

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200671Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Durlaza™, Acetylsalicylic acid, Controlled-release capsules  
Indication: Secondary prevention of acute cardiovascular events  
(Anti-platelet therapy)  
Applicant: New Haven Pharmaceuticals, Brandford CT  
Review Division: Cardiovascular and Renal Products  
(DCRP/ODE1/OND/CDER)  
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# 1 Executive Summary

## 1.1 Introduction

The therapeutic utility of acetylsalicylic acid (ASA) is believed to stem from inhibition of platelet-derived production of thromboxane A<sub>2</sub> (TXA<sub>2</sub>), which is a potent stimulator of platelet aggregation and vascular smooth muscle contraction. ASA decreases the formation of TXA<sub>2</sub> synthesis by irreversibly inactivating prostaglandin G/H synthase via acetylation of the serine residue at the active site of the enzyme cyclooxygenase (COX). It has been suggested that the antithrombotic efficacy ASA could be optimized by minimizing its systemic levels to that needed to inhibit TXA<sub>2</sub> generation by platelets in the portal vein, while (b) (4) the beneficial vasodilator effects of prostacyclin (PGI<sub>2</sub>) synthesis by the (b) (4) endothelium.

The sponsor has developed a controlled release formulation of ASA, NHP-554C, formulated in microparticles (b) (4). The film coating acts as a semipermeable membrane that allows NHP-554C to diffuse progressively over the length of the gastrointestinal tract, resulting in extended absorption over 24 hours, and subsequently prolong the duration of action. NHP-554C is expected to exhibit low systemic exposures of ASA, but provide adequate levels in the portal vein to inhibit platelet TXA<sub>2</sub> production, and consequently prevent platelet aggregation. Information regarding the safety and efficacy of ASA are relied upon the previously approved products to support this application. The sponsor is seeking approval of a NDA for a controlled release formulation of ASA (NHP-554C) under 505(b)(2) application.

## 1.2 Brief Discussion of Nonclinical Findings

In this NDA, the nonclinical studies compared the acute gastrointestinal toxicity of NHP-554C to the standard ASA oral formulation in rats. A single oral dose administration of NHP-554C at 2500 mg/kg showed no pathological lesions in the stomach, whereas the conventional ASA showed macroscopic evidence of GI toxicity, including red petechiae, discoloration and thickening of the stomach wall at oral gavage dosages of ≥1670 mg/kg. Mortality was observed at an estimated LD<sub>50</sub> of 1432 mg/kg in the standard ASA dose groups. In these studies, thromboxane B<sub>2</sub> (TXB<sub>2</sub>), the stable metabolite of TXA<sub>2</sub>, and arachidonic acid or collagen-induced platelet aggregation were not measured, which are considered to be surrogate indices of ASA bioavailability and platelet cyclooxygenase-1 (COX-1) activity. Thus, it is uncertain whether the control-release formulation of NHP-554C delivers adequate ASA to block TXA<sub>2</sub> synthesis by platelets in the portal vein. Overall, the nonclinical studies on NHP-554C control-release formulation showed no gastric ulceration, with safe profiles at dosages up to 2500 mg/kg (HED 405 mg/kg), estimated to several orders of magnitude higher than the clinical dosage of NHP-554C 162.5 mg (2.7mg/kg).

## 1.3 Recommendations

### 1.3.1 Approvability:

The preclinical data using a single dose of NHP-554C controlled release formulation showed a safe profile in the gastrointestinal tract. The approvability of NHP-554C controlled release formulation will rely on the clinical pharmacokinetic study results on bioavailability, inhibition of serum TXA<sub>2</sub> levels and platelet functional assays.

### 1.3.2 Nonclinical Comments

- In the preclinical studies, tests of comparability of the NHP-554C to the standard ASA preparation in respect to serum TXB<sub>2</sub> and arachidonic acid or collagen-induced platelet aggregation were not performed. Measurement of stable metabolite TXB<sub>2</sub> in serum is considered as a surrogate measure of ASA bioavailability and an index of platelet COX-1 activity. Complete inhibition of TXB<sub>2</sub> formation is required to achieve full platelet inhibition, because minimal residual capacity to generate TXA<sub>2</sub> may be enough to sustain TXA<sub>2</sub>-dependent platelet activation. Thus, <95% inhibition of TXB<sub>2</sub> formation would be considered treatment failure, 95% - 99% inhibition as incomplete, and >99% would be successful TXB<sub>2</sub> inhibition.

- In the preclinical studies, the bioavailability of ASA based on salicylate concentrations from NHP-554C was not determined.

- ASA has been shown to prolong bleeding time likely due to complete inhibition of platelet aggregation, but bleeding time was not measured in NHP-554C study in the rat to assess incidence of excess bleeds.

- 6-Keto-prostaglandin F1 $\alpha$  (6-keto-PGF1 $\alpha$ ), the stable hydrolysis metabolite of PGI<sub>2</sub>, was not measured to assess the extent of preservation of PGI<sub>2</sub> biosynthesis by the controlled-release formulation of NHP-554C

### 1.3.3 Labeling

The proposed prescribing information includes an appropriate description of the genotoxicity, carcinogenicity, and reproductive and developmental toxicology.

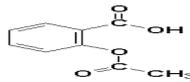
## 2 Drug Information

### 2.1 Drug

**Trade Name:** Durlaza™  
**Code Name:** NHP-554C,  
**Generic Name:** Aspirin (ASA) microencapsulated  
**Chemical Name:** Acetylsalicylic acid  
**Empirical formula:** C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>

**Molecular Weight:** 180.16 g/mol

**Structure:**



**Pharmacologic Class:** Nonsteroidal anti-inflammatory drug (NSAID)  
Platelet aggregation inhibitor (Cyclooxygenase inhibitor)

**Route of administration:** Oral administration, 162.5 mg capsules once daily

## 2.2 Related INDs, NDAs

NHP-554C 162.5 mg is approved in Europe, but not yet marketed.  
(ASA microencapsulated: - Flamasacard<sup>®</sup>, Caspac<sup>®</sup>, Asacard<sup>®</sup>, Therasacard<sup>®</sup>)

## 2.3 Dug Formulation

NHP-554C is a control-release formulation of ASA (aspirin) microencapsulated ethylcellulose, that (b) (4) with the gastric mucosa, and allow drug delivery to the gastrointestinal tract.

**Inactive Ingredients:** Ethylcellulose, povidone, castor oil, magnesium stearate, tartaric acid, colloidal anhydrous silica, and talc.

## 2.3 Clinical Indication and dosing regimen

NHP-554C capsules are indicated for the secondary prevention of acute cardiovascular events. The proposed dose of NHP-554C is 162.5 mg once orally.

## 3 Studies Submitted

**Studies Reviewed:** Sponsor's data on single dose toxicology study on NHP-554C in comparison with the conventional release of ASA formulation. The previously approved ASA studies are referenced to describe the pharmacology, pharmacokinetics, general toxicology, genotoxicity, carcinogenicity and reproductive toxicology.

## 4 Pharmacology

### 4.1 Primary Pharmacology

ASA is an irreversible inhibitor of the enzyme COX, and prevents the formation TXA<sub>2</sub>, which leads to inhibition of platelet aggregation for their life span of about 7-10 days (Figure 1). ASA covalently acetylates serine residues in the active site of COX enzymes, thereby causing irreversible inhibition, distinguishing it from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors. At higher dosages, ASA is an effective anti-inflammatory agent, due to inhibition of inflammatory mediators via COX isoforms (COX-1 and COX-2) in

the peripheral tissues, and also inhibits formation of PGI<sub>2</sub>, an arterial vasodilator. Low-dosage of ASA has been shown to be cardioprotective, but it is also associated with adverse effects of gastric irritation.

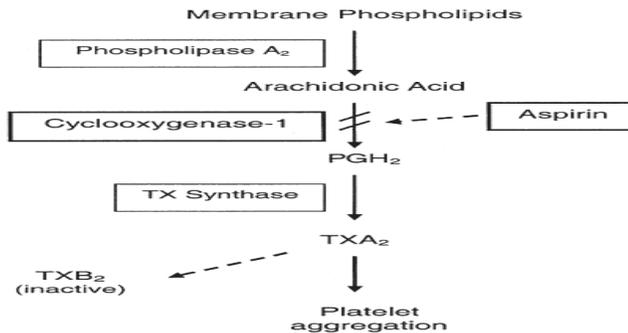


Figure 1. Inhibitory site of ASA in the cyclooxygenase-1 pathway (TXA<sub>2</sub> =thromboxane A<sub>2</sub>, PGH<sub>2</sub> = prostaglandin H<sub>2</sub>).

## 4.2 Secondary Pharmacology

Secondary pharmacodynamics assessment of NHP-554C was not conducted.

### Pharmacological activity of ASA

Several *ex vivo/in vitro* and *in vivo* studies with ASA have shown platelet inhibition and increase bleeding time in several animal species including the rat, rabbit, guinea pig and dog. Previous reports have shown that ASA impairs hemostasis, prolongs platelet survival and diminishes coagulation factors in extracorporeal shunts. Bleeding was observed in the rat at single oral gavage dosages of 3 to 10 mg/kg that prolong bleeding time by about 50%. The adverse effects of ASA are described by its effects on phospholipid metabolism, which are broken down by phospholipase A<sub>2</sub> to arachidonic acid, the substrate for the COX enzymes (Figure 1). ASA targets both COX-1 and COX-2 enzymes. COX-1 is constitutively expressed in the stomach, kidneys, and intestinal endothelium, where it generates TXA<sub>2</sub> leading to vasoconstriction and platelet aggregation. COX-2 is upregulated during times of inflammation, via the migration of macrophages, leukocytes, and fibroblasts.

### ASA-induced GI damage

ASA-induced gastrointestinal damage is postulated to be via prostaglandin-dependent modulation of mucus-bicarbonate secretion, acid secretion and regional tissue blood flow. An alternative mechanism involves inhibition of cyclooxygenase pathway leading to overproduction of leukotrienes (LTC<sub>4</sub> and LTD<sub>4</sub>), and free radical production, which may cause local tissue injury, microvascular constriction and subsequent ischemia. Ultrastructural studies of the pathological changes after ASA oral dosing in rats revealed damage to the gastric mucosal blood vessels (capillary endothelial cells) within 5 minutes after dosing. Focal injury to capillaries and post capillary venules, including dilation of vessels, increase in fenestrations and eventual rupture and death of endothelial cells. The gastric mucosal damage, including microvascular disruption and mitochondrial swelling, occurs within 5 to 60 minutes post-dose. Erosions that follow these initial events are proposed to occur as the result of ischemic infarcts in the gastric mucosa.

### **Antithrombotic efficacy of ASA**

Measurement of stable metabolite TXB<sub>2</sub> in serum is considered to be a surrogate measure of ASA bioavailability and an index of platelet COX-1 activity. To achieve the desired antithrombotic effect, at least 95% of all circulating platelets which are regenerated daily, need to be acetylated, since even a fraction of normal platelets equal to 10% of the total are sufficient to produce a full aggregation response. Thus, NHP554C is expected to provide sustained exposure of ASA at levels sufficient to acetylate newly formed platelets while avoiding adverse effects associated with higher exposure levels. In addition, urinary excretion of 11-dehydro TXB<sub>2</sub> metabolite are also used as an index of TXA<sub>2</sub> biosynthesis *in vivo*. The caveat of the urinary 11-dehydro TXB<sub>2</sub> assay is that about 30% may be derived from extra-platelet sources in inflammatory conditions, and therefore may not be highly specific for monitoring the effects of ASA on platelet COX-1 activity.

### **Rational for control-release ASA formulation**

Higher daily conventional ASA doses may lead to complete acetylation of cyclooxygenase in platelets as well as in many other tissues (epithelial cells in gastric mucosa, kidney glomeruli, smooth muscle, vascular endothelium), which may lead to inhibition of PGI<sub>2</sub> formation. PGI<sub>2</sub> causes inhibition of platelet aggregation and relaxation of blood vessels, which are opposite to those of TXA<sub>2</sub>. Therefore, blocking PGI<sub>2</sub> with higher sustained ASA doses may cause vasoconstriction, platelet aggregation and bleeding. The objective of low-dose and long-term ASA is to selectively block the formation of TXA<sub>2</sub> in platelets and prevent platelet aggregation, while preserving the beneficial vasodilator effects of PGI<sub>2</sub>.

## **4.3 Safety Pharmacology**

Since the pharmacology of ASA is well-documented, no additional safety pharmacology studies with NHP-554C were conducted. One of the safety risk issues with ASA is gastrointestinal irritation, and thus the nonclinical study was limited to the acute gastrointestinal toxicity assessment of NHP-554C.

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **5.1 PK/ADME**

No nonclinical pharmacokinetics studies were conducted with NHP-554C. Previously published studies are referenced to describe the pharmacokinetics of ASA.

#### **5.1.1 Absorption**

Following absorption from the GI tract, ASA is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 - 2 hours of dosing. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH, and other physiological factors.

### 5.1.2 Distribution

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system, breast milk and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart and lungs. The protein binding of salicylate is concentration-dependent, i.e., non-linear. At low concentrations, approximately 90% of plasma salicylate is bound to albumin, while at higher concentrations 75% is bound.

### 5.1.3 Metabolism

ASA is rapidly hydrolyzed in the plasma to salicylic acid via esterases such that plasma levels of ASA are essentially undetectable 1 - 2 hrs 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. Salicylic acid is unable to acetylate circulating platelets, and has been shown to lack the activity to inhibit the aggregation of platelets mediated by TXA<sub>2</sub>.

### 5.1.4 Excretion

ASA is eliminated from the circulation slowly and therefore may accumulate in blood with repeated conventional oral ASA dosing. The elimination of salicylic acid follows zero order pharmacokinetics; i.e., the rate of drug elimination is constant in relation to plasma concentration. Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalinization of the urine is a key concept in the management of salicylate overdose. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% and 5% as the phenolic and acyl glucuronides, respectively.

## 5.2 Toxicokinetics

A single oral dose of 200 mg/kg ASA administered to Sprague-Dawley rats was reported to be eliminated rapidly with a clearance of 45 mL/min/kg and  $t_{1/2}$  8 minutes. Only about 25% of the administered oral dose is absorbed intact, and systemic availability of an oral dose is highly variable. Approximately 2/3rds of orally administered ASA in the rat is hydrolyzed in the gastrointestinal tissue and the remaining 1/3<sup>rd</sup> is eliminated via portal vein transport to the liver by first-pass metabolism. The PK of ASA in rats is nonlinear, but is linear in humans. However, the PK of salicylic is nonlinear in both human and rat, due to slower elimination of salicylic compared to ASA and the complexity of continuous salicylic formation from ASA during the initial time following dosing (about 1 hour in rat and humans).

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

A GLP study in the rat was conducted to compare the acute toxicity of NHP-554C with that of conventional ASA.

### 6.1.1 Comparative acute toxicity of single dose of NHP-554C vs. ASA in rat

Study no.: 7208 TAR  
 Study report location: (b) (4)  
 Date of study completion: 4/16/1991  
 GLP compliance: Yes, QA statement: ✓  
 Drug: NHP-554C vs. Conventional ASA, Batch No: 45/89  
 Vehicle: Carboxymethylcellulose 0.5%  
 Dosages: NHP-554C: 2500 mg/kg vs. ASA: 740, 1110, 1670, 2500 mg/kg  
 Route: Oral gavage, (10 ml/kg dose volume)  
 Species: Sprague-Dawley rat, Age: 6 weeks old  
 Weight: Males 178±5 g, Females 151±5 g  
 Number/sex/group: 5/sex/dose group

**Mortality:** In the rats receiving standard ASA formulation, mortality was noted in one male and one female receiving 740 mg/kg, five females receiving 1110 mg/kg, one male and two females receiving 1670 mg/kg, and five males and four females receiving 2500 mg/kg. Animals were found dead within the first few hours of administration of 1670 and 2500 mg/kg dosages, showing abnormally black liver and intestines with thickening of the wall. In the 740 and 1110 mg/kg dose groups, death occurred within 3 days post-dose.

**Body Weights:** Mean body weight gains were decreased in a dose-related manner between Day 1 and Day 5 in the conventional ASA groups. Body weights were not affected in the NHP-554C group.

**Clinical signs:** Treatment-related clinical signs were noted in all treatment groups and included hypokinesia, sedation, piloerection, lateral decubitus, and/or dyspnea in the conventional ASA groups. By Day 7 post-dose, all surviving animals appeared normal. No significant clinical signs were observed in the NHP-554C group.

**Pathology:** In the rats found dead that were treated with 1670 mg/kg and 2500 mg/kg of ASA, findings at necropsy included hemorrhages, gastritis lesions, blackish discoloration of the liver; discoloration and thickening of the wall of the intestines; and red petechiae, discoloration and thickening of the wall of the stomach were observed. No abnormalities were revealed by macroscopic examinations in the animals found dead in the 740 and 1110 mg/kg dose groups. The remaining animals appeared normal at gross necropsy. No pathological lesions was observed in the NHP-554C group.

**Summary:** A single oral dose of 2,500 mg/kg NHP-554C in rats was tolerated and did not produce clinical effects or gastric mucosal injury. Whereas the standard ASA caused lethality at single oral doses of 740 - 2,500 mg/kg, and gastric mucosal damage at doses of 1,670 - 2,500 mg/kg. In summary, a single dose of NHP-554C slow release formulation at 2500 mg/kg (HED 405 mg/kg) showed no gastrointestinal tract intolerance in the rat.

## 6.2 Repeat-Dose Toxicity

No repeat-dose studies were performed.

## 7 Genetic Toxicology

Previous reports showed that ASA was not mutagenic in the Ames salmonella assay, however, ASA did induce chromosome aberrations in cultured human fibroblasts. *In vivo* chromosomal aberration assays in bone marrow micronucleus test with rats and mice were negative. However, testing of lymphocytes for chromosomal damage from normal human subjects given oral doses of 2.4 grams ASA per person per day for one month were negative. The weight of evidence supports the conclusion that ASA is not genotoxic.

## 8 Carcinogenicity

ASA has been evaluated in six rodent carcinogenicity studies and is not considered to be carcinogenic. Administration of ASA for 68 weeks at 0.5% in the feed of rats was not carcinogenic.

## 9 Reproductive and Developmental Toxicology

Previous studies with oral ASA in pregnant rats and rabbits demonstrated the occurrence of fetal malformations at oral doses at or above 250 mg/kg. ASA was also reported to inhibit ovulation in rats. In developmental toxicology study of ASA using MTD in Sprague-Dawley and Wistar rats, single dose or segmental dosing schedule during the period of organogenesis (gestation day 6 to 17) showed malformations. Thus, ASA at doses that achieve the MTD ( $\geq 250$  mg/kg) exhibit the potential to produce developmental anomalies.

### Pregnancy

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

### Nursing Mothers

Salicylate is excreted in breast milk, and thus nursing mothers should avoid using ASA.

## 10 Special Toxicology Studies

### Local Tolerance

No specific local tolerance studies were conducted with NHP-554C.

### Juvenile studies

No specific juvenile toxicology studies were conducted using the NHP-554C. The controlled released NHP-554C (ASA capsules 162.5 mg) is not indicated for use in pediatric patients.

## 11 Integrated Summary and Safety Evaluation

The main toxicological risks of chronic ASA administration are the potential for bleeding, and GI intolerance including mucosal irritation and ulcers. NHP-554C was developed to deliver a very low, continuous amount of ASA in the intestine but not high enough to saturate liver metabolic mechanisms; essentially little ASA passes through the liver to enter the systemic circulation. The systemic concentration of ASA achieved may be sufficient to block TXA<sub>2</sub> synthesis by platelets in the portal vein, while sparing the production of PGI<sub>2</sub> and other beneficial prostaglandins. In concept, sustained minimal exposure to ASA at levels sufficient to acetylate newly formed platelets while avoiding adverse effects associated with higher doses is a desirable therapeutic objective. Higher daily conventional ASA dosages may lead to complete acetylation of cyclooxygenase in platelets as well as in many other tissues (epithelial cells in gastric mucosa, kidney glomeruli, and smooth muscle, and vascular endothelium) and may also lead to bleeding and vasoconstriction. The preclinical studies do not address whether NHP-554C provides low systemic exposure to ASA while providing adequate exposures in the portal vein to inhibit platelet TXA<sub>2</sub> production and consequent prevention of platelet aggregation. The bioavailability, and extent of inhibition of serum TXA<sub>2</sub> levels and platelet aggregation by NHP-554C are addressed in the clinical pharmacokinetic studies.

The nonclinical study of NHP-554C was limited to the acute gastrointestinal toxicity assessment in rats comparing the NHP-554C formulation with a conventional ASA formulation. A single oral dosing toxicity study in the rat demonstrated that NHP-554C at 2500 mg/kg induced no pathological lesions in the stomach, whereas the conventional ASA showed macroscopic evidence of GI toxicity, including red petechiae, discoloration and thickening of the stomach wall, at oral gavage doses  $\geq 1670$  mg/kg. Mortality was observed at an estimated LD<sub>50</sub> of 1432 mg/kg. In summary, a single dose of NHP-554C slow release formulation at 2500 mg/kg (HED 405 mg/kg) was well-tolerated in the gastrointestinal tract of the rat, at a dosage estimated to be about 150-fold higher than the human daily dose of 2.7 mg/kg (162.5 mg capsule).

### Comments from non-clinical studies:

- One of the main safety issues associated with ASA treatment is bleeding, but bleeding time was not measured in NHP-554C rat study.
- In the preclinical studies, effects of NHP-554C on serum TXB<sub>2</sub> and arachidonic acid or collagen-induced platelet aggregation was not compared to that of a standard ASA preparation. Measurement of stable metabolite TXB<sub>2</sub> in serum is considered as a surrogate measure of ASA bioavailability and as an index of platelet COX-1 activity. Complete inhibition of TXB<sub>2</sub> formation is required to achieve full platelet inhibition, and minimal residual capacity to generate TXA<sub>2</sub> may be enough to sustain TXA<sub>2</sub>-induced platelet activation. Thus, to achieve the desired antithrombotic effect, at least 95% of all circulating platelets which are regenerated daily, need to be acetylated, because a full aggregation response requires only 10% of the total platelets to intact.
- The bioavailability of ASA based on salicylate concentrations from the controlled-release formulation in the NHP-554C was not determined. Arachidonic acid- and collagen-

induced platelet aggregation could be considered as secondary endpoints to compare NHP-554C and the traditional ASA formulation.

- It is unclear how much of the PGI<sub>2</sub> biosynthesis is spared by the controlled-release formulation of NHP-554C, measured as 6-Keto-prostaglandin F1α (6-keto-PGF1α), the stable hydrolysis metabolite of PGI<sub>2</sub>.

### OVERALL CONCLUSIONS AND RECOMMENDATIONS

Overall, the current study showed NHP-554C control-release formulation showed no gastric ulceration, and that it exhibited safe profile at dosages of 2500 mg/kg (HED 405 mg/kg), which is estimated to several orders of magnitude higher than the clinical dosage of 162.5 mg (2.7mg/kg). The approvability of NHP-554C control release formulation release formulation will rely on the clinical pharmacokinetic study results on bioavailability, and inhibition of serum TXA<sub>2</sub> levels and platelet functional tests.

**Labeling:**

(b) (4)

(b) (4)

## 12 Appendix/Attachments

Literature References (Sponsor's submission)

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/s/  
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BELAY TESFAMARIAM  
04/23/2015

ALBERT F DEFELICE  
04/24/2015

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

**NDA Number:** 200671

**Applicant:** New Heaven  
Pharmaceuticals Co

**Stamp Date:** 9/9/2014

**Drug Name:** NHP-554C capsules  
Acetylsalicylic acid (ASA)

**NDA Type:** 505(b)(2)

**Amendments:**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		e-submission, eCTD format
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		Reviewable submission
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		Acceptable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		NHP-554C is (b) (4) to ASA, and the non-clinical pharmacology and toxicology information were obtained from published literature. ASA was shown to be non-genotoxic and non-carcinogenic. ASA was reported to cause developmental abnormalities. Juvenile studies were not performed.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		√	The formulation of NHP-554C in the toxicology studies were the same as that to be marketed. NHP-554C is formulated to deliver low and continuous amount of ASA. In this NDA, the nonclinical studies with NHP-554C were limited to the acute gastrointestinal toxicity assessment in the rat.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	√		Oral route.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	√		GLP and QA statements are included.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		The safety of ASA is relied on information in the public domain and previous clinical experience. No special toxicology studies were requested. NHP-554C is approved for marketing in Europe.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	√		The oral dose of NHP-554C 162.5 mg is the same as the approved ASA.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		√	The inactive ingredients are GRAS, which includes ethylcellulose, povidone, castor oil, magnesium stearate, tartaric acid, colloidal anhydrous silica and talc.
11	Has the applicant addressed any abuse potential issues in the submission?		√	Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		√	Not applicable

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

**If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.**

The preclinical data to address gastric ulceration of NHP-554C is adequate to assess its safety, and hence it is fileable.

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

There are no preclinical review issues to be conveyed to the sponsor.

The stable metabolite thromboxane B<sub>2</sub> in the serum, which is considered to be a surrogate measure of aspirin bioavailability, and the adequacy of platelet inhibition to NHP-554C treatment were not addressed in the preclinical studies, but were assessed in the clinical studies.

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Belay Tesfamariam	10/27/2014
Reviewing Pharmacologist	Date

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Albert DeFelice	10/27/2014
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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BELAY TESFAMARIAM  
10/27/2014

ALBERT F DEFELICE  
10/28/2014