CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203697Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	12/21/2012
From	Daiva Shetty, M.D.
Subject	Cross-Discipline Team Leader Review
NDA # Supplement#	203697
Applicant	PLx Pharma Inc.
Date of Submission	March 14, 2012
PDUFA Goal Date	January 14, 2013
Proprietary Name / Established (USAN) names	Aspirin
Dosage forms / Strength	325 mg Capsule
Proposed Indication(s)	1. For the temporary relief of minor aches and pains associated with: a cold, headache, toothache, premenstrual & menstrual cramps, minor pain of arthritis 2. Temporary reduces fever
Recommended:	Approval pending satisfactory results of the manufacturing facility inspection

1. Introduction

This NDA proposes a new lipid suspension capsule of aspirin, 325 mg, for over-the-counter (OTC) marketing. Aspirin is marketed OTC under the Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products tentative final monograph (TFM) for the same indications that the sponsor is requesting for this new formulation. In addition, aspirin is allowed for professional labeling under the 21 CFR 343 final monograph for the prevention of cardiovascular events and the treatment of rheumatologic disorders. (b) (4) the sponsor, PLx Pharma Inc. (PLx) is not requesting for these indications.

The sponsor submitted a 505(B)(2) application referencing monograph aspirin as the reference drug. The proposed formulation could not be marketed under the OTC monograph system because the amount of the main excipient in the formulation, soy lecithin, (b) (4) the limit allowed in the FDA inactive ingredient database for drugs approved for oral use. This formulation contains (b) (4)

This review summarizes all discipline reviews of this application.

2. Background

Discussions between FDA and PLx about the development of this new formulation of aspirin (also referred as Aspirin PC or PL2200) started in 2007 under the IND 74290. (b) (4)

(b) (4)

At the pre-NDA stage of their development program, the sponsor stated that their 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.

For more details on the regulatory history of this application, please refer to Dr. Hu's clinical review.

3. CMC/Device

CMC review has been done by Dr. Muthukumar Ramaswamy (see his reviews entered in DARRTS on 8/29/12 and 12/10/12).

The active ingredient and excipients in the proposed product are either known or present in previously approved products. The sponsor provided adequate data to support the drug substance and each excipient.

Container closure system was found to be acceptable. However, the requested shelf life, based on the stability of the product packaged in bottles, was found to be unacceptable. (b) (4) CMC team requested the sponsor to set consistent specification criteria for release and stability to support the shelf life. The sponsor submitted additional data which supports an 18 month shelf life for the products packaged in bottles and blisters.

CMC reviewer concluded that both, the manufacturing process as well as the proposed specifications for the drug product, are acceptable.

Inspection of the manufacturing facility is pending at the time of this review.

Environmental assessment - this application contains a claim for categorical exclusion under CFR 25.31, which was found to be acceptable.

The only outstanding CMC issue is the overall recommendation on the manufacturing facility inspection from the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

Please refer to the pharmacology-toxicology review by Dr. Cindy Li entered in DARRTS on 12/10/12.

There are no nonclinical toxicology studies conducted with PL2200. The nonclinical section of the NDA referenced the TFM and included a review of the literature on nonclinical safety of

aspirin. The reviewer concluded that information supporting TFM and the more recent published literature on aspirin do not provide new findings or unexplained toxicity.

There were two issues noticed during the current nonclinical review with regards to the excipients and impurities/degradants of the drug product:
(1) The proposed drug product contains [redacted] in the formulation. The applicant claims [redacted] is lecithin and functions as an inactive ingredient.

To support safety of [redacted] as inactive ingredient, the sponsor provided the following:

- letter of authorization from [redacted] manufacturer to access the corresponding DMF
- reference to the United States Pharmacopeia-National Formulary USP/NF monograph for lecithin
- reference to the 21 CFR 184 1400 which supports lecithin's safety as a direct food substance
- comprehensive literature review on the toxicity of lecithins
- two rat toxicity studies with [redacted]

The reviewer concluded that based on the data submitted, there is no nonclinical concern related to the proposed use of lecithin under the condition specified in the proposed labeling in PL2200.

(2) The applicant has proposed separate specifications for monitoring the levels of free salicylic acid (SA) in the product during release [redacted] and stability ([redacted]

CMC team did not agree with those proposed specifications because they are not consistent with the levels allowed for USP aspirin tablets or capsules. The sponsor revised the stability specification level of SA at Not More Than (NMT) [redacted] SA and NMT [redacted] Total Related Substances.

Dr. Li concluded that the stability specification level of SA at [redacted] in PL2200 does not raise safety concerns from a nonclinical perspective.

Since [redacted] is a soybean-derived lecithin with [redacted], the Botanical Review Team (BRT) was consulted to assess the quality and safety of lecithin. See Dr. Jinhui Dou review entered in DARRTS on 11/19/12. BRT team has identified no safety nor quality issues concerning [redacted], which has similar specifications as those listed in the USP-NF lecithin monograph. In addition, the changes made by the applicant in the preparation of [redacted] (e.g., [redacted] do not alter the safety profiles of soy lecithin. Dr. Dou concluded that from BRT's perspective, the use of [redacted] as an USP-NF equivalent lecithin is appropriate and does not impact the approvability of the NDA.

There are no outstanding pharmacology-toxicology issues for this NDA.

5. Clinical Pharmacology/Biopharmaceutics

Primary review of bioequivalence (BE) studies was done by Dr. Suresh Naraharisetti (entered in DARRTS on 12/7/12).

The sponsor submitted two clinical pharmacology studies to support the application:

- PL-ASA-001 - single dose bioequivalence study comparing Aspirin PC versus Genuine Bayer aspirin in healthy volunteers.
- PL-ASA-003 food effect study

To-be-marketed formulation was used in study PL-ASA-003, however, a test formulation was used in study PL-ASA-001. To bridge the test formulation and the to-be-marketed formulation, the sponsor conducted in-vitro dissolution data which was reviewed by Dr. Tien Mien Chen (see his review entered in DARRTS on 12/10/12) Dr. Chen has determined that based on mean dissolution profiles using in-vitro dissolution method, the link is established between the test and the final formulation.

The Office of Scientific Investigations (OSI) audited the study PL-ASA-001 and has recommended the exclusion of four subjects (see Dr. Joythi Patel's review entered in DARRTS on 10/31/12). Those subjects were excluded from the analysis.

A total of 32 subjects were enrolled and 30 of them completed the study PL-ASA-001. Two dose levels were evaluated - 325 mg and 650 mg (administered as two 325 mg capsules). As previously agreed with the FDA, salicylic acid (the active moiety for pain) was used as the primary metabolite for the assessment of bioequivalence. Following is the summary of the results as stated in Dr. Naraharisetti's review. The results of BE analysis showed that, Aspirin PC meets the BE criteria for salicylic acid at 325 mg dose, but not at 650 mg dose. At 325 mg level, the upper limit of 90% confidence interval (CI) for log transformed salicylic acid C_{max} AUC_{0-t}, AUC_{0-inf} ratios for the test product to the reference product are within 80-125%. At 650 mg dose level, the lower limit of 90% CI for log transformed salicylic acid AUC_{0-t}, AUC_{0-inf} ratios for the test product to the reference product is 75.8 and 78.0, respectively. Dr. Naraharisetti concluded that the Aspirin PC capsule is bioequivalent to the Bayer Aspirin tablet at 325 mg, but not at 650 mg dose level under fasted conditions. However, as it was discussed in a review team meeting, even though 650 mg dose level failed to meet BE on the lower CIs, this is not clinically significant.

Study PL-ASA-003 evaluated food effect on single dose Aspirin PC administered as two 325 mg capsules. A total of 20 subjects were enrolled and completed this study. Based on the OSI's recommendations, two subjects were excluded from the analysis. Following are the conclusions by Dr. Naraharisetti: "Aspirin-PC capsules with food resulted in a 6% lower AUC (AUC_{0-t} and AUC_{inf}) and a 22% lower C_{max} for salicylic acid, respectively, and an approximately 1.64-hour delay in salicylic acid mean T_{max} (4.58 hours vs 2.94 hours) compared to fasted conditions. The observed food effect for the Aspirin-PC product is not considered clinically significant and requires no dose adjustments."

(b) (4)

Study PL-ASA-001 evaluated pharmacodynamic (PD)

effects. These PD data were reviewed by the clinical pharmacology team supporting the Division of Cardiology and Renal Products (DCRP). See Dr. Divya Menon-Andersen's clinical pharmacology review (entered in DARRTS on 11/14/12) and Dr. Thomas Marciniak's clinical review (entered in DARRTS on 11/30/12).

PK study PL-ASA-001 assessed aspirin's anti-platelet activity by measuring serum tromboxane B2 (sTxB2) and agonist induced platelet aggregation. These methods were found to be acceptable; however, these two methods are not sensitive enough to assess the difference between different ASA concentrations. A dose dependent effect on sTxB2 is observed in dose range of up to 100 mg, with 90% inhibition of sTxB2 at 100 mg. Doses used in PL-ASA-001 were 325 and 650 mg. Both of them achieved maximal inhibition of sTxB2 and platelet aggregation.

Dr. Marciniak made the following conclusions:
"While PL2200 meets the BE criteria for AUC0-4h, it does not meet the usual criteria for Cmax. (b) (4)

(b) (4)

(b) (4)

In summary, PK-PD data show that the PL2200 (325 mg and 650 mg) is bioequivalent to the reference aspirin in its PK and PD parameters, and is acceptable for the pain and fever indications. (b) (4) (b) (4)

There are no outstanding clinical pharmacology issues for this application.

6. Clinical Microbiology

Not applicable. There was no microbiology information in this NDA.

7. Clinical/Statistical- Efficacy

There are no specific clinical efficacy studies for the PL2200. The sponsor supports efficacy by referencing the FDA's prior findings of safety and efficacy set forth in the monograph. For the relief of pain and fever indications, aspirin is marketed under the tentative IAAA OTC monograph. It has been generally recognized as safe and effective (GRAS/E - Category I) for its safety and efficacy. However, since the IAAA monograph is not final, at the End of Phase 2 meeting FDA agreed that PLx can use publicly available literature and the data in the final monograph for the professional labeling of aspirin, to support the conclusion that aspirin is

safe and effective as an OTC analgesic at the recommended doses. Specifically, FDA asked for data from well-conducted trials for two different pain models plus data in fever and menstrual pain. The sponsor, therefore, submitted three papers on antipyretic indication, seven papers on headache analgesia, two studies on pain relief with common cold, five studies for the treatment of dysmenorrhea, two in musculoskeletal pain, and nine in general pain conditions.

Dr. Christina Fang from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) summarized and evaluated the efficacy data (see her review entered in DARRTS on 12/11/2012). The reviewer selected the studies for review based on the following criteria: randomized, double-blind, placebo-controlled study design and published later than 1988, except an additional fever study published in 1979 and three dysmenorrhea studies published in the early eighties were included because only one fever study and no dysmenorrhea studies were published in the specified time frame. A total of 13 studies met these criteria.

The reviewer found that aspirin works for treating aches and pains and/or fever in an OTC setting, based on the estimated effect size of treatment differences from pairwise comparisons between various aspirin doses and placebo, using time-specific PID measurements in multiple studies of fever, headache, sore throat, primary dysmenorrhea, and dental pain. Dr. Fang made a conclusion that the findings in the cited literature support a finding of efficacy for the use of aspirin for OTC indications of temporary relief of minor aches and pains and temporary reductions of fever as stated in the tentative IAAA OTC monograph.

I agree with this assessment. There are no outstanding efficacy issues for this application.

8. Safety

Please refer to the Clinical Review by Dr. Linda Hu entered in DARRTS on 12/10/2012.

The proposed product is a novel immediate-release formulation of aspirin in a lipid suspension of soybean-derived lecithin; it is not marketed anywhere in the world. However, the active ingredient, aspirin, has a long marketing history dating back to the 19th century. Safety data for the proposed formulation comes from the three clinical trials conducted by PLx:

- PL-ASA-001 comparative singe dose PK study
- PL-ASA-002 randomized, single-blind, parallel 7-day GI safety and tolerability study
- PL-ASA-003 single dose food-effect PK study

These three trials provided favorable, but limited, safety experience. A total of 151 subjects were exposed to aspirin PC: 100 subjects received 325 mg for 7 days, 20 subjects received two doses of 650 mg each, and 31 subjects received single doses of 325 mg or 650 mg. There were no deaths, serious or unexpected adverse events reported.

In addition to the above discussed trials, PLx submitted postmarketing safety data for aspirin from the published literature and the FDA's Adverse Event Reporting System (AERS) for the ten year period, from January 1, 2001 through December 31, 2010.

AERS database identified a total of 9,704 individual case reports with a total of 37,953 associated events for oral aspirin products. Of these, 98.3% (37,324) were serious adverse

events, the most common of which were gastrointestinal disorders. A total of 8,058 adverse events were from fatal cases. The reviewer also noted that there was a notable number of Stevens-Johnson syndrome (87 cases) and toxic epidermal necrolysis (93 cases) reports. It is difficult to interpret these postmarketing data. Aspirin is the most widely used drug. No details of the cases were provided, only the line listings. The events could also be related to the underlying conditions, concomitant medications, or the conditions for which aspirin was taken.

Review of the published literature included publications reporting efficacy trials (these were described in the section 7 of this review), studies and meta-analyses focusing on GI risks, as well as consensus statements from professional societies. Data showed that aspirin, when used for short-term pain or fever relief, is well tolerated; most common AEs reported: nausea, vomiting, abdominal pain, headache, dizziness, and tinnitus.

Overall, data from different sources confirms known safety profile for aspirin. Even though this NDA is proposing a new formulation, there is no reason to believe that this new product will have a different safety profile than other nonprescription aspirin formulations.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

PLx requested a full waiver from the Pediatric Research Equity Act (PREA) pediatric assessment requirement for all pediatric age groups for both indications, i.e., fever and pain, because it 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.

During review of this application, decision has been made by the regulatory and CMC staff that this product formulation does not trigger PREA, because capsule formulation is considered an acceptable dosage form to be marketed under the IAAA TFM.

The sponsor proposed to label this product for adults and children 12 years and older, which is consistent with TFM. I find this acceptable.

11. Other Relevant Regulatory Issues

All clinical studies conducted to support this application were carried out in accordance with the US CFR, Good Clinical Practice, 21 CFR 50 and 312.

12. Labeling

PLx proposes to market their aspirin capsules in several different package sizes and configurations:

- 30-count bottle

- 120-count bottle
- 7-count blister card
- 28-count package containing four 7-count blister cards

Three different proprietary names were proposed by the sponsor: (b) (4) None of these were found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). This, however, does not preclude an approval. The product can be approved without a trade name. DMEPA also provided several labeling recommendations to prevent potential medication errors.

The proposed dosing directions are consistent with the TFM:

- for adults and children 12 years and over: take 1 or 2 capsules every 4 hours or 3 capsules every 6 hours
- do not exceed 12 capsules in 24 hours

This is acceptable.

Detailed labeling review has been conducted by Elaine Abraham from the Division of Nonprescription Regulation Development (see her review entered in DARRTS on 12/10/12). Labeling change recommendations were communicated to the sponsor on 12/10/12. All of the requested changes were accepted by the sponsor in their 12/19/12 submission.

Labeling for the product is consistent with the IAAA TFM drug facts labeling information.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval pending satisfactory results of the manufacturing facility inspection.

- Risk Benefit Assessment

Aspirin is marketed for over 100 years and has well established favorable risk/benefit profile. Based on data submitted in the application, there is no reason to believe that this new product will have a different risk benefit profile compared to other nonprescription aspirin formulations.

All review disciplines recommended approval of this application.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

DAIVA SHETTY
12/26/2012