NSAID/ASA use. The study may have been underestimated the number of deaths since death due to GI complications may occur at home in patients that do not seek hospital attention or after hospital discharge. The authors concluded that it is important to heighten physician and public awareness of GI adverse events associated with NSAID therapy. The authors also feel that to provide estimates of GI mortality due to low-dose aspirin use is important since aspirin is widely used in the population where benefits and risks of prevention strategies should be carefully balanced.*

Lanza et al. 1979 performed endoscopic studies of NSAID effects on gastric mucosa with gastroscopy was carried out before and after seven days of aspirin (3600 mg/d); placebo; ibuprofen (1600 mg/d and 2400 mg/d); indomethacin (100 mg/d and 150 mg/d); naproxen (500

mg/d and 750 mg/d). There were 5 subjects in the aspirin group (total 40, all drugs and doses). Severe gastric mucosal injury occurred with aspirin ($P < 0.05$), both doses of indomethacin, and the higher dose of naproxen. Lesser changes were seen with the lower dose of naproxen, both doses of ibuprofen and placebo. Aspirin patients all had some degree of GI symptoms but to a lesser degree than expected from endoscopic findings.

Similarly, Lanza et al. 1984 endoscopically evaluated sixty volunteers to compare gastric mucosal injury following oral administration of sulindac, naproxen, aspirin, or placebo for two consecutive seven-day periods. The following dosages were employed for the two study periods: sulindac, 150 and 200 mg. b.i.d., naproxen, 250 and 375 mg, b.i.d., and aspirin, 650 and 975 mg, q.i.d. There were 15 aspirin subjects. The graded endoscopy scores of gastric irritation were higher for aspirin than for naproxen, sulindac, or placebo. AEs were reported by 14/15 aspirin users, and half of reported events were GI events, primarily dyspepsia and nausea. Tinnitus was reported 9 times and an invasive ulcer was seen on day 8 with 2 subjects taking aspirin and on day 15 with 3 subjects taking aspirin.

**MO Comment.** *Both endoscopic studies were single-blind (the PI and the endoscopist were blinded to identity of drug). Both also used a gastric injury grading scale similar to that used in the endoscopy study in the present submission.*

Wojcicki et al. 1995 reported a clinical study of plasma lipid composition following oral administration of soybean lecithin in 32 patients with primary hyperlipidemia. Lecithin granulate (3.5 g tid) was given for 30 days. The mean total cholesterol concentration was decreased by 33% while LDL-level was reduced by 38%. HDL-cholesterol was increased by 46%. The mean triglyceride concentration was decreased by 33%. These changes were statistically significant.

Sirtori et al. 1985 performed a trial with 65 patients who underwent sequential 4-week dietary treatments using low-lipid diets with and without substitution of animal proteins by textured soy protein containing 6% lecithin (L-TVP). The L-TVP substitution exerted a marked hypocholesterolemic action in type II hyperlipidemic patients and produced a significant increase in levels of high-density lipoprotein (HDL) cholesterol ($p < 0.01$) in the subgroup of hypercholesterolemia patients with low starting HDL. Hypercholesterolemia was significantly reduced during both periods of L-TVP administration, by 18% during total replacement ($p < 0.001$), and by 13.2% during partial replacement ($p < 0.01$).

**MO Comment.** *No side effects were reported by Wojcicki et al. or by Sirtori et al. A meta-analysis of 38 clinical studied (Anderson et al. 1995) found that soy protein was effective in lowering serum cholesterol only for patients with cholesterol >260 mg/dL and found no significant effect in those with cholesterol <200 mg/dL.*

*There is no reason to believe that the new formulation PL2200 will have a different safety profile than other nonprescription aspirins.*

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## 9.2 Labeling Recommendations

The proposed label is shown in Figure 5. The trade names (b) (4) were not found to be acceptable by DMEPA. The latest proposed name (b) (4) was submitted on December 6, 2012. It is currently under review by DMEPA. The Drug Facts labeling is consistent with the monograph.

The sponsor has proposed to include the following bullets under the "Ask a doctor or pharmacist before use" subheading:

(b) (4)

See DNRD and DMEPA reviews for additional label comments.


**Figure 5 Proposed Label**

## 9.3 Advisory Committee Meeting

NA

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

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/s/

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LINDA S HU
12/10/2012

DAIVA SHETTY
12/10/2012

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 203,697** **Applicant: PLx Pharma Inc.** **Stamp Date: March 14, 2012**

**Drug Name: PL2200 Aspirin Capsules, 325 mg** **NDA/BLA Type: 505(b)(2)**

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

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | | | | electronic |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | | | | 505(b)(2)<br>Reference Drug = Bayer Aspirin, 325 mg |
| **DOSE** | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size: Arms:<br>Location in submission: | | | X | |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1: PL-ASA-001<br>Indication: Comparative PK study of 2 doses of PL2200 to assess BE, safety, and | X | | | The application provides two PK studies demonstrating bio-equivalence with marketed Aspirin along with |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | confirm anti-platelet activity after treatment<br><br>Pivotal Study #2: PL-ASA-003<br>Indication: Determine the effect of food on single-dose pharmacokinetics of PL2200 | | | | documented efficacy information from published literature. |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | | | X | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | X | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 23. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | X | |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | |
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| **CASE REPORT FORMS** | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | X | | | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Priscilla Callahan Lyon

Reviewing Medical Officer Date

Clinical Team Leader Date

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

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/s/

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PRISCILLA C LYON
05/01/2012

DAIVA SHETTY
05/01/2012