# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204957Orig1s000

# NON-CLINICAL 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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| Application number: | NDA 204957 |
| Supporting document/s: | SDN 28 |
| Applicant's letter date: | October 24, 2019 (SDN 28) |
| CDER Stamp Date: | October 24, 2019 (SDN 28) |
| Product: | Acetaminophen Injection in the PAB® Container |
| Indication: | Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever |
| Applicant: | B. Braun Medical, Inc. |
| Review Division: | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| Reviewer: | Carlic K. Huynh, PhD |
| Team Leader: | Newton H. Woo, PhD |
| Supervisor: | R. Daniel Mellon, PhD |
| Division Director: | Rigoberto A. Roca, MD |
| Project Manager: | Ogochukwu Ogoegbunam |

*Template Version: September 1, 2010*

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**Executive Summary:**
This is the third cycle review of NDA 204957. The Applicant, B. Braun Medical, Inc., is developing and submitting a 505(b)(2) application for an intravenous solution of acetaminophen (10 mg/mL) that is packaged in PAB® containers with a total volume of 100 mL (1000 mg of acetaminophen) and 50 mL (500 mg of acetaminophen). The Applicant is relying upon the Agency's previous finding of safety to Mallinckrodt's Ofirmev® (NDA 22450). The PAB containers have been used in other FDA-approved drug products. The NDA was not approved in the previous two review cycles because compliance issues were noted following inspection of the manufacturing facility (FEI 2021236). These issues were required to be addressed prior to NDA approval.

In the first cycle, the nonclinical pharmacology toxicology review team concluded that the extractable leachable studies for the container closure were not adequate. However, the team recommended that the NDA may be approved based on the prior history of use of this drug product container closure system in comparable FDA approved drug products. Several non-approval issues related to the container closure system qualification were provided in the complete response letter (dated September 18, 2017). In the second cycle, two of the three nonclinical concerns were adequately addressed. However, several questions remained regarding the adequacy of the container closure system characterization. As such, two comments were communicated to the Applicant as non-approval issues in the complete response letter (dated March 27, 2019).

In the third resubmission, the two non-approval nonclinical issues were addressed. One was the Applicant's reporting of leachable compounds at and above (b) (4) mcg/mL (or (b) (4) mcg/day) threshold based on the maximum daily of the proposed product, which was deemed unacceptable. The Applicant reanalyzed the leachables data using a Limit of Quantitation (LOQ) of (b) (4) mcg/mL, which is below the Reviewer's calculated Analytical Evaluation Threshold (AET) of (b) (4) mcg/mL based on the maximum daily dose of the proposed product and no new leachable compounds were observed and as such, the response to the first issue is considered acceptable. Another issue was the lack of adequate safety justification for the unknown compound at RRT of (b) (4) min. The Applicant submitted data demonstrating that the unknown compound is an (b) (4) impurity in the drug product that is not a leachable compound from the container closure system. The highest amount of the (b) (4) impurity in stability studies is NMT (b) (4)%, which is below ICH Q3B(R2) identification and qualification thresholds and ICH M7 acceptable intake levels and as such, is adequately qualified. Thus, all nonclinical issues from the second cycle review have been adequately addressed.

From a Pharmacology Toxicology perspective, the proposed drug product is recommended for approval.

**Background and Prior Regulatory History (Nonclinical):**
The clinical development program was conducted under IND 111161. The first cycle submission was originally submitted on December 13, 2016 and at the conclusion of the



Reference ID: 4588695

first cycle review, there were no nonclinical deficiencies identified (see nonclinical review dated September 18, 2017). However, this submission was deemed a Complete Response based on a withhold recommendation from the Office of Facilities following their inspection of the manufacturing facility. Although there were no nonclinical deficiencies, there were a number of items that should be addressed prior to a subsequent NDA resubmission in the Complete Response letter dated September 28, 2017.

The second cycle submission was originally submitted on September 27, 2018 and at the conclusion of the second cycle review, there were no nonclinical deficiencies identified as the container closure is used in a number of FDA-approved products (see nonclinical review dated March 22, 2019). Again, this submission was deemed a Complete Response based on facility inspection and withhold recommendation from the Office of Facilities following a reinspection. Although there were no nonclinical deficiencies, there were a number of comments regarding the characterization of the container closure system that should be addressed prior to a subsequent NDA resubmission as shown in the following excerpt from the Complete Response letter (dated March 27, 2019):

> We have the following comments/recommendations that are not approvability issues, however, they should be addressed in your complete response to this action:
>
> 1. Your reporting of leachables compounds at and above (b) (4) mcg/mL (i.e., (b) (4) mcg/day taking into consideration the maximum daily dose of acetaminophen) is not acceptable as this exceeds the recommended qualification threshold of 5 mcg/day. Identify all leachable compounds above 5 mcg/day and submit a toxicological risk assessment for any newly identified compound that exceeds the 5 mcg/day threshold of concern.
>
> 2. You not provided adequate safety justification for the unknown compound at RRT (b) (4) Identify this unknown compound and submit an accompanying toxicological risk assessment.

In this submission, the Applicant provided responses to these issues.

**Applicant's Response to Item 1:**
The original leachables report (RPT-PH-1007289, Version 4) was updated to report all leachable compounds above 5 mcg/day (RPT-PH-1007289, Version 5). The Applicant calculated an analytical evaluation threshold (AET) of (b) (4) mcg/mL (b) (4) mcg/day/ (b) (4) mL/day = (b) (4) mcg/mL). The following table illustrates the required LOQ (limit of quantitation needed to detected compounds of at least 5 mcg/day (from the Applicant's submission):

Table 1: Calculations for Qualification Threshold (QT) and AET for unknown leachables

| | QT Level (µg/day) | Estimated AET (µg/mL) | Required Method LOQ (µg/mL) |
|---|---|---|---|
| Acceptable Daily Intake (DI) = 120µg/day Per ICH M7 (≤1 month) | (b) (4) | | |
| Acceptable Daily Intake (DI) Per PQRI for "Irritation and Sensitization Toxicity" DI = 5µg/day | | | (b) (4) |
| Acceptable Daily Intake (DI) Per PQRI for "Systemic Toxicity" DI = 50µg/day | | | |

As shown in the table above, the required method LOQ is (b) (4) mcg/mL, which can detect compounds at the AET of (b) (4) mcg/mL. This is acceptable.

In the leachable study (TP-PH-1001220, Version 3.0 and TP-PH-1001220, Version 3.4), the limit of detection (LOD) and limit of quantitation (LOQ) using (b) (4) as a marker was (b) (4) and (b) (4) mcg/mL, respectively, and are deemed acceptable because they are below the AET of (b) (4) mcg/mL. The original leachables report (RPT-PH-1007289, Version 4) reported leachables that were at and above (b) (4) mg/mL and 3 unknown compounds were identified. The leachable results were re-evaluated at and above (b) (4) mcg/mL (more sensitive detection than the calculated AET) in the revised leachables report (RPT-PH-1007289, Version 5) and the same 3 unknowns were reported with no additional peaks detected. Two of the unknown leachables were addressed in the second cycle NDA as the Applicant provided data that these two unknown compounds are present in other FDA-approved marketed drugs that use the identical PAB bags (see second cycle PT review). The remaining unknown compound is identified to be an (b) (4) impurity (see below for further discussion).

As the peaks identified using revised extractable and leachable analytical methods (at and above (b) (4) mcg/mL) were the same as those reported previously (at and above (b) (4) mcg/mL) and that no additional compounds that exceed 5 mcg/day were observed, Item 1 is considered adequately resolved.

**Applicant's Response to Item 2:**

In the previous leachable study (TP-PH-1001220) using the HPLC/PDA analytical method showed a peak at RRT = (b) (4) min that was not identified. In this submission, additional efforts were made to identify the unknown peak at RRT = (b) (4) min using HPLC/PDA/MS analytical methods (RPT-PH-1010378). Other studies with the drug product formulation in a glass container (48 and 50 months storage samples at 25ºC) had the same peak at RRT = (b) (4) The identification results showed that this unknown is a degradation product of (b) (4) and not a leachable from the PAB container closure (see the following table from the Applicant's RPT-PH-1010378):

Table 1: Summary of identification of RRT (b) (4)

(b) (4)

As shown in the table above, the structure of the unknown at RRT= (b) (4) min is analogous to (b) (4) the structure of which is shown in the following figure (from the Applicant's submission):

(b) (4)

It is noted that the unknown at RRT = (b) (4) min is (b) (4) (b) (4) In discussions with the Chemistry, Manufacturing, and Controls (CMC) review team, this unknown has (b) (4) (b) (4) The highest amount of this drug product impurity is (b) (4)% (w/w) of the 10 mg/mL proposed product in 8 stability batches (STBJ5H721, STBJ5H722, STBJ5H723, STBJ5H725, STBJ5H726, STBJ5J677, STBJ5H724, and STBJ5H728) and 2 leachable batches (PTRA# 4206 and PTRA# 4207) for up to 24 months storage at 25°C (RPT-PH-1007742, version 5 and RPT-PH-1007289, version 5). At NMT (b) (4)%, the maximum daily exposure to the degradant is (b) (4) mcg/day (b) (4) (b) (4) As the unknown peak at RRT = (b) (4) min is a degradant of (b) (4) ICH Q3B(R2) qualification threshold of NMT (b) (4)% for drug products with a maximum daily dose of > (b) (4)g may be applied. The highest amount of the degradant at NMT (b) (4)% is below the ICH Q3B(R2) qualification threshold of NMT (b) (4)% and identification threshold of (b) (4)% and as such, is adequately qualified.

Thus, Item 2 is considered adequately resolved.

**Conclusions and Recommendations:**

This is the third cycle review of NDA 204957. Several issues were identified at the conclusion of the second review cycle. One issue was identification of leachable compounds above the 5 mcg/day threshold and providing a revised toxicological risk assessment. At the 5 mcg/day threshold, the analytical evaluation threshold (AET) is (b) (4) mcg/mL given the maximum daily dose via the proposed product. The Applicant verified that their method Limit of Quantitation (LOQ) is (b) (4) mcg/mL and is of sufficient sensitivity to detect compounds down to (b) (4) mcg/mL. No new leachables were identified above the 5 mcg/day threshold. As a result, no revised toxicological risk assessment was required. As such, this issue is adequately resolved.

The other issue was the unknown compound at RRT = (b) (4) min. The Applicant provided data that the unknown compound at RRT = (b) (4) min is an (b) (4) impurity. In discussions with the CMC review team, the unknown was concluded to be (b) (4) As the unknown is an *(b) (4)* impurity observed in the drug product, ICH Q3B(R2) qualification thresholds apply. The highest amount of the unknown compound in the 8 stability batches is NMT (b) (4) %, which meets ICH Q3B(R2) qualification thresholds of NMT 0.15% and identification threshold of 0.10% for drug products with a maximum daily dose of > 2g. It is noted that the Applicant did not address the genotoxicity potential of this impurity, however, the highest observed levels are well below ICH M7 acceptable levels for a mutagenic/carcinogenic compound present in an acute-use product and therefore does not pose a safety concern from a genetic toxicology perspective. As such, this issue is adequately resolved.

Thus, all nonclinical concerns have been addressed and are considered adequately resolved. From a Pharmacology Toxicology perspective, the proposed product is recommended for approval.



Reference ID: 4588695

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/s/

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

# PHARMACOLOGY/TOXICOLOGY and DIVISION DIRECTOR'S NDA REVIEW AND EVALUATION

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|---|---|
| Application number: | NDA 204957 |
| Supporting document/s: | SDN 21, 22, and 25 |
| Applicant's letter date: | September 27, 2018 (SDN 21); October 18, 2018 (SDN 22); and February 19, 2019 (SDN 25) |
| CDER Stamp Date: | September 27, 2018 (SDN 21); October 18, 2018 (SDN 22); and February 19, 2019 (SDN 25) |
| Product: | Acetaminophen Injection in the PAB® Container |
| Indication: | Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever |
| Applicant: | B. Braun Medical, Inc. |
| Review Division: | Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| Reviewer: | Carlic K. Huynh, PhD |
| Team Leader: | Newton H. Woo, PhD |
| Supervisor: | R. Daniel Mellon, PhD |
| Division Director: | Sharon Hertz, MD |
| Project Manager: | Ogochukwu Ogoegbunam |

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**Executive Summary:**
This is the second cycle review of NDA 204957. The Applicant, B. Braun Medical, Inc., is developing and submitting a 505(b)(2) application for an intravenous solution of acetaminophen (10 mg/mL) that is packaged PAB® containers with a total volume of 100 mL (1000 mg of acetaminophen) and 50 mL (500 mg of acetaminophen). The Applicant is relying upon the Agency's previous finding of safety to Mallinckrodt's Ofirmev® (NDA 22450). The PAB containers have been used in other FDA-approved drug products. The NDA was not able to be approved in the first cycle because compliance issues were noted following inspection of the manufacturing facility (FEI 2021236). These issues were required to be addressed prior to NDA approval.

The CMC review team has reviewed CMC drug product information and data that were submitted in response to the nonclinical nonapproval issues communicated to the Applicant, which included revised to specifications for 4-aminophenol and 4-nitrophenol, updated stability data, and updated leachables data. The CMC review team concluded that the submitted material in the resubmission and response to IR were adequate. However, as there were outstanding compliance issues with the B. Braun manufacturing facility leading to a withhold recommendation by the OPQ Office of Facilities, the overall OPQ recommendation for this resubmission is a Complete Response.

In the first cycle, the nonclinical pharmacology toxicology review team concluded that the extractable leachable studies for the container closure were not adequate based on current expectations. However, the team recommended that the NDA may be approved based on the prior history of use of this drug product container closure system in comparable FDA approved drug products. Several nonapproval issues related to the container closure system qualification were provided in the complete response letter. In this second submission two of the three nonclinical concerns have been adequately addressed, however, several questions remain regarding the adequacy of the container closure system characterization. As such, the nonclinical team continues to recommend that the NDA may be approved from a nonclinical pharmacology toxicology perspective with several comments to be communicated to the Applicant as nonapproval issues.

**Division Director's Comment:**
Following completion of the first cycle review of NDA 204957, the only only deficiency preventing approval of the NDA was the facility inspection and withhold recommendation. Several nonapproval comments related to the characterization of the container closure system were also included in the complete response letter. Following reinspection, the Office of Facilities continues to recommend withholding approval. I concur with the recommendation from the Office of Facilities and the chemistry manufacturing and controls review team that based on the withhold recommendation from the facilities reinspection, this NDA resubmission is a Complete Response. I also concur with the recommendations from the pharmacology toxicology review team requesting further characterization of the container closure system as nonapproval issues.



Reference ID: 4408114

**Background and Prior Regulatory History (Nonclinical):**
The clinical development program was conducted under IND 111161. The first cycle submission was originally submitted on December 13, 2016 and at the conclusion of the first cycle review, there were no nonclinical deficiencies identified (see nonclinical review dated September 18, 2017). However, this submission was deemed a Complete Response based on a withhold recommendation from the Office of Facilities following their inspection of the manufacturing facility. Although there were no nonclinical deficiencies, there were a number of items that should be addressed prior to a subsequent NDA resubmission in the Complete Response letter dated September 28, 2017 and are as follows:

> We have the following comments and recommendations that are not approvability issues that should be addressed prior to a subsequent NDA resubmission:
>
> 1. Tighten the drug product specification for 4-aminophenol and 4-nitrophenol based on long-term stability data to as low as technically feasible.
>
> 2. In your leachables study, 3 unknown compounds (RT (b) (4)) under normal conditions as well as 5 unknown compounds (RT (b) (4) (b) (4)) under accelerated conditions were present in your leachable samples. As we cannot conduct a toxicological risk assessment on unknowns, either provide identification for these unknown compounds along with an adequate toxicological risk assessment or confirm that these compounds are present in other FDA-approved products that use the same container closure system at comparable total daily intake levels.
>
> 3. The safety of (b) (4) has not been adequately addressed by the submitted 28-day and 14-day toxicology studies. Either provide data that demonstrates (b) (4) and related compounds are present at comparable total daily intake levels in other FDA-approved products that use the same container closure system or conduct an adequately designed 14-day toxicology study that identifies a NOAEL that establishes adequate safety margins.

In this submission, the Applicant provided responses to these issues.

**Applicant's Response to Item 1:**
The Applicant has tightened the specifications for 4-aminophenol and 4-nitrophenol as shown in the following table (from the Applicant's submission):

| Name of Impurities | Current Specification | Updated Specification | Justification for Updated Specification | References |
|---|---|---|---|---|
| 4-aminophenol (%w/w) | (b) (4) | | Use method LOQ at (b) (4)% as low as technically feasible and based on long-term Stability data up to 24 months | TP-PH-1001221<br>RPT-PH-1008521 (v. 4)<br>RPT-PH-1007742 (v. 4) |
| 4-nitrophenol (%w/w) (Impurity F) | (b) (4) | | | |

At the maximum daily dose of acetaminophen of 4 g/day (4000 mg/day), the specification of NMT (b) (4)% results in (b) (4) mcg (b) (4) (b) (4) of 4-aminophenol or 4-nitrophenol.

The new specifications for 4-aminophenol and 4-nitrophenol of NMT (b) (4)% were based on stability batch analyses of the IV APAP drug product manufactured from the Mallinckrodt and (b) (4) drug substances (see nonclinical review dated September 18, 2017 for the previous review cycle). Levels of 4-aminophenol and 4-nitrophenol were both (b) (4)% at all time points tested (3-, 6-, 9-, and 12-months). As such, these revised specifications are as low as technically feasible.

Thus, Item 1 has been adequately addressed.

**Applicant's Response to Item 2:**
The leachables study with the PAB containers were evaluated in the previous nonclinical review (see nonclinical review dated September 18, 2017). However, because the container closure was used in several comparable FDA-approved products, the lack of complete characterization of the unknown compounds was not considered an approval issue but several items were identified to be resolved in subsequent NDA submissions. One of these items is the identification of unknown leachables from the APAP product stored under normal and accelerated conditions. To address this issue, the Applicant identifies several of the unknowns and compares the leachables from the APAP product (in (b) (4) PAB® containers with (b) (4) and (b) (4) inks) and the FDA-approved metronidazole (in PAB® containers with (b) ( ) Ink). The methodology of the leachables studies with metronidazole are similar to the APAP product. It is noted that the Applicant included information about a leachable compound, (b) (4) which had an RRT of (b) (4) The safety of (b) (4) was reviewed in the initial NDA review and deemed acceptable (see nonclinical review dated 9/18/2017). (b) (4) was detected under normal and accelerated conditions. The unknown compound at RRT (b) (4) was only detected under accelerated conditions and as such, (b) (4) and the unknown compound at RRT (b) (4) are not the same compound.

The Applicant summarized the unknown leachables from normal and accelerated conditions in the following table (from the Applicant's submission):

Table 2: Comparison results of unknown leachables from PAB® Container Closure System

(b) (4)

[redacted]

The Applicant has identified the unknowns with RTs of (b) (4) and (b) (4) as (b) (4) and (b) (4) respectively (see Applicant's table below):

**Table 1: Update RT and RRT from RPT-PH-1007289 (version 2 and version 3)**

| RPT-PH-1007289 version 2.0 | RPT-PH-1007289 version 3.0 (Table 2 of the document entitled "0021 quality information amendment") |
|---|---|
| (b) (4) | |

Table 1 above also demonstrates that the apparently different RTs from the different versions of the analytical method RPT-PH-1007289 are the same unknown leachable. Table 2 above demonstrates that (b) (4) was detected in the APAP product and not detected in FDA-approved metronidazole. The unknown with the RRT of (b) (4) was only detected under accelerated conditions at 6 months. The unknowns with RRTs at (b) (4) (b) (4) and (b) (4) have not been identified to date. The Applicant demonstrates that the maximum daily levels of these unknowns (RRTs at (b) (4) are greater in FDA-approved metronidazole than in this APAP product (see Applicant's table below):

**Table 4**: Comparison calculation results of each Maximum Unknown leachable (impurity) level reported in Table 2 of "0021 quality information amendment" in Section 1.11.1

| RPT-PH-1007289 V3.0, 24 months, Acetaminophen Injection in PAB, 400 mL/day | RPT-PH-1008805 V2.0, 24 months, Metronidazole Injection, USP in PAB (FDA Approved product): 800mL/day |
|---|---|
| (b) (4) | |

The maximum daily levels of the unknowns at RRT of (b) (4), and (b) (4) are greater in the FDA-approved metronidazole product than their APAP product, demonstrating that the systemic exposure to all these unknown compounds combined are covered by Metronidazole. However, the concentration of the unknown compound at RRT (b) (4) is slightly greater in the APAP product ((b) (4) mcg/mL) than the FDA-approved Metronidazole ((b) (4) mcg/mL). Technically, there is no local safety coverage for the concentration of (b) (4) mcg/mL); However, the difference in RRT (b) (4) concentration is minor and not expected to result in a clinically meaningful different in local tissue effects.

In discussions with the Chemistry, Manufacture, and Controls (CMC) Reviewer, the Applicant's analytical methods to detect known and unknown leachables and the grouping of the unknowns between different analytical methods are adequate. The reader is referred to the quality review for details.

It is noted in Table 2 that the limit of detection for all unknowns listed as ND (not detected) was below (b) (4) mcg/mL. The Applicant has confirmed that their analytical method was able to detect leachables down to a concentration of (b) (4) mcg/mL. The Reviewer's calculated AET is (b) (4) mcg/mL (b) (4) As such, the sensitivity of the Applicant's analytical method is capable of detecting compounds of at least 5 mcg in their APAP product at the maximum daily volume of 400 mL. However, the Applicant states that unknown leachables observed below (b) (4) mcg/mL are not reported for the following reasons:

1. Based on ICH M7(R1), the acceptable intake for individual impurity is 120 mcg/day for duration of treatment of less than 1 month and as such, the Applicant's AET is (b) (4) mcg/mL (b) (4) *Reviewer's*



Reference ID: 4408114

*comment: This is not appropriate as ICH M7 addresses the genetic toxicity of impurities and not the general toxicity of impurities. For general toxicity of extractable/leachable compounds, the Division has utilized a qualification threshold of 5 mcg/day.*

2. The PAB® containers used in the 28-day mouse toxicity studies with 0.9% NaCl injection have not been changed since the mouse study was performed. The study (Study P1203007) concluded that there was no evidence of toxicity associated with 0.9% NaCl in the PAB® containers. *Reviewer's comment: This study was not reviewed during the first cycle because the study used saline and not the test article. Instead, the more pivotal 28-day rat toxicity study with APAP (Study HC-G-A-1602) was reviewed. Moreover, there was no information regarding the leachable compounds from the saline bag that were administered to the mice.*

3. The materials of the PAB® container closure system were previously qualified and approved in several NDAs and ANDAs. *Reviewer's comment: As such, the identified issues were not deemed approvability issues.*

Summary Table 1

| Unknown Leachable Compound By RRT (RRT range) | Detected under Normal (N) and/or Accelerated (A) Conditions | Identified? | Highest Levels in APAP under normal conditions | | Highest Levels in metronidazole under normal conditions | | Acceptable? |
|---|---|---|---|---|---|---|---|
| | | | Concentration (mcg/mL) | TDI (mcg/day) | Concentration (mcg/mL) | TDI (mcg/day) | |
| (b) (4) | | | | | | | Yes; not a leachable compound under normal conditions |
| | | | | | | | Yes; not a leachable compound under normal conditions |
| | | | | | | | No; not identified and was not detected in metronidazole under normal conditions |
| | | | | | | | Yes; it is at higher levels in metronidazole |
| | | | | | | | Yes; it is at higher levels in metronidazole |

**Applicant's Response to Item 3:**
The Applicant has analyzed the levels of (b) (4) and related compounds in the approved metronidazole in comparison to their APAP product (see Applicant's table below):

Table 3: Comparison results of (b) (4) and related compound leachables from PAB® Container Closure System

| Reference Leachables report | RPT-PH-1007289 V3, 24 months, Acetaminophen Injection in PAB | RPT-PH-1008805 V2.0, 24 months, Metronidazole Injection, USP in PAB ( FDA Approved products) |
|---|---|---|
| Sterilization condition | (b) (4) | |
| Fill volume/PAB container size | | |
| Daily dose of drug product in PAB Containers ( mL/day) | | |
| Storage condition | | |

As shown in the table above, the maximum daily exposure for the combination of (b) (4) and (b) (4) is greater in the FDA-approved metronidazole product than the APAP product, demonstrating that there is systemic support for the combination of (b) (4) and (b) (4) However, the concentrations of (b) (4) and (b) (4) individually are greater in the APAP product than the FDA-approved metronidazole product and the concentration of (b) (4) is greater in the FDA-approved metronidazole product than the APAP product. However, the difference in concentrations are minor ((b) (4) mcg/mL) and not expected to result in clinically meaningful differences in local tissue effects.

It is also noted that the concentration of (b) (4) in Table 3 and Table 2 above are inconsistent (e.g. Table 2 reports not detected whereas in Table 3 levels were detected in the metronidazole). However, as levels were qualified in both tables (see Summary Table 1 and 2), additional clarification will not be further requested.

Summary Table 2

| Leachable Compound | Highest Levels in APAP under normal conditions | | Highest Levels in metronidazole under normal conditions | | Acceptable? |
|---|---|---|---|---|---|
| | Concentration (mcg/mL) | TDI (mcg/day) | Concentration (mcg/mL) | TDI (mcg/day) | |
| [redacted] (b) (4) | | | | | Yes; it is at higher levels in metronidazole |
| | | | | | Yes; it is at higher levels in metronidazole |
| | | | | | Yes; it is at higher levels in metronidazole |

Thus, Item 3 has been adequately addressed.

**Conclusions and Recommendations:**

The revised drug product specification for 4-aminophenol and 4-nitrophenol to NMT [redacted] (b) (4) % each is acceptable and as such, this issue has been adequately addressed. With regards to the second issue, the Applicant did not provide identification of all unknowns from the leachable studies conducted on product stored under normal and accelerated conditions but submitted data that these unknowns exist at higher levels in an FDA-approved drug product, which is deemed acceptable. However, one unknown compound (RRT [redacted] (b) (4) was not adequately justified as this compound was not identified and was present in APAP at higher levels under both normal and accelerated conditions than in the metronidazole product, which was not present under normal conditions but only accelerated conditions. To resolve the third issue, the Applicant compared the levels of [redacted] (b) (4) and [redacted] (b) (4) in the APAP product and demonstrated that these compounds are at higher levels in another FDA-approved metronidazole product. Therefore, Issue 3 has been adequately addressed. A new nonapproval issue that was identified in the current resubmission was that the Applicant set reporting of leachables at and above [redacted] (b) (4) mcg/mL, which is not adequate to detect leachables at 5 mcg/day. This Reviewer calculates that leachables at and above [redacted] (b) (4) mcg/mL must be identified and an accompanying toxicological risk assessment must be performed for any leachable above the 5 mcg/day qualification threshold.

This submission is deemed a Complete Response again due to outstanding facility inspection deficiencies. The Applicant has attempted to address all the nonclinical nonapproval issues that were conveyed to the Applicant in the complete response letter. However, only one of the nonapproval issues was adequately addressed. The unresolved issues still do not preclude approval from a pharmacology toxicology perspective because the container closure system (PAB® bags) are found in several FDA-approved products.



Reference ID: 4408114

You have adequately addressed nonclinical Items 1 and 3 in the complete response letter dated 9/28/2017. However, we have the following outstanding nonclinical concerns that are not approvability issues but should be addressed prior to a subsequent NDA resubmission:

1. Your reporting of leachables compounds at and above (b) (4) mcg/mL (i.e. (b) (4) mcg/day taking into consideration the maximum daily dose of acetaminophen) is not acceptable as this exceeds the recommended qualification threshold of 5 mcg/day. Identify all leachable compounds above 5 mcg/day and submit a toxicological risk assessment for any newly identified compound that exceeds the 5 mcg/day threshold of concern.

2. You have not provided adequate safety justification for the unknown compound at RRT (b) (4) Identify this unknown compound and submit an accompanying toxicological risk assessment.



Reference ID: 4408114

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/s/

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CARLIC K HUYNH
03/22/2019 12:22:44 PM

NEWTON H WOO
03/22/2019 12:25:17 PM

RICHARD D MELLON
03/22/2019 01:32:15 PM

SHARON H HERTZ
03/22/2019 03:08:42 PM

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

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | NDA 204957 |
| Supporting document/s: | SDN 1, 5, 9, 11, and 16 |
| Applicant's letter date: | December 13, 2016 (SDN 1); March 16, 2017 (SDN 5); May 5, 2017 (SDN 9); May 24, 2017 (SDN 11); and August 11, 2017 (SDN 16) |
| CDER Stamp Date: | December 13, 2016 (SDN 1); March 16, 2017 (SDN 5); May 5, 2017 (SDN 9); May 24, 2017 (SDN 11); and August 11, 2017 (SDN 16) |
| Product: | Acetaminophen Injection in the PAB® Container |
| Indication: | Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever |
| Applicant: | B. Braun Medical, Inc. |
| Review Division: | Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| Reviewer: | Carlic K. Huynh, PhD |
| Team Leader: | Newton H. Woo, PhD |
| Supervisor: | R. Daniel Mellon, PhD |
| Division Director: | Sharon Hertz, MD |
| Project Manager: | Ogochukwu Ogoegbunam |

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204957 are owned by B. Braun Medical, Inc. or are data for which B. Braun Medical, Inc. has obtained a written right of reference.
Any information or data necessary for approval of NDA 204957 that B. Braun Medical, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204957.



Reference ID: 4154306

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# 1 Executive Summary

## 1.1 Introduction

The Applicant, B. Braun Medical, Inc., is submitting a 505(b)(2) application for an intravenous solution of acetaminophen (10 mg/mL) that is packaged in PAB® containers with a total volume of 100 mL (1000 mg of acetaminophen) or 50 mL (500 mg of acetaminophen). The Applicant is relying upon the Agency's previous finding of safety to Mallinckrodt's Ofirmev® (NDA 22450).

## 1.2 Brief Discussion of Nonclinical Findings

To support the safety of the APAP intravenous product, the Applicant submitted a 28-day rat IV comparative toxicology study with their proposed formulation (ivAPAP) and an in vitro a blood compatibility assessment of their proposed product. In addition, a negative Ames assay with the drug substance impurity (b) (4) which contains a structural alert for mutagenicity, was submitted to support a specification that exceeds ICH M7. The proposed drug substance and drug product specifications are acceptable.

The proposed PAB container closure system has been used in other FDA-approved drug products. To support safety of the container closure system for this new drug product formulation, the Applicant submitted a series of study reports from other approved products that also utilize the PAB container closure system. The extractable/leachable assessment resulted in 3 known compounds (b) (4) (b) (4) as well as several unknown compounds. In the toxicological risk assessment, (b) (4) and (b) (4) are adequately qualified but (b) (4) is not adequately qualified. Moreover, a total of 3 unknowns and 5 unknowns were detected in leachable studies with the PAB® container above the recommended qualification threshold under normal and accelerated conditions, respectively. Therefore, there is a lack of adequate data to support the safety of the container closure system based on current approaches employed by the Division. However, as this container closure system has been used in several FDA-approved drug products with similar physicochemical properties and for similar doses and durations of treatment, the lack of a modern assessment will not be considered an approval issue if this NDA can be approved in this cycle. If approved this cycle, we would recommend further assessments as a post-marketing requirement.

To confirm that the reformulated drug product should not result in any differential safety profile compared to the referenced drug product, a 28-day IV toxicology study in the rat and in vitro blood compatibility studies were completed. In the 28-day comparative IV toxicology study, similar toxicological findings were present both in the ivAPAP groups and the comparator Ofirmev® group, indicating the proposed formulation did not present a greater risk than Ofirmev®. The local NOAEL was the high dose of 400 mg/kg/day administered at a concentration of 10 mg/mL. At the systemic NOAEL of 200 mg/kg/day, the average $C_{max}$ is 34.65 mcg/mL and the average $AUC_{0-t}$ is 42.6 mcg*h/mL on Day 1. The systemic and local exposure margins are approximately 1.

In the blood compatibility assessment of the proposed formulation ivAPAP, ivAPAP inhibited platelet aggregation, which is an expected pharmacology effect, but did not induce hemolysis of red blood cells or flocculation of proteins. There was no difference between the effects of the proposed ivAPAP product and the referenced product Ofirmev®.

In summary, the data support the conclusion that the change in formulation compared to the referenced drug product should not result in any differential safety profile.

## 1.3 Recommendations

### 1.3.1 Approvability

From the nonclinical pharmacology toxicology perspective, NDA 204957 may be approved. Several nonclinical issues were identified but were not deemed approvability issues. These issues can be addressed as postmarketing requirements should this NDA be approved in this cycle. If the NDA is not approved this cycle, we recommend that these issues be addressed, if possible, prior to resubmission.

### 1.3.2 Additional Non Clinical Recommendations

Although the following nonclinical concerns are not approvability issues, the following comments should be addressed prior to a subsequent NDA submission:

1. Tighten the drug product specification for 4-aminophenol and 4-nitrophenol based on long-term stability data to as low as technically feasible.

2. In your leachables study, 3 unknown compounds (RT (b) (4) under normal conditions as well as 5 unknown compounds (RT (b) (4) (b) (4) under accelerated conditions were present in your leachable samples. As we cannot conduct a toxicological risk assessment on unknowns, either provide identification for these unknown compounds along with an adequate toxicological risk assessment or confirm that these compounds are present in other FDA-approved products that use the same container closure system at comparable total daily intake levels.

3. The safety of (b) (4) has not been adequately addressed by the submitted 28-day and 14-day toxicology studies. Either provide data that demonstrates (b) (4) and related compounds are present at comparable total daily intake levels in other FDA-approved products that use the same container closure system or conduct an adequately designed 14-day toxicology study that identifies a NOAEL that establishes adequate safety margins.

### 1.3.3 Labeling

The proposed labeling is the same as Ofirmev®. There are no recommended changes to the label at this time.

# 2 Drug Information

## 2.1 Drug

CAS Registry Number
103-90-2

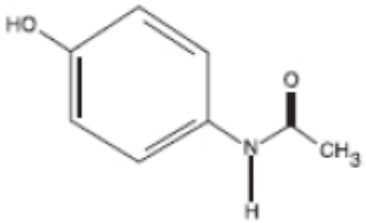
Generic Name
Acetaminophen, paracetamol

Code Name

Chemical Name
N-(4-hydroxyphenyl)-acetamide;
Acetamide, N-(4-hydroxyphenyl)-;
N-acetyl-p-aminophenol;
N-acetyl-4-aminophenol;
4-(Acetylamino)phenol; and
4-Hydroxyacetanilide

Molecular Formula/Molecular Weight
$C_8H_9NO_2$ / 151.16 g/mol

Structure or Biochemical Description




Pharmacologic Class
There is no FDA Established Pharmacologic Class for acetaminophen. The Agency intentionally elected not to designate an EPC to date given the lack of clear understanding of the mechanism of acetaminophen.

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

| IND# | Drug | Status | Division | Indication | Stamp Date | Sponsor |
|---|---|---|---|---|---|---|
| 111161 | Acetaminophen in the PAB® | Active (December | DAAAP | Management of mild to moderate pain, for the | 24-May-1999 | B. Braun Medical, Inc. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Container | 17, 2015) | | management of moderate to severe pain with adjunctive opioid analgesics and for the reduction of fever | | |

| NDA# | Drug Name | Div | Strength (route) | Marketing Status | AP Date | Indication | Company |
|---|---|---|---|---|---|---|---|
| **22450** | OFIRMEV® (Acetaminophen) | DAAAP | 1000 mg/ 100 mL (10 mg/mL) (IV infusion) | Prescription | November 2, 2010 | Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever | Mallinckrodt IP |

| MF# | Subject of MF | Holder | Submit Date | Reviewer's Comment |
|---|---|---|---|---|
| | | | (b) (4) | Acceptable to support numerous solution NDAs and ANDAs. |
| | | | | Acceptable to support IV solution of acetaminophen (see nonclinical review dated February 17, 2015). |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. Deemed adquate in solutions for injection (see quality review dated February 11, 2014). |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. Deemed addquate in solutions for injection (see quality review dated June 15, 2017). |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. Deemed addquate in solutions for injection (see quality review dated October 1, 2013). |
| | | | | The DMF has been referenced in numerous FDA-approved drug products. |

## 2.3 Drug Formulation

The following table illustrates the proposed drug product formulation (from the Applicant's submission):

**Table 1: Composition of Proposed Product and Comparison to the Referenced Drug**

| Name of Ingredient | Name | Acetaminophen Injection | Ofirmev® |
|---|---|---|---|
| | **Description** | Acetaminophen (10 mg/mL) Solution in PAB® Container | Acetaminophen (10 mg/mL) Solution in Glass Vials |
| | **NDC No:** | 0264-4500-80 & 0264-(b) (4) 90 | 43825-102-01 |
| | **Container Type** | Plastic (PAB®) | Glass vials |
| | **Container Size** | 100 mL & 150 mL | 100 mL |
| | **Fill Volume** | 50 mL & 100 mL | 100 mL |
| | **Function** | 100 mL contains: (w/v, %) | 100 mL contains: (w/v, %) |
| Acetaminophen USP, g | Active | 1.00 | 1.00 |
| Sodium Citrate $2H_2O$ USP, g | (b) (4) | 0.03 | N/A |
| Mannitol USP, g | | 3.80 | 3.85 |
| Glacial Acetic Acid USP, g* | pH Adjuster | (b) (4) | N/A |
| Water for Injection, g** | (b) (4) | QS | QS |
| HCl, g* | | N/A | pH Adjuster |
| NaOH, g* | | N/A | pH Adjuster |
| Cysteine HCl, $H_2O$, USP, mg | | N/A | 25.0 |
| $Na_2HPO_4$, USP, mg | | N/A | 10.4 |
| pH | | (b) (4) | ~5.5 |
| (b) (4) | | | |
| Osmolality, mOs/kg[5] | | ~290 | ~290 |

* AR: As required, used for pH adjustments.
** QS: Quantity sufficient to bring to volume.

Both presentations (500 mg/50 mL or 1000 mg/100 mL) have an APAP concentration of 10 mg/mL. To achieve the 4000 mg/day daily limit of APAP, a total of 400 mL of solution is used.

## 2.4 Comments on Novel Excipients

There are no novel excipients in the proposed drug product formulation.

## 2.5 Comments on Impurities/Degradants of Concern

### Drug Substance Specifications

The following table illustrates the drug substance specifications (adapted from the Applicant's submission):

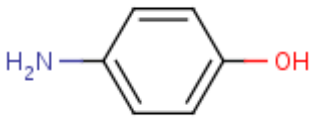
**Table 2: Drug Substance Specifications**

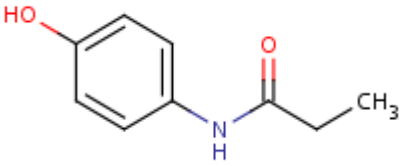
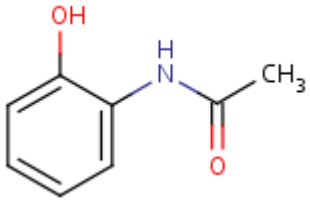
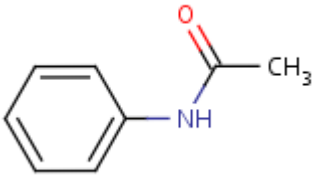
**Table 1:** Test Specifications Identified in SPEC-PH-1001939

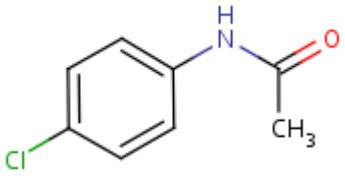
| Type of Test/Release Required | Test Specifications |
|---|---|
| Limit of free 4-aminophenol, (w/w) | ≤ 0.005 |
| Related Compound (b) (4) (b) (4) (% w/w) | ≤ 0.001 |
| Related Compound B (N-(4-Hydroxyphenyl) propanamide), (%w/w) | ≤ 0.05 |
| Related Compound C (N-(2-Hydroxyphenyl) acetamide), (% w/w) | ≤ 0.05 |
| Related Compound D (N-Phenylacetamide), (% w/w) | ≤ 0.05 |
| 4-Nitrophenol (Impurity F) (% w/w) | (b) (4) |
| (b) (4) (b) (4) (% w/w) | (b) (4) |
| Individual unspecified impurity, % w/w | ≤ 0.05 |
| Total Impurities, % w/w | ≤ 0.1 |
| Residual Solvents, % (by LOD) | (b) (4) |
| (b) (4) | |

The following table illustrates whether the proposed drug substance specifications are acceptable:

**Table 3: Assessment of Drug Substance Impurities**

| Name | CAS | Structure | Comments |
|---|---|---|---|
| 4-Aminophenol (aka p-aminophenol) | 123-30-8 |   | • Literature: Negative in Ames, Positive Chromosomal Aberrations in vitro and vivo; NOAEL demonstrated<br>• Regulated at NMT 0.005% as per current USP - Acceptable |

| | | | |
|---|---|---|---|
| USP Compound B<br>N-(4-hydroxyphenyl)propanamide | 1693-37-4 |  | • No genotoxicity data<br>• Computational Toxicology Ames prediction negative.<br>• Predicted **positive** for chromosomal aberrations, but not for carcinogenicity<br>• At NMT 0.05%, with on a MDD of 4 g = 2 mg/day<br>• Same structural alert as parent; therefore, in terms of Ames deemed qualified via studies of the parent molecule<br>• Acceptable |
| USP Compound C<br>N-(2-hydroxyphenyl)acetamide | 614-80-2 |  | • No genotoxicity data<br>• Computational Toxicology Ames prediction was positive<br>• At NMT 0.05%, with on a MDD of 4 g = 2 mg/day<br>• Same structural alert as parent; therefore, in terms of Ames deemed qualified<br>• Acceptable |
| USP Compound D<br>N-phenylacetamide<br>(aka Acetanilide) | 103-84-4 |  | • Negative in the Ames (Zeiger et al. 1988)<br>• No clastogenicity data<br>• Same structural alert as parent; therefore, in terms of Ames |

| | | | |
|---|---|---|---|
| | | | deemed qualified<br>• Acceptable |
| USP Compound J<br>N-(4-chlorophenyl)acetamide (aka p-chloroacetanilide) | 539-03-7 |  | • No genotoxicity data; Historically regulated at NMT 0.001%, based on a MDD of 4 g, 40 mcg/day<br>• Computational Toxicology predicts Ames negative<br>• Regulate at NMT 0.001% as per USP - Acceptable |

The specifications for 4-nitrophenol and [redacted] (b) (4) are described in further detail below.

**4-Nitrophenol.** The specification of 4-nitrophenol is NMT [redacted] (b) (4) %, which would result in 400 mcg/day based on the maximum daily dose of 4 g/day APA via the proposed formulation. It is noted that in the original IND submission, the specification of 4-nitrophenol was NMT [redacted] (b) (4) %. However, 4-nitrophenol contains a structural alert for mutagenicity and should be reduced to 120 mcg/day for an acute product as per ICH M7 for the NDA. A search of the published literature did identify several studies that suggested that the compound has been tested in the Ames assay (*Salmonella typhimurium* mutagenesis only) and found to be negative (McCann et al., 1975).

McCann et al. (1975) tested the ability of p-nitrophenol (4-nitrophenol) to form mutations in several *Salmonella typhimurium* strains (TA100, TA1535, TA1537, and TA98) with and without S9 metabolic activation (McCann et al., 1975). The doses used in McCann et al. were up to 1000 mcg for non-toxic compounds. McCann et al. is a review paper and does not contain the raw data as seen in final study reports. Although the standard 5000 mcg/plate and *E. coli* WP2 strain were not used, Bruce Ames was one of the authors listed as contributing to the study and more than likely, the methods used are appropriate for a valid study.

In addition, Haworth et al. (1983) tested the ability of p-nitrophenol (4-nitrophenol) to form mutations in several *Salmonella typhimurium* strains (TA1535, TA1537, TA98, and TA100) with and without S9 metabolic activation (Haworth et al., 1983). The doses used in Haworth et al. were up to 10 mg/plate, which is greater than the 5 mg/plate current limit concentration. The appropriate positive controls were used for each strain. However, the *E. coli* WP2 strain was not used and this paper does not contain the raw data as seen in final study reports. Nonetheless, the method developed by Bruce Ames was used. Thus, the methods used are more than likely appropriate for a valid study.

4-Nitrophenol was later reported to test negative in the presence and absence of S9 in strains TA98, TA1538, TA1537, and TA1535 (Shimizu and Yano, 1986) and in studies conducted by the National Toxicology Program (National Toxicology Program, 1993).

There are limited data on the potential clastogenicity of 4-nitrophenol; however, it has been reported to test positive as a clastogen in human peripheral lymphocytes (Huang, et al., 1996) and in Chinese hamster ovary cells in the presence of S9 (National Toxicology Program, 1993). This profile is actually very similar to that of 4-aminophenol. Although the data in the published literature suggest that 4-nitrophenol is not a mutagen, it does appear to be a clastogen and there are no in vivo data to attempt to establish a threshold for genotoxicity. Therefore, this impurity must be tightened to as low as technically feasible.


**Drug Product Specifications**

The following table illustrates the drug product specifications (adapted from the Applicant's submission):

**Table 4: Drug Product Specifications**

**Applicable Part/Catalog Numbers: DA4500; DA4100**

| Type of Test/Release Required | Test Method | Test Specifications |
|---|---|---|
| 8. Related Substances | TP-PH-1001221 | |
| Known Impurities | | |
| 4-Aminophenol, %(w/w) | | ≤ (b) (4) |
| (b) (4) % (w/w) | | ≤ (b) (4) |
| Related compound B (N-(4-Hydroxyphenyl)propanamide), % (w/w) | | Record |
| Related Compound D (N-Phenylacetamide), % (w/w) | | Record |
| 4-Nitrophenol (Ph. Eur. Impurity F), % (w/w) | | Record |
| Unknown Impurities | | |
| Any other single impurity, % (w/w) | | ≤ (b) (4) |
| Total Unknown Impurities, % (w/w) | | ≤ |
| Total Impurities | | |
| Total Impurities, % (w/w) (Including Known and Unknown Impurities) | | ≤ |
| 9. (b) (4) | USP (b) (4) | (b) (4) |

* Statement of compliance, test is not performed (see RPT-PH-1007124 for justification)

There is presently no specification for Related Compound B (N-(4-hydroxyphenyl)propanamide), Related Compound D (N-phenylacetamide), and 4-nitrophenol in the original submission. The Applicant has updated the drug production specification in SDN 11 as shown in the following table (from the Applicant's submission):

**Table 5: Updated Drug Product Specifications**

| Specified Indentified Impurities | ICHQ3B(R2), >2g/day (RT) (w/w%) | ICHQ3B(R2), >2g/day (IT) (w/w%) | ICHQ3B(R2), >2g/day (QT) (w/w%) | B. Braun acceptance criteria (AC) (w/w%) | Justification for B.Braun AC (w/w%) |
|---|---|---|---|---|---|
| Related Compound B | (b) (4) | | | | |
| Related Compound D | | | | | |
| Imp F (4-Nitrophenol) | | | | | |

Note: RT= reporting threshold; IT = Identification Threshold; QT = Quantification Threshold

The following table illustrates whether the proposed drug product specifications are acceptable:

**Table 6: Acceptability of the Drug Product Specifications**

| Degradant | Proposed Specification | ICH Q3B(R2) Qualification Threshold | Reviewer's Comments |
|---|---|---|---|
| 4-aminophenol | NMT (b) (4)% | -- | See below[a] |
| (b) (4) | NMT (b) (4)% (release)<br>NMT (b) (4)% (shelf-life) | NMT 0.15% | Acceptable |
| Related Compound B (N-(4-hydroxyphenyl)propanamide) | NMT (b) (4)% | NMT 0.15% | Acceptable |
| Related Compound D (N-phenylacetamide) | NMT 0.(b) (4)% | NMT 0.15% | Acceptable |
| 4-nitrophenol | NMT (b) (4)% | -- | See below[a] |
| Any other single impurity | NMT (b) (4)% | NMT 0.15% | See Quality review |
| Total unknown impurities | NMT (b) (4)% | -- | |
| Total impurities | NMT (b) (4)% | | |

a = These impurities contain and structural alert for genotoxicity

**4-aminophenol.** The drug product degradant 4-aminophenol contains a structural alert for genotoxicity and published data suggest the compound is clastogenic. As such, ideally it should be reduced to as low as low reasonably possible. The specification for 4-aminophenol at NMT (b) (4)% results in 2000 mcg/day based on the maximum daily dose of 4 g/day APAP via the proposed formulation. This specification is comparable to the specification in Ofirmev® and is considered acceptable.

**4-Nitrophenol.** The drug product degradant 4-nitrophenol contains a structural alert for genotoxicity and published data suggest that it is clastogenic. As such, should be reduced to as low as reasonably possible. The specification for 4-nitrophenol at NMT (b) (4)% results in 2000 mcg/day based on the maximum daily dose of 4 g/day APAP via the proposed formulation. This specification is the same as the 4-AP specification, which appears to have the same risk profile. If this is indeed as low as reasonably possible, the specification is considered acceptable.

Although the drug product specifications for 4-aminophenol and 4-nitrophenol are acceptable, these specifications appear to be able to be tightened further as demonstrated by the drug product stability batch analyses made from (b) (4) and (b) (4) acetaminophen drug substance (adapted from the Applicant's submission):

**Table 7: Stability Batch Analyses of ivAPAP Drug Product**

**Acetaminophen Injection 1000 mg/100 mL**
**Mallinckrodt (Z16-829)**

| Catalog No.: DA4100 | Lot No.: S6C683 | Batch Size: (b) (4) | | | | Manufacture Date: 03/01/16 |
|---|---|---|---|---|---|---|
| | | Zero Time | 25°C ± 2°C/≤ 40% RH (Inverted) | | | |
| | | | 3 Mos. | 6 Mos. | 9 Mos. | 12 Mos. |
| | Sample Pull Date | 03/02/16 | 06/08/16 | 09/07/16 | 12/06/16 | 03/22/17 |
| Test | Method | Specification | | | | |
| Related Substances | TP-PH-1001221 | | | | | |
| Known Impurities | | | | | | |
| 4-Aminophenol, % (w/w) | | ≤ (b) (4) | | | | |
| (b) (4) | | (b) (4) | | | | |
| % (w/w) | | ≤ (b) (4) | | | | |
| Related compound B (N-(4-Hydroxyphenyl) propanamide), % (w/w) | | ≤ | | | | |
| Related Compound D (N-Phenylacetamide), % (w/w) | | ≤ (b) (4) | | | | |
| 4-Nitrophenol, % (w/w) | | ≤ | | | | |

**Acetaminophen Injection 500 mg/50 mL**
(b) (4)

| Catalog No.: DA4500 | Lot No.: STBJ5H721 | Batch Size: (b) (4) | | | | | Manufacture Date: 06/24/15 |
|---|---|---|---|---|---|---|---|
| | | Zero Time | 25°C ± 2°C/≤ 40% RH (Inverted) | | | | |
| | | | 3 Mos. | 6 Mos. | 9 Mos. | 12 Mos. | 18 Mos. |
| | Sample Pull Date | 06/25/15 | 10/07/15 | 01/06/16 | 04/05/16 | 07/06/16 | 01/03/17 |
| Test | Method | Specification | | | | | |
| Related Substances | TP-PH-1001221 | | | | | | |
| Known Impurities | | | | | | | |
| 4-Aminophenol, % (w/w) | | < (b) (4) | | | | | |
| (b) (4) | | (b) (4) | | | | | |
| % (w/w) | | ≤ (b) (4) | | | | | |
| Related compound B (N-(4-Hydroxyphenyl) propanamide), % (w/w) | | ≤ | | | | | |
| Related Compound D (N-Phenylacetamide), % (w/w) | | ≤ (b) (4) | | | | | |
| 4-Nitrophenol, % (w/w) | | ≤ | | | | | |

It is noted that in the drug product stability batch analyses, 4-aminophenol and 4-nitrophenol tested at (b) (4) %, demonstrating that the specifications for 4-aminophenol and 4-nitrophenol should be able to be tightened to lower specifications. We discussed this with the CMC review team, who concurred that these should be able to be tightened. Ultimately we defer to the CMC review team to ascertain an appropriate specification based on the existing data.

**Container Closure System**
The following figure and table illustrates the container closure system (from the Applicant's submission):

**Figure 1: Illustration of the Container Closure (PAB® Container)**


**Table 8: Components of Figure 1**

**Table 2:** Summary of Components Shown in Figure 1 (above)

| Item Number | Component |
|---|---|
| (b) (4) | |

The following table illustrates the components of the container closure with the associated manufacturers (adapted from the Applicant's submission):

**Table 9: Components and Manufacturers of the Container Closure**

| Component | Composition | Function | Category of Solution Contact | Manufacturer |
|---|---|---|---|---|
| (b) (4) | | | | |


It is important to note that the (b) (4) ink is used in the 100 mL volume label and the (b) (4) ink in the 50 mL volume label that is printed on the bag (Item 6 in the Applicant's figure 1 above). The (b) (4) ink is used for the barcode that is printed on the bag (item 7 in the Applicant's figure 1 above). There is no overwrap of individual bags. There are 24 bags in 1 box case.

Moreover, the PAB® containers used in the proposed drug product formulation are also used in other FDA-approved products as illustrated in the following table (from the Applicant's submission):

**Table 10: Applicant's List of FDA-Approved Products Using the PAB® Container**

**Table 1:** FDA-Approved Drug Products Packaged in the PAB® Container

| Application Number | | Product Name | Approval Dates | |
|---|---|---|---|---|
| | | | Original Application | Supplement to Add PAB® Container (if not included in Original Application) |
| NDA[1] | 016730 | 5% Dextrose Injection USP | 12/21/1973 | 09/30/1981 (S-018/019) |
| NDA[1] | 017464 | 0.9% Sodium Chloride Injection USP | 02/08/1978 | 09/30/1981 (S-012/013) |
| NDA[1] | 018900 | Metro IV (0.5% Metronidazole Injection USP) | 09/29/1983 | N/A |
| NDA | 019212 | Theophylline and 5% Dextrose Injection | 11/07/1984 | N/A |
| ANDA | 062814 | Gentamicin Sulfate in 0.9% Sodium Chloride Injection | 08/28/1987 | N/A |
| ANDA | 076414 | Milrinone Lactate in 5% Dextrose Injection | 08/18/2004 | N/A |

[1]Application Transferred from ANDA to NDA by the FDA

Of the FDA-approved products using the PAB® container, there are four FDA-approved PAB® products using the (b) (4) Stoppers as illustrated in the table below (from the Applicant's submission):

**Table 11: Applicant's List of FDA-Approved PAB® Products Using (b) (4) Stoppers**

**Table 3:** FDA-Approved PAB® Products Using (b) (4) Rubber Stopper

| Application Number | | Product Name | Supplement Numbers and Approval Dates (b) (4) | |
|---|---|---|---|---|
| NDA[1] | 016730 | 5% Dextrose Injection USP | S-049 Approved: 04/27/2006 | S-052 / (b) (4) Approved: 09/29/2014 |
| NDA[1] | 017464 | 0.9% Sodium Chloride Injection USP | (b) (4) | |
| NDA[1] | 018900 | Metro IV (0.5% Metronidazole Injection USP) | (b) (4) | S-030 Approved: 3/25/2014 |
| ANDA | 062814 | Gentamicin Sulfate in 0.9% Sodium Chloride Injection | (b) (4) | N/A |

[1]Application Transferred from ANDA to NDA by the FDA

The listed NDAs above are for acute use products with a similar dosing schedule as the proposed product. These products use the same (b) (4) rubber stopper and PAB® container materials as the proposed product.

**Extractable Study of the Container Closure System**

Based on the certificate of analyses of the (b) (4) and the (b) (4) the potential extractable of the (b) (4) stopper as provided by (b) (4) and the (b) (4) information, the following table summarizes the potential extractables/leachables (from the Applicant's submission):

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is identical to Ofirmev®, which is for adults and pediatric patients aged 2 years and older. In adults and adolescent aged 13 years and older weighing greater than or equal to 50 kg, the dosing regimen is 650 mg every 4 hours or 1000 mg every 6 hours with a maximum daily dose of 4000 mg/day. For adults and adolescents weighing less than 50 kg and for children between 2 to 12 years of age, the dosing regimen is 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours with a maximum daily dose of 75 mg/kg in 24 hours (or up to 3750 mg/day).

### 2.7 Regulatory Background

The clinical development program was conducted under IND 111161.

Pre-IND written responses were communicated to the Sponsor (see preliminary meeting comments dated April 24, 2012). A 28-day repeat-dose toxicology study in a single species was required to support the safety of the formulation prior to use in repeat-dose clinical studies and the NDA.

The opening IND submission was received by the Agency on January 20, 2015 and the proposed clinical protocol was put on full Clinical Hold on February 18, 2015 via teleconference and the Full Clinical Hold Letter was sent to the Sponsor on March 19, 2015. The IND was placed on hold due to clinical concerns regarding (b) (4) (b) (4) which was an excipient in the formulation that has been highlighted by the Agency to cause kidney injury and mortality. The following non-hold nonclinical comments were communicated to the Sponsor in the hold letter:

To support an NDA submission:

1. The DS specifications for 4-nitrophenol and (b) (4) and the DP specification for 4-aminophenol must be lowered to as technically feasible;

2. Conduct a 28-day IV toxicology study in a single species that mimics the clinical dosing regimen of 4 times a day (QID) dosing and include a local tissue assessment; and

3. Conduct blood compatibility testing on your proposed drug formulation.

A Complete Response to Clinical Hold was submitted to the Division on November 20, 2015. Due to the concerns of (b) (4) this excipient was omitted from the formulation. Subsequently, there was a Removal of Full Clinical Hold Letter sent to the Sponsor on December 17, 2015.

There were no other interactions with the Applicant, such as an EOP2 or preNDA meeting prior to NDA submission.

# 3 Studies Submitted

### 3.1 Studies Reviewed

28-Day IV toxicity study in rats (Study HC-G-A-1602)
Blood compatibility assessment (Study 6000344STF)
Ames assay on (b) (4) (Study 848-471-1364)

### 3.2 Studies Not Reviewed

None.

### 3.3 Previous Reviews Referenced

There were no previous reviews referenced.

# 4 Pharmacology

### 4.1 Primary Pharmacology

There were no new primary pharmacology studies with IV APAP in this submission.

### 4.2 Secondary Pharmacology

There were no new secondary pharmacology studies with IV APAP in this submission.

### 4.3 Safety Pharmacology

There were no new safety pharmacology studies with IV APAP in this submission.

# 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

There were no new PK/ADME studies with IV APAP in this submission.

### 5.2 Toxicokinetics

See the 28-day rat IV toxicology study with IV APAP below.

# 6 General Toxicology

### 6.1 Single-Dose Toxicity

There were no new single-dose toxicity studies with IV APAP in this submission.



Reference ID: 4154306

## 6.2 Repeat-Dose Toxicity

**Study title: A 28-Day Study of B. Braun Acetaminophen Injection (ivAPAP) by Intravenous Infusion in Rats with a 14-Day Recovery Period**

| | |
|---|---|
| Study no.: | HC-G-A-1602 |
| Study report location: | \\cdsesub1\evsprod\nda204957\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\hc-g-a-1602\5001841-afr-tox.pdf |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | May 12, 2016 |
| GLP compliance: | Yes. Signature provided on November 28, 2016 |
| QA statement: | Yes. Signature provided on November 28, 2016 |
| Drug, lot #, and % purity: | ivAPAP, Lot STBJ5J677, 100% |

**Key Study Findings**

- Sprague Dawley rats were administered IV doses of 0, 80, 200, and 400 mg/kg/day of ivAPAP as well as a 400 mg/kg/day of Ofirmev® four times a day for 28 consecutive days via an indwelling catheter placed in the vena cava at the level of the kidneys.
- Increases in the red blood cell distribution width and spleen weight parameter (absolute weight, spleen to body weight ratio, and spleen to brain weight ratio) were observed in ivAPAP groups but were within levels of the Ofirmev® comparator group.
- There were several histopathological findings in individual organs but these findings were comparable to the Ofirmev® control.
- At the infusion site, the incidence and severity of the gross and microscopic changes in the main study rats were no worse than in the Ofirmev® comparator group. These changes were not seen in the recovery groups.
- The systemic NOAEL was 200 mg/kg/day (50 mg/kg/dose) based on mild degeneration/atrophy of the testis, moderate thrombus in the kidney as well as moderate hemorrhage, severe thrombus, and moderate fibrosis of the liver in the 400 mg/kg/day dose group. The local NOAEL was 400 mg/kg/day administered at a concentration of 10 mg/mL.

**Methods**

| | |
|---|---|
| Doses: | 0, 80, 200, and 400 mg/kg/day |
| Frequency of dosing: | 4 times/day over a 15-minute infusion each time |
| Route of administration: | IV infusion |
| Dose volume: | 10 (vehicle control), 2, 5, and 10 mg/kg/dose |
| Formulation/Vehicle: | 0.9% NaCl Injection, USP (saline) |
| Species/Strain: | Rat/Crl:CD(SD) Sprague Dawley rats |
| Number/Sex/Group: | 10/sex/group of which 5/sex/group each from the saline control, Ofirmev® control, and high dose group were used for recovery. It is important to note that the recovery groups includes the saline control, Ofirmev® control, and the 400 mg/kg/day ivAPAP dose groups and not the 80 and 200 mg/kg/day ivAPAP dose groups. As such, evaluation of all recovery dose groups was not performed. |
| Age: | 12 weeks |
| Weight: | 286-421 g (males); 215-281 g (females) |
| Satellite groups: | 3/sex for the saline control and 6/sex/group for the treatment groups were used for toxicokinetics |
| Unique study design: | The vehicle control, positive control (Ofirmev®), and high dose 400 mg/kg/day ivAPAP were used for recovery |
| Deviation from study protocol: | See below |

**Deviations:**

The following deviations were noted by the Study Director:

***Formulation and Dosing:***

- The names of the Test Item were not written on the label of the end of use samples. All appropriate information to attribute the sample to an analysis timepoint was included.

***Surgery:***

- There were no data to confirm that the surgery wound of Animal No. 2519 was flushed with saline before being sutured. Animal No. 2519 recovered well from the surgery.
- On Day 13, no antibiotics were given to Animal No. 3003 following surgical repair. Animal No. 3003 was in good general condition following surgery.

***In-life Observations, Measurements, and Evaluations:***

- On occasion, a detailed examination was performed on toxicokinetic animals although not required.
- On occasion, the food consumption could not be evaluated as the remaining food of some animals was not weighed. Sufficient data are available for adequate food consumption evaluation.

***Laboratory Evaluations:***

- On Day 1, the 6 hours post-dose TK sample of Animal Nos. 2121, 2617, and 4612 were collected after the second daily dose administration.



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- On Day 1, the 6 hours post-dose TK sample of Animal No. 2617 was processed the following day.
- On Day 1, the 5 minutes post-dose TK sample of Animal No. 2021 was collected 2 minutes late. The animal was replaced.
- Animal No. 2021 was unnecessarily bled at 6 hours post-dose as it has been replaced.
- On Day 28, the 5 minutes post-dose TK sample of Animal No. 2020 was collected 2 minutes early as the linefill was not given prior to dosing.
- On Day 28, the 5 minutes, 1 and 6 hours post-dose TK sample of Animal No. 4612 were collected too early as the animal was dosed over 25 minutes.
- On occasion, blood samples were collected at termination unnecessarily.

***Postmortem and Pathology:***

- The lungs of Animal Nos. 3508 and 4501 were infused before weighing
- Some tissues were not available for microscopic evaluation.

None of these deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

The following table illustrates the experimental design (from the Applicant's submission):

Experimental Design

| Group No./ Test Material | Dose Level (mg/kg/day) | Dose Level (mg/kg/dose) | Dose Volume (mL/kg/dose) | Dose Conc. (mg/mL) | Dose Rate (mL/kg/hr) | No. of Animals | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Main (Recovery) Study | | TK Study | |
| | | | | | | M | F | M | F |
| 1/Saline Control | 0 | 0 | 10 | 0 | 40 | 10 (5) | 10 (5) | 3 | 3 |
| 2/Ofirmev RLD | 400 | 100 | 10 | 10 | 40 | 10 (5) | 10 (5) | 6 | 6 |
| 3/Braun ivAPAP | 80 | 20 | 2 | 10 | 10 | 10 | 10 | 6 | 6 |
| 4/Braun ivAPAP | 200 | 50 | 5 | 10 | 20 | 10 | 10 | 6 | 6 |
| 5/Braun ivAPAP | 400 | 100 | 10 | 10 | 40 | 10 (5) | 10 (5) | 6 | 6 |

Conc. : Concentration; M: males; F: females; TK : toxicokinetic

It is noted that the test article is designated as ivAPAP. Prior to the initiation of the dosing period, catheters were surgically implanted into each rat. The catheter was inserted in the vena cava at approximately the level of the kidneys and brought subcutaneously to the exteriorization point at the nape of the neck.

## Observations and Results

### Mortality

Rats were observed for general health/mortality and moribundity twice daily. There were 3 unscheduled deaths in the study, 2 in the comparator group (male No. 2010 and female No. 2509) and 1 in the low dose female 80 mg/kg/day dose group (female No. 3505).

A male (No. 2010) in the comparator group (i.e., Ofirmev®) was euthanized on Day 11 due to clinical observations of skin pallor and cool to the touch. Clinical pathology changes include increased liver enzymes, lymphocytes, coagulation parameters, and fibrinogen as well as decreased red cell mass parameters and platelets. Gross pathology changes include a blood clot around the brain, dark focus in the sclera of the left eye, adrenal gland enlargement, dark discoloration and pale foci in the kidney, pale foci in the liver, lung discoloration, and thickening around the infusion site. Microscopic findings include hemorrhage in numerous locations (brain, spinal cord, eye, and lungs), adrenal gland hypertrophy, mixed inflammatory cell infiltrates in the kidney with numerous bacterial colonies, and necrosis in the liver. The presence of hemorrhage in multiple tissues, liver necrosis, and kidney inflammation with bacteria is consistent with sepsis, possibly originating from the infusion site, leading to the moribundity/death of this rat as per the Pathology Report.

A control female (No. 2509) from the comparator group was found dead on Day 16 with no prior clinical signs; however, labored breathing and skin pallor was observed on Day 12. A single gross pathology finding was a dark focus in the subcutis of the left hindlimb which extended to the adjacent muscle. Microscopic findings include mononuclear cell infiltrates, multifocal necrosis, and hemorrhage in the liver, and hemorrhage in the subcutis of the left hindlimb. A cause of death was not determined as per the Pathology Report.

The female from the low dose 80 mg/kg/day dose ivAPAP group (No. 3505) was sacrificed on Day 24 with decreased activity, labored breathing, and abnormal respiratory sounds. Clinical pathology changes include increases in ALT, glucose, and triglycerides. There were no gross pathology changes. Microscopic findings include mixed inflammatory cell infiltrates in the lumen of the trachea and thrombus formation at the infusion site. A cause of death was not determined. As this early termination was noted in a single low-dose female and not in other dosing groups, it was not considered treatment-related as per the Pathology Report.

As these unscheduled deaths occurred in the comparator (Ofirmev®) group and in the low dose 80 mg/kg/day ivAPAP dose group, these incidences of unscheduled deaths are not considered treatment-related.

**Clinical Signs**

Detailed clinical observations were performed weekly.

On Day 10, one male from the comparator group was noted with red urine. There were no further occurrences of this finding for this dose group or any other dose group. According to the Pathology Report, this finding is considered incidental. Observations across all groups and sexes include teeth caught in infusion jacket, dehydration, wet fur on lower jaw, skin changes (redness, lesions, and scabs), unkept and/or ungroomed fur, and hypersensitivity. According to the Pathology Report, these findings were considered procedure-related and commonly seen in rats. All other observations were

not considered treatment-related because they were observed in the vehicle control, occurred in isolated incidence without dose dependency, or are typically observed in rats of this age and strain.

Thus, there were no treatment-related changes in clinical signs.

**Body Weights**

Rats were weighed weekly. A fasted weight was recorded on the day of necropsy. Terminal body weights were not recorded for rats found dead. There were no treatment-related changes in body weights.

**Food Consumption**

Food consumption was quantitatively measured weekly throughout the dosing and recovery periods. There were no treatment-related changes in food consumption.

**Ophthalmoscopy**

Ophthalmic examinations were performed once prestudy and again during Week 4. There were no treatment-related changes in ophthalmology.

**ECG**

ECG was not performed in this study.

**Hematology**

Rats were fasted overnight before blood sampling. Blood was collected from the abdominal aorta for hematology, coagulation, and clinical chemistry. Blood and urine samples were collected according to the following table (from the Applicant's submission):

Text Table 5
Samples for Clinical Pathology Evaluation

| Group Nos. | Time Point | Hematology | Coagulation | Clinical Chemistry | Urinalysis |
|---|---|---|---|---|---|
| 1 to 5 | Day 29[a] | X | X | X | X |
| 1, 2 and 5 | End of recovery | X | X | X | X |
| Unscheduled euthanasia (when possible) | Before euthanasia | X | X | X | - |

X = Sample collected; - = Not applicable.
[a] Samples were only collected from those animals scheduled for euthanasia on Day 29.

The following hematology and coagulation parameters were measured (from the Applicant's submission):



Reference ID: 4154306

Text Table 6
Hematology Parameters

| | |
|---|---|
| Red blood cell count<br>Hemoglobin concentration<br>Hematocrit<br>Mean corpuscular volume<br>Red Blood Cell Distribution Width<br>Mean corpuscular hemoglobin concentration<br>Mean corpuscular hemoglobin<br>Reticulocyte count (absolute) | Platelet count<br>White blood cell count<br>Neutrophil count (absolute)<br>Lymphocyte count (absolute)<br>Monocyte count (absolute)<br>Eosinophil count (absolute)<br>Basophil count (absolute)<br>Large unstained cells |

Text Table 7
Coagulation Parameters

| | |
|---|---|
| Activated partial thromboplastin time<br>Fibrinogen | Prothrombin time<br>Sample quality |

The following table illustrates the changes in hematology (data from the Applicant's submission):

**Table 19: Hematology Findings**

| **Treatment Group** | **Day 29** | | | **Recovery** |
|---|---|---|---|---|
| | **MCHC (g/dL)** | **RDW (%)** | | **EOS ($10^3$/mcL)** |
| 1M | 33.8 (0%) | 13.5 (0%) | | 0.19 (0%) |
| 2M | **33.0 (-2.4%)** | **15.6 (+15.6%)** | | 0.16 (-15.8%) |
| 3M | 33.6 (-0.6%) | 13.1 (+3.0%) | | N/A |
| 4M | 33.6 (-0.6%) | 14.0 (+3.7%) | | N/A |
| 5M | **33.0 (-2.4%)** | **14.8 (+9.6%)** | | **0.11 (-42.1%)** |
| | **MCV (fL)** | **MCH (pg)** | **RDW (%)** | **MCH (pg)** |
| 1F | 54.5 (0%) | 18.5 (0%) | 11.7 (0%) | 18.4 (0%) |
| 2F | **57.3 (+5.1%)** | **19.3 (+4.3%)** | **13.5 (+15.4%)** | **18.1 (-1.6%)** |
| 3F | 54.4 (-0.2%) | 18.4 (-0.5%) | 12.3 (+1.7%) | N/A |
| 4F | **55.9 (+2.6%)** | 18.9 (+2.2%) | 12.3 (+5.1%) | N/A |
| 5F | **56.5 (+3.7%)** | 18.8 (+1.6%) | **13.3 (+13.7%)** | 18.8 (+2.2%) |

M = male
F = female
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
3 = Braun ivAPAP 80 mg/kg/day
4 = Braun ivAPAP 200 mg/kg/day
5 = Braun ivAPAP 400 mg/kg/day
N/A = not applicable

In the treatment males at the end of the treatment period (Day 29), there was a significant decrease in the mean corpuscular hemoglobin concentration (MCHC) and a significant increase in the red blood cell distribution width (RDW) in the male ivAPAP 400 mg/kg/day dose group compared to saline control but was comparable to the Ofirmev® comparator group. The changes in MCHC are within historical controls for

this strain of rat (Derelanko, 2008) and as such, do not represent a safety concern and are not considered treatment-related. There were no further treatment-related hematology changes in the males at the end of the treatment period. The only changes in the recovery males was a significant increase in the eosinophil count (EOS) in the ivAPAP 400 mg/kg/day recovery male dose group with no further treatment-related hematology changes in the recovery males.

In the treatment females at the end of the treatment period (Day 29), there was a significant dose-dependent increase in the mean corpuscular volume (MCV) in the ivAPAP 200 and 400 mg/kg/day dose groups as well as a significant increase in the RDW in the ivAPAP 400 mg/kg/day dose group compared to saline control but was comparable to the Ofirmev® comparator group. Moreover, there was a significant increase in the mean corpuscular hemoglobin (MCH) in the Ofirmev® control compared to saline control. There were no further treatment-related hematology changes in the females at the end of the treatment period. The only changes in the recovery females was a significant decrease in MCH in the Ofirmev® control with no further treatment-related hematology changes in the recovery females. As such, the changes in MCH were not related to ivAPAP in the treatment and recovery females as the observation was only seen in the Ofirmev® control. Changes in MCV and MCH are within historical controls for this strain of rat (Derelanko, 2008) and as such, do not represent a safety concern and are not treatment-related.

The differences in hematology parameters were judged to be due to biological or individual variation or considered unrelated to ivAPAP based on the inconsistency of the changes.

There were no treatment-related changes in the coagulation parameters in the main study and recovery groups.

**Clinical Chemistry**

The following clinical chemistry parameters were measured (from the Applicant's submission):

Text Table 8
Clinical Chemistry Parameters

| | |
|---|---|
| Alanine aminotransferase | Albumin |
| Aspartate aminotransferase | Globulin |
| Alkaline phosphatase | Albumin/globulin ratio |
| Gamma-glutamyltransferase | Glucose |
| Creatine Kinase | Cholesterol |
| Total bilirubin[a] | Triglycerides |
| Urea nitrogen | Sodium |
| Creatinine | Potassium |
| Calcium | Chloride |
| Phosphorus | Sample quality |
| Total protein | |

[a] When total bilirubin was > 0.5 mg/dL, indirect and direct bilirubin were also measured.



Reference ID: 4154306

The following table illustrates the changes in clinical chemistry at the end of the treatment period on Day 29 (data from the Applicant's submission):

**Table 20: Clinical Chemistry Findings**

| Treatment Group | Day 29 | |
|---|---|---|
| | **Na (mmol/L)** | **K (mmol/L)** |
| 1M | 144 (0%) | 4.5 (0%) |
| 2M | **143 (-0.69%)** | 5.2 (+15.6%) |
| 3M | 144 (0%) | 4.8 (+6.7%) |
| 4M | 144 (0%) | **5.0 (+11.1%)** |
| 5M | 145 (+0.69%) | **4.9 (+8.9%)** |
| | **Phos (mg/dL)** | |
| 1F | 7.9 (0%) | |
| 2F | 8.7 (+10.1%) | |
| 3F | 7.8 (-1.3%) | |
| 4F | 8.6 (+8.9%) | |
| 5F | **9.0 (+13.9%)** | |

M = male
F = female
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
3 = Braun ivAPAP 80 mg/kg/day
4 = Braun ivAPAP 200 mg/kg/day
5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, there was a significant decrease in sodium (Na) levels in the Ofirmev® control group in the main study males compared to saline control. As such, the changes in sodium levels were not related to ivAPAP in the treatment males as the observation was only seen in the Ofirmev® control. There was a significant increase in the potassium (K) levels in the male 200 and 400 mg/kg/day ivAPAP groups in the main study compared to saline control. In females, there was a significant increase in phosphate (Phos) levels in the 400 mg/kg/day ivAPAP dose group in the main study compared to saline control. Changes in the sodium, potassium, and phosphate levels are all within historical controls (Derelanko, 2008) and as such, do not represent a safety concern and are not treatment-related.

There were no treatment-related changes in clinical chemistry in the recovery groups.

### Urinalysis

Urine was collected overnight from individually housed rats. Rats were deprived of food during urine collection. The following urinalysis parameters were measured (from the Applicant's submission):

Text Table 9
Urinalysis Parameters

| | |
|---|---|
| Color<br>Appearance/Clarity<br>Specific gravity<br>pH<br>Protein | Glucose<br>Bilirubin<br>Ketones<br>Blood |

The following table illustrates the changes in urinalysis at the end of the treatment period on Day 29 (data from the Applicant's submission):

**Table 21: Urinalysis Findings**

| Treatment Group | Day 29 Specific Gravity |
|---|---|
| 1M | 1.017 (0%) |
| 2M | **1.025 (+0.79%)** |
| 3M | **1.026 (+0.88%)** |
| 4M | **1.022 (+0.49%)** |
| 5M | **1.024 (+0.69%)** |
| | **Specific Gravity** |
| 1F | 1.018 (0%) |
| 2F | **1.027 (+0.88%)** |
| 3F | **1.022 (+0.39%)** |
| 4F | 1.025 (+0.69%) |
| 5F | **1.023 (+0.49%)** |

M = male
F = female
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
3 = Braun ivAPAP 80 mg/kg/day
4 = Braun ivAPAP 200 mg/kg/day
5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, there was a significant increase in specific gravity in all ivAPAP dose groups in the males as well as in the 80 and 400 mg/kg/day ivAPAP dose groups in the females, compared to saline control, in the main study. Changes in specific gravity are within historical controls (Derelanko, 2008) and as such, do not represent a safety concern and are not treatment-related.

There were no treatment-related changes in urinalysis in the recovery groups.

**Gross Pathology**

*Main Study*
On the day of scheduled sacrifice, main study and recovery rats were subjected to a complete necropsy examination, which included an evaluation of the carcass and



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musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and the thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

The following table illustrates the necropsy findings in the main study groups (adapted from the Applicant's submission):

**Table 22: Gross Findings in the Main Study**

| Removal Reason: TERMINAL EUTHANASIA | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 |
| Number of Animals: | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| **GLAND, ADRENAL** | | | | | | | | | | |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| **GLAND, PROSTATE** | | | | | | | | | | |
| Focus; pale | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| Discoloration; pale | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| **GLAND, SEMINAL VESICLE** | | | | | | | | | | |
| Discoloration; pale | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| **LARGE INTESTINE, CECUM** | | | | | | | | | | |
| Dilatation | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **LIVER** | | | | | | | | | | |
| Small | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mass | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **LUNG** | | | | | | | | | | |
| Focus; dark | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| **LYMPH NODE** | | | | | | | | | | |
| Enlargement | 1 | 4 | 1 | 1 | 2 | . | 2 | 1 | 1 | 2 |
| Discoloration; dark | 0 | 1 | 0 | 1 | 0 | . | 0 | 0 | 0 | 0 |
| Swelling | 0 | 1 | 0 | 0 | 0 | . | 0 | 0 | 0 | 0 |
| **SMALL INTESTINE, JEJUNUM** | | | | | | | | | | |
| Diverticulum | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **SPLEEN** | | | | | | | | | | |
| Enlargement | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **STOMACH** | | | | | | | | | | |
| Focus; dark | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| **TESTIS** | | | | | | | | | | |
| Enlargement | 0 | 1 | 0 | 0 | 0 | . | . | . | . | . |
| **THYMUS** | | | | | | | | | | |
| Focus; dark | 1 | 0 | 0 | 1 | 3 | 0 | 1 | 0 | 0 | 0 |
| Small | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **URINARY BLADDER** | | | | | | | | | | |
| Thick | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **UTERUS** | | | | | | | | | | |
| Cyst; pale | . | . | . | . | . | 0 | 1 | 0 | 0 | 0 |

As shown in the table above, enlargement of the lymph node in the ivAPAP groups (4/20 in the 400 mg/kg/day male and female groups) were of lower incidence compared

to the Ofirmev® control, which does not represent a greater risk with the proposed product. A dark focus in the stomach was observed at an incidence of 1/10 in the male 200 mg/kg/day dose group in of 1/10 in the female 400 mg/kg/day dose group as well as in the thymus at an incidence of 3/10 in the male 400 mg/kg/day dose group. These findings were dismissed in the Pathology Report as a common observation in Sprague Dawley rats of similar age.

Enlargement of the adrenal gland, pale focus and discoloration in the prostate gland, discoloration of the seminal vesicle, small liver and mass on liver, a dark focus in the lung, swelling and dark discoloration of the lymph node, diverticulum of the jejunum in the small intestine, enlargement of the spleen, enlargement of the testis, small thymus, and a cyst in the uterus were only observed in the Ofirmev® control group. As such, these findings were not considered ivAPAP treatment-related.

In addition, there were a number of infusion site observations in the main study as shown in the table below (adapted from the Applicant's submission):

**Table 23: Infusion Site Gross Findings in the Main Study**

| Removal Reason: TERMINAL EUTHANASIA | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 |
| Number of Animals: | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| **SITE, INFUSION** | | | | | | | | | | |
| Submitted | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Thick | 3 | 0 | 1 | 2 | 2 | 2 | 4 | 2 | 1 | 1 |
| Mass | 1 | 4 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 3 |
| Swelling | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Abnormal consistency; firm | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

The infusion site was described as thick, mass, swelling, and/or abnormal consistency (firm) with similar incidence between the controls and B Braun ivAPAP groups. In fact, the incidence of thick, mass, and swelling was greater in the Ofirmev® control compared to any of the B Braun ivAPAP groups, demonstrating that B Braun ivAPAP did not pose a greater risk compared to Ofirmev®. These infusion site findings were not observed in the recovery groups. These observations at the infusion site were considered procedural and not treatment-related.

*Recovery*

The following table illustrates the necropsy findings in the recovery groups (adapted from the Applicant's submission):

**Table 24: Gross Findings in Recovery**

| Removal Reason: RECOVERY EUTHANASIA | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 400 mg/kg /day Group 5 |
| Number of Animals: | 5 | 5 | 5 | 5 | 5 | 5 |
| **GLAND, PITUITARY** | | | | | | |
| Enlargement | 0 | 0 | 0 | 0 | 0 | 1 |
| **LUNG** | | | | | | |
| Focus; pale | 0 | 0 | 1 | 0 | 0 | 0 |
| **TESTIS** | | | | | | |
| Small | 0 | 1 | 1 | . | . | . |
| **THYMUS** | | | | | | |
| Focus; dark | 0 | 0 | 0 | 0 | 1 | 1 |

As shown in the table above, small testis was observed in the Ofirmev® control and the male recovery 400 mg/kg/day ivAPAP groups as well as pale focus in the lung in the male recovery 400 mg/kg/day ivAPAP group compared to none in the recovery saline control. A dark focus in the thymus was observed in the Ofirmev® control and the female recovery 400 mg/kg/day ivAPAP groups as well as pituitary gland enlargement in the female recovery 400 mg/kg/day ivAPAP group compared to none in the recovery saline control. Small testis correlated with the microscopic findings of testicular degeneration/atrophy. All other gross findings were dismissed in the Pathology Report.

### Organ Weights

The following organ weights were taken and recorded (from the Applicant's submission):

Text Table 14
Organs Weighed at Necropsy

| | |
|---|---|
| Brain | Liver |
| Epididymis[a] | Lung[b] |
| Gland, adrenal[a] | Ovary[a] |
| Gland, pituitary | Spleen |
| Gland, prostate | Testis[a] |
| Gland, thyroid | Thymus |
| Heart | Uterus |
| Kidney[a] | |

[a] Paired organ weight.
[b] For exception, see Appendix 1.

The following organ weight parameters were calculated (from the Applicant's submission):

| | |
|---|---|
| Body Weight Gains | Calculated between at least each interval as well as between the beginning and end of each phase. |
| Organ Weight Relative to Body Weight | Calculated against the terminal body weight for scheduled intervals. |
| Organ Weight Relative to Brain Weight | Calculated against the brain weight for scheduled intervals. |

*Main Study*
There were increases in the spleen organ weight parameters (absolute, spleen to body weight ratio, and spleen to brain weight ratio) in the male and female 400 mg/kg/day Ofirmev® control group as shown in the following table (adapted from the Applicant's submission):

**Table 25: Spleen Organ Weight Parameter Changes in the Main Study**

| Spleen Organ Weight Parameter Changes (Main Study) | | | | |
|---|---|---|---|---|
| **Treatment Group** | | **Absolute Weight (g)** | **Spleen to Body Weight Ratio** | **Spleen to Brain Weight Ratio** |
| 1M | Mean<br>% change | 0.816<br>0 | 0.1966<br>0 | 39.0388<br>0 |
| 2M | Mean<br>% change | **1.059**<br>**+29.8%** | **0.2644**<br>**+34.5%** | **50.9398**<br>**+30.5%** |
| 3M | Mean<br>% change | 0.886<br>+8.58% | 0.2082<br>+5.90% | 41.8741<br>+7.26% |
| 4M | Mean<br>% change | 0.818<br>+0.245% | 0.1987<br>+1.07% | 38.8251<br>-0.546% |
| 5M | Mean<br>% change | 0.813<br>-0.368% | 0.1973<br>+0.356% | 39.4054<br>+0.939% |
| 1F | Mean<br>% change | 0.576<br>0 | 0.2198<br>0 | 29.9179<br>0 |
| 2F | Mean<br>% change | **0.799**<br>**+38.7%** | **0.3025**<br>**+37.6%** | **40.9992**<br>**+37.0%** |
| 3F | Mean<br>% change | 0.493<br>-14.4% | 0.1922<br>-12.6% | 25.1016<br>-16.1% |
| 4F | Mean<br>% change | 0.568<br>-1.39% | 0.2177<br>-0.955% | 28.6767<br>-4.15% |
| 5F | Mean<br>% change | 0.656<br>+13.8% | 0.2489<br>+13.2% | 33.7685<br>+12.9% |

M = male
F = female
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
3 = Braun ivAPAP 80 mg/kg/day
4 = Braun ivAPAP 200 mg/kg/day

5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, the spleen organ weight parameters (absolute weight, spleen to body weight ratio, and spleen to brain weight ratio) were significantly increased in both the male and female Ofirmev® control groups (Group 2) compared to the saline control. However, there were no treatment-related changes in the spleen organ weight parameters in any of the ivAPAP groups.

There was an increase in the testis to body weight ratio in the male 400 mg/kg/day Ofirmev® control group as shown in the following table (adapted from the Applicant's submission):

**Table 26: Testis-to-Body-Weight Ratio Changes in the Main Study**

| Testis to Body Weight Ratio in Main Study | | |
|---|---|---|
| **Treatment Group** | | **Testis to Body Weight Ratio** |
| 1M | Mean<br>% change | 0.7923<br>0% |
| 2M | Mean<br>% change | **0.8616**<br>**+8.75%** |

M = male
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)

As shown in the table above, the increase in the testis to body weight ratio in the male 400 mg/kg/day Ofirmev® control group is statistically significant, compared to saline control. However, there were no treatment-related changes to the absolute testis weight and the testis to brain weight ratio. Moreover, there were no treatment-related changes to the testis organ weight parameters (absolute organ weight, organ to body weight ratio, and organ to brain weight ratio) in any of the ivAPAP groups.

As the changes in the organ weight parameters in the spleen and testis only occurred in the Ofirmev® control, these changes are not ivAPAP treatment-related. There were no further treatment-related changes in the organ weight parameters in the BBraun ivAPAP groups in the main study.

*Recovery*
The following table illustrates other treatment-related changes in the absolute organ weight in the recovery groups (adapted from the Applicant's submission):

**Table 27: Spleen Organ Weight Parameter Changes in Recovery**

| Spleen Organ Weight Parameters (Recovery) | | | | |
|---|---|---|---|---|
| **Treatment Group** | | **Absolute Weight (g)** | **Spleen to Body Weight Ratio** | **Spleen to Brain Weight Ratio** |
| 1F | Mean | 0.540 g | 0.2047 | 27.1890 |

| | | | | |
|---|---|---|---|---|
| | % change | 0% | 0% | 0% |
| 2F | Mean<br>% change | 0.566 g<br>+4.81% | 0.2122<br>+3.66% | 29.1176<br>+7.09% |
| 5F | Mean<br>% change | **0.683 g**<br>**+26.5%** | **0.2418**<br>**+18.1%** | **33.2094**<br>**+22.1%** |

F = female
1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, the absolute spleen weight in the female ivAPAP 400 mg/kg/day recovery group was significantly increased compared to control. As noted below, there were no histopathological correlates noted in the Group 5 spleens.

The following table summarizes the treatment-related changes in testis organ weight parameters in the recovery groups (from the Applicant's submission):

**Table 28: Summary of Testis Organ Weight Data in Recovery**

Summary of Organ Weight Data - Scheduled Euthanasia (Day 43)

| | Males | |
|---|---|---|
| **Group** | **2** | **5** |
| **Dose (mg/kg/day)** | **400** | **400** |
| **No. Animals per Group** | **5** | **5** |
| **Testis (No. Weighed)[a]** | 5 | 5 |
| Absolute value | -17 | -16 |
| % of body weight | -12 | -10 |
| % of brain weight | -15 | -14 |

2 = Ofirmev® control (400 mg/kg/day)
5 = Braun ivAPAP 400 mg/kg/day
a = All values expressed as percent difference of control group means

The changes in testis organ weight parameters are not statistically significant between the Ofirmev® control and 400 mg/kg/day ivAPAP groups and do not appear to represent a greater risk compared to the Ofirmev® control.

There was a significant increase in the prostate to body weight ratio in the recovery male 400 mg/kg/day ivAPAP group as shown in the table below (adapted from the Applicant's submission):

**Table 29: Prostate-to-Body-Weight Ratio Changes in Recovery**

| **Prostate to Body Weight Ratio in Recovery** | | |
|---|---|---|
| **Treatment Group** | | **Prostate to Body Weight Ratio** |
| 1M | Mean<br>% change | 0.2885<br>0% |
| 5M | Mean | **0.3622** |

| | | |
|---|---|---|
| | % change | +25.5% |

M = male
1 = Saline control
5 = Braun ivAPAP 400 mg/kg/day

There were no further changes in the organ weight parameters in the recovery groups.

**Histopathology**

Adequate Battery
The following tissues and organs were examined microscopically (from the Applicant's submission):

Text Table 15
Tissue Collection and Preservation

| | |
|---|---|
| Administration (infusion) site | Large intestine, colon |
| Animal identification | Large intestine, rectum |
| Artery, aorta | Larynx |
| Bone marrow smear | Liver |
| Bone marrow | Lung |
| Bone, femur | Lymph node, mandibular |
| Bone, sternum | Lymph node, mesenteric |
| Brain | Small intestine, duodenum |
| Cervix | Small intestine, ileum |
| Epididymis | Small intestine, jejunum |
| Esophagus | Muscle, skeletal |
| Eye | Nerve, optic[a] |
| Gland, adrenal | Nerve, sciatic |
| Gland, harderian | Ovary |
| Gland, mammary | Pancreas |
| Gland, parathyroid | Skin |
| Gland, pituitary | Spinal cord |
| Gland, prostate | Spleen |
| Gland, salivary | Stomach |
| Gland, seminal vesicle | Testis[b] |
| Gland, thyroid | Thymus |
| Gross lesions/masses | Tongue |
| Gut-associated lymphoid tissue | Trachea |
| Heart | Urinary bladder |
| Kidney | Uterus |
| Large intestine, cecum | Vagina |

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.

This is an adequate battery of organs and tissues for histopathology. It is noted that 7 slices of the brain were microscopically examined.

Peer Review
The Pathology Report was peer reviewed and signed (signature provided on November 23, 2016).

Histological Findings

*Main Study*

The following table illustrates the microscopic findings at the scheduled sacrifice of the main study rats (from the Applicant's submission):

**Table 30: Summary of Microscopic Findings in the Main Study**

Text Table 4
Summary of Microscopic Findings - Scheduled Euthanasia (Day 29)

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **5** | **1** | **2** | **3** | **4** | **5** |
| **Dose (mg/kg/day)** | **0** | **400** | **80** | **200** | **400** | **0** | **400** | **80** | **200** | **400** |
| **No. Animals Examined** | **10** | **9** | **10** | **10** | **10** | **10** | **9** | **9** | **10** | **10** |
| **Site, Infusion (No. Examined)** | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Thrombus | (7)[a] | (6) | (5) | (5) | (5) | (8) | (3) | (3) | (5) | (7) |
| Minimal | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| Mild | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 3 |
| Moderate | 4 | 1 | 2 | 0 | 2 | 1 | 0 | 1 | 1 | 1 |
| Marked | 0 | 2 | 1 | 3 | 3 | 1 | 1 | 1 | 1 | 0 |
| Severe | 1 | 2 | 1 | 2 | 0 | 1 | 1 | 0 | 2 | 3 |
| **Testis (No. Examined)** | 10 | 9 | 10 | 10 | 10 | - | - | - | - | - |
| Degeneration/Atrophy | (1) | (4) | (2) | (2) | (5) | - | - | - | - | - |
| Minimal | 1 | 4 | 2 | 2 | 3 | - | - | - | - | - |
| Mild | 0 | 0 | 0 | 0 | 2 | - | - | - | - | - |
| **Epididymis (No. Examined)** | 10 | 9 | 10 | 10 | 10 | - | - | - | - | - |
| Cellular debris | (0) | (0) | (0) | (1) | (1) | - | - | - | - | - |
| Minimal | 0 | 0 | 0 | 1 | 0 | - | - | - | - | - |
| Mild | 0 | 0 | 0 | 0 | 1 | - | - | - | - | - |

1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
3 = Braun ivAPAP 80 mg/kg/day
4 = Braun ivAPAP 200 mg/kg/day
5 = Braun ivAPAP 400 mg/kg/day
a = Numbers in parentheses represent the number of animals with the finding

As shown in the table above, the microscopic changes at the infusion site (thrombus) was observed in all treatment groups and was comparable to the Ofirmev® control in incidence and severity. Degeneration/atrophy of the testis was observed in all treatment groups; however, the finding was slightly higher in incidence and severity in the male 400 mg/kg/day ivAPAP dose group. Cellular debris in the epididymis was observed in the male 200 and 400 mg/kg/day ivAPAP dose groups compared to none in the saline and Ofirmev® controls. Although these slight increases in incidence and severity were noted for cellular debris in the epididymis, it does not seem that this proposed formulation would represent a greater risk than Ofirmev®.

*Recovery*

The following table illustrates the microscopic findings in the recovery rats (from the Applicant's submission):

**Table 31: Summary of Microscopic Findings in Recovery**

Text Table 5
Summary of Microscopic Findings - Scheduled Euthanasia (Day 43)

| | Males | | |
|---|---|---|---|
| **Group** | **1** | **2** | **5** |
| **Dose (mg/kg/day)** | **0** | **400** | **400** |
| **No. Animals Examined** | **5** | **5** | **5** |
| **Testis (No. Examined)** | 5 | 5 | 5 |
| Degeneration/Atrophy | (0)[a] | (3) | (2) |
| Minimal | 0 | 2 | 1 |
| Moderate | 0 | 1 | 1 |
| **Epididymis (No. Examined)** | 5 | 5 | 5 |
| Cellular debris | (0) | (1) | (1) |
| Mild | 0 | 1 | 1 |

1 = Saline control
2 = Ofirmev® control (400 mg/kg/day)
5 = Braun ivAPAP 400 mg/kg/day
a = Numbers in parentheses represent the number of animals with the finding

As shown in the table above, degeneration/atrophy in the testis was observed in the Ofirmev® control and the recovery male 400 mg/kg/day ivAPAP dose group at similar incidence and severity. Cellular debris in the epididymis was observed in the Ofirmev® control and the recovery male 400 mg/kg/day ivAPAP dose group at similar incidence and severity. These findings do not represent a greater risk compared to Ofirmev®.

The following table illustrates the other findings at the infusion site (adapted from the Applicant's submission):

**Table 32: Other Findings at the Infusion Site in the Main Study**

| Removal Reason: TERMINAL EUTHANASIA | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 |
| Number of Animals: | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| **SITE, INFUSION** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Infiltrate, mixed cell, vascular/perivascular | 2 | 2 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| .... minimal | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| .... mild | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| .... moderate | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... marked | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | 2 | 1 | 4 | 1 | 3 | 0 | 0 | 0 | 1 | 0 |
| .... minimal | 1 | 0 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 0 |
| .... mild | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... moderate | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Necrosis | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... severe | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fibrosis | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... marked | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intimal proliferation | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| .... minimal | 1 | 2 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| .... mild | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

In addition, the following table illustrates other microscopic findings in the main study (adapted from the Applicant's submission):

## Table 33: Additional Microscopic Findings in the Main Study

| Removal Reason: TERMINAL EUTHANASIA | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 80 mg/kg /day Group 3 | 200 mg/kg /day Group 4 | 400 mg/kg /day Group 5 |
| Number of Animals: | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| **EPIDIDYMIS** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | . | . | . | . | . |
| Infiltration, mononuclear cell | 0 | 0 | 0 | 0 | 1 | . | . | . | . | . |
| .... minimal | 0 | 0 | 0 | 0 | 1 | . | . | . | . | . |
| **GLAND, ADRENAL** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Vacuolation; zona fasciculata | 0 | 4 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| .... minimal | 0 | 4 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| **GLAND, HARDERIAN** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Infiltration, mononuclear cell | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **GLAND, PITUITARY** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Cyst | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| .... minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **KIDNEY** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Chronic progressive nephropathy | 0 | 3 | 2 | 2 | 3 | 1 | 2 | 1 | 0 | 1 |
| .... minimal | 0 | 2 | 2 | 2 | 3 | 1 | 1 | 1 | 0 | 1 |
| .... mild | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Infiltration, mixed cell | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| .... minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Dilatation, pelvis | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 0 | 0 |
| .... minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| .... mild | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Thrombus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **LIVER** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Necrosis | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... marked | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infiltration, mononuclear cell | 9 | 8 | 9 | 9 | 8 | 7 | 8 | 7 | 8 | 8 |
| .... minimal | 9 | 8 | 9 | 9 | 7 | 7 | 7 | 7 | 7 | 8 |
| .... mild | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Tension lipidosis | 1 | 0 | 0 | 2 | 0 | 1 | 3 | 1 | 1 | 2 |
| .... minimal | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 1 | 0 | 0 |
| .... mild | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 |
| .... moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .... moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Thrombus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| .... moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **LYMPH NODE** | | | | | | | | | | |
| Examined | 1 | 3 | 1 | 2 | 2 | 0 | 2 | 1 | 1 | 2 |
| Hyperplasia; lymphoid | 1 | 3 | 0 | 2 | 1 | . | 2 | 1 | 1 | 2 |
| .... mild | 1 | 1 | 0 | 2 | 1 | . | 2 | 1 | 1 | 1 |
| .... moderate | 0 | 1 | 0 | 0 | 0 | . | 0 | 0 | 0 | 1 |
| .... severe | 0 | 1 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| **SPLEEN** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| Increased hematopoiesis | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 2 |
| .... mild | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 2 |
| **THYMUS** | | | | | | | | | | |
| Examined | 10 | 9 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 |
| No Visible Lesions | 9 | 5 | 7 | 9 | 8 | 9 | 6 | 8 | 7 | 9 |
| Hemorrhage | 1 | 3 | 3 | 1 | 2 | 1 | 2 | 1 | 3 | 1 |
| .... minimal | 1 | 3 | 3 | 1 | 1 | 1 | 2 | 1 | 3 | 1 |
| .... mild | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Group 1 = Saline control
Group 2 = Ofirmev® control (400 mg/kg/day)
Group 3 = Braun ivAPAP 80 mg/kg/day
Group 4 = Braun ivAPAP 200 mg/kg/day
Group 5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, single incidences of findings were reported that included minimal mononuclear cell infiltration in the epididymis, mild mononuclear cell infiltration in the Harderian gland, cyst in the pituitary, dilatation of the pelvis and moderate thrombus in the kidney, and moderate hemorrhage, severe thrombus, and moderate fibrosis of the liver were observed in the 400 mg/kg/day ivAPAP dose group only. The incidence of tension lipidosis in the liver as well as hemorrhage in the thymus were observed with no dose-dependency as the finding was observed in all treatment groups; however, the severity of these findings was greatest in the 400 mg/kg/day dose group. The findings of thrombi are of concern and cannot be readily dismissed. However, it is recognized that the rat model is known for producing a robust foreign body reaction and the insertion of an indwelling catheter likely resulted a foreign body response that led to the severe thrombi findings. Therefore many of these findings are likely the result of the indwelling catheter and the repeated dosing for 28 days. When comparing the formulations between ivAPAP and Ofirmev® there does not appear to be a greater risk associated with the ivAPAP formulation as the pH, tonicity, pH adjusters appear to be comparable. Taken together the weight of evidence suggests that the ivAPAP does not appear to be associated with a greater risk than Ofirmev®. All of these findings were dismissed in the Pathology Report.

*Reviewer's Comment:* It was noted that in 1 unscheduled death in the Ofirmev® comparator group had elevated AST, ALT, and ALP that were greater than 10-fold higher than control levels.

Vacuolation of the zona fasciculata in the adrenal gland, chronic progressive nephropathy and mixed cell infiltration in the kidney, necrosis and mononuclear cell infiltration in the liver, lymphoid hyperplasia in the lymph node, and increase hematopoiesis in the spleen were of either greater incidence or severity in the Ofirmev® control than the ivAPAP treatment groups and as such, can be dismissed as not representing a greater risk with the proposed product.

In addition, the following table illustrates other microscopic findings in the recovery rats (adapted from the Applicant's submission):

**Table 34: Additional Microscopic Findings in Recovery**

| Removal Reason: RECOVERY EUTHANASIA | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 400 mg/kg /day Group 5 | 0 mg/kg /day Group 1 | 400 mg/kg /day Group 2 | 400 mg/kg /day Group 5 |
| Number of Animals: | 5 | 5 | 5 | 5 | 5 | 5 |
| **EYE** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Rosette | 0 | 0 | 1 | 0 | 1 | 0 |
| .... mild | 0 | 0 | 0 | 0 | 1 | 0 |
| .... minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| **GLAND, ADRENAL** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Vacuolation; zona fasciculata | 0 | 1 | 0 | 0 | 0 | 0 |
| .... minimal | 0 | 1 | 0 | 0 | 0 | 0 |
| **KIDNEY** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Cast; hyaline | 0 | 0 | 1 | 0 | 0 | 0 |
| .... minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| Dilatation, pelvis | 0 | 1 | 1 | 0 | 0 | 0 |
| .... minimal | 0 | 1 | 0 | 0 | 0 | 0 |
| .... mild | 0 | 0 | 1 | 0 | 0 | 0 |
| **LIVER** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Infiltration, mononuclear cell | 4 | 5 | 5 | 4 | 5 | 4 |
| .... minimal | 4 | 5 | 5 | 4 | 5 | 4 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 0 |
| **SITE, INFUSION** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Thrombus | 5 | 5 | 3 | 3 | 3 | 2 |
| .... minimal | 1 | 0 | 1 | 0 | 0 | 1 |
| .... mild | 3 | 2 | 0 | 0 | 0 | 1 |
| .... moderate | 0 | 1 | 1 | 1 | 2 | 0 |
| .... marked | 0 | 2 | 0 | 2 | 1 | 0 |
| .... severe | 1 | 0 | 1 | 0 | 0 | 0 |
| Hemorrhage | 1 | 1 | 2 | 0 | 0 | 0 |
| .... minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| .... mild | 1 | 0 | 1 | 0 | 0 | 0 |
| .... moderate | 0 | 1 | 0 | 0 | 0 | 0 |
| Intimal proliferation | 1 | 0 | 1 | 0 | 0 | 1 |
| .... minimal | 1 | 0 | 1 | 0 | 0 | 1 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 0 |
| **SPLEEN** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Pigment | 0 | 0 | 0 | 0 | 1 | 1 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 1 |
| .... moderate | 0 | 0 | 0 | 0 | 1 | 0 |
| **THYMUS** | | | | | | |
| Examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Hemorrhage | 0 | 1 | 0 | 0 | 1 | 1 |
| .... minimal | 0 | 1 | 0 | 0 | 1 | 1 |
| .... mild | 0 | 0 | 0 | 0 | 0 | 0 |

Group 1 = Saline control
Group 2 = Ofirmev® control (400 mg/kg/day)
Group 5 = Braun ivAPAP 400 mg/kg/day

As shown in the table above, vacuolation of the zona fasciculate in the adrenal gland was observed only the recovery Ofirmev® control and as such, is not considered

ivAPAP treatment-related. The incidence and severity of thrombus and intimal proliferation in the infusion site was not different between the saline control and 400 mg/kg/day dose group or were no worse than the Ofirmev® control in the recovery rats and as such, can be dismissed. Mononuclear cell infiltration in the liver was observed in all recovery dose groups; however, the incidence and severity was greatest in the recovery Ofirmev® control and as such, there is no added risk with the proposed product. The incidence and severity of hemorrhage in the thymus were no different between the Ofirmev® control and the 400 mg/kg/day dose group in the recovery rats and as such, these is no added risk with the proposed product. Although the incidence of rosette in the eye and dilatation of the pelvis in the kidney was no different between the 400 mg/kg/day dose group and the Ofirmev® control in the recovery rats, the severity of these findings was greater in the recovery 400 mg/kg/day dose group. The severity and incidence of pigment in the spleen was not greater than in the Ofirmev® control and as such, there is no added risk with the proposed product. Hyaline cast in the kidney was observed in the recovery 400 mg/kg/day dose group only. All these findings were dismissed in the Pathology Report.

**Special Evaluation**

There were no special evaluations performed in this rat toxicology study.

**Toxicokinetics**

The following table illustrates the toxicokinetics sample collection schedule (from the Applicant's submission):

Text Table 10
Toxicokinetic Sample Collection Schedule

| Group No. | Subgroup | No. of Males/ Females | Sample Collection Time Points (Time Post End of Infusion*) on Days 1 and 28 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 0[a] hr | 5 mins | 15 mins | 1 hr | 2 hrs | 6[b] hrs |
| 1 | A | 3/3 | - | - | - | X | - | - |
| 2 | A | 3/3 | X | - | X | - | X | - |
| | B | 3/3 | - | X | - | X | - | X |
| 3 | A | 3/3 | X | - | X | - | X | - |
| | B | 3/3 | - | X | - | X | - | X |
| 4 | A | 3/3 | X | - | X | - | X | - |
| | B | 3/3 | - | X | - | X | - | X |
| 5 | A | 3/3 | X | - | X | - | X | - |
| | B | 3/3 | - | X | - | X | - | X |

X = Sample collected; - = Not applicable.
[a] Sample collected before dosing of the day.
[b] Sample collected before the second daily dosing.
* Sample collected following the first dosing on Day 1 and the last dosing on Day 28.
For exceptions, see Appendix 1.

Blood samples from the collection times were process and analyzed. The following toxicokinetic parameters were estimated using Phoenix pharmacokinetic software (adapted from the Applicant's submission):

| Parameter | Description of Parameter |
|---|---|
| Tmax | The time after dosing at which the maximum observed concentration was observed. |
| Cmax | The maximum observed concentration measured after dosing. |
| AUC(0-t) | The area under the concentration versus time curve from the start of dose administration to the time after dosing at which the last quantifiable concentration was observed, using the linear or linear/log trapezoidal method. |
| AUC(0-t)/D | The AUC(0-t) divided by the dose administered. |
| RAUC | The area under the curve from T1 to T2 at steady state divided by the area under the curve from T1 to T2 during the initial dosing interval. |
| T1/2 | The apparent terminal elimination half life. |
| CL | The apparent clearance rate of parent Test Item or Ofirmev RLD from the analyzed test matrix. |
| Vd | The apparent volume of distribution of the parent Test Item or Ofirmev RLD in the test system. |

The following table illustrates the toxicokinetic parameters of ivAPAP in rats (from the Applicant's submission):

**Table 35: TK Data in Rats**

Day 1

| Dose (mg/kg/ dose) | Gender | Tmax (hr) | Cmax ± SE (µg/mL) | Cmax/D (µg/mL/ (mg/kg)) | $AUC_{(0-t)}$ ± SE (hr*µg/mL) | $AUC_{(0-t)}$* (hr*µg/mL/ (mg/kg)) | $T_{1/2}$ (hr) | CL (mL/hr /kg) | Vd (mL/k g) |
|---|---|---|---|---|---|---|---|---|---|
| 20 | Female | 0.333 | 26.0 ± 1.91 | 1.30 | 21.2 ± 1.14 | 1.06 | NR | NR | NR |
| 20 | Male | 0.333 | 26.9 ± 3.34 | 1.35 | 15.9 ± 1.29 | 0.795 | 0.446 | 1210 | 781 |
| 50 | Female | 0.333 | 29.7 ± 6.82 | 0.594 | 45.8 ± 3.76 | 0.916 | 1.29 | 1050 | 1940 |
| 50 | Male | 0.333 | 39.6 ± 1.17 | 0.793 | 39.4 ± 2.36 | 0.788 | 0.870 | 1260 | 1580 |
| 100 | Female | 0.333 | 88.1 ± 1.0 | 0.881 | 123 ± 3.05 | 1.23 | 1.32 | 774 | 1480 |
| 100 | Male | 0.333 | 87.1 ± 2.9 | 0.871 | 146 ± 13.4 | 1.46 | 0.934 | 678 | 913 |

* = $AUC_{(0-t)}$ equals to $AUC_{(0-6)}$

Day 28

| Dose (mg/kg/ dose) | Gender | Tmax (hr) | Cmax ± SE (µg/mL) | Cmax/D (µg/mL/ (mg/kg)) | $AUC_{(0-t)}$ ± SE (hr*µg/mL) | $AUC_{(0-t)}$/D (hr*µg/mL/ (mg/kg)) | $T_{1/2}$ (hr) | CL (mL/hr /kg) | Vd (mL/k g) | $R_{AUC}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Female | 0.333 | 27.2 ± 1.84 | 1.36 | 22.9 ± 1.23 | 1.14 | 1.91 | 879 | 2430 | 1.08 |
| 20 | Male | 0.333 | 25.9 ± 0.688 | 1.30 | 16.3 ± 0.598 | 0.816 | NR | NR | NR | 1.03 |
| 50 | Female | 0.333 | 51.9 ± 12.8 | 1.04 | 42.8 ± 6.23 | 0.856 | NR | NR | NR | 0.934 |
| 50 | Male | 0.333 | 40.6 ± 4.83 | 0.812 | 35.1 ± 2.64 | 0.701 | NR | NR | NR | 0.890 |
| 100 | Female | 0.333 | 88.5 ± 4.94 | 0.885 | 89.6 ± 4.08 | 0.896 | 1.18 | 1120 | 1910 | 0.726 |
| 100 | Male | 0.333 | 71.7 ± 18.3 | 0.717 | 124 ± 11.2 | 1.24 | 1.13 | 811 | 1320 | 0.848 |

NR: Result not reported because extrapolation exceeds 20%, or R-squared is less than 0.800.
* = $AUC_{(0-t)}$ equals to $AUC_{(0-6)}$.
$R_{AUC}$ = Day 28 $AUC_{(0-t)}$/Day 1 $AUC_{(0-t)}$.

As shown in the table above, the time to $T_{max}$ was approximately 0.33 hours. $C_{max}$ and $AUC_{(0-t)}$ decreased slightly from Day 1 to Day 28. At the NOAEL of 50 mg/kg/dose, $C_{max}$ was an average of 35 and 46 mcg/mL on Day 1 and Day 28, respectively. $AUC_{(0-t)}$ was an average of 43 and 39 h*mcg/mL on Day 1 and Day 28, respectively. The $T_{1/2}$ was approximately 1 hour.

The following table illustrates the dose proportionality of ivAPAP compared to Ofirmev® in rats (from the Applicant's submission):

**Table 36: Dose Proportionality in Rats**

Table 3.1: Mean Acetaminophen Dose Ratios in Sprague-Dawley Rat Plasma Following IV Infusion Administration of ivAPAP

| Dose Comparison | Dose Ratio | Gender | Day | Ratio $C_{max}$ | Ratio $AUC_{(0-t)}$ |
|---|---|---|---|---|---|
| 50/20 | 2.5 | Male | 1 | 1.47 | 2.48 |
| | 2.5 | Male | 28 | 1.57 | 2.15 |
| | 2.5 | Female | 1 | 1.14 | 2.16 |
| | 2.5 | Female | 28 | 1.91 | 1.87 |
| 100/50 | 2 | Male | 1 | 2.20 | 3.71 |
| | 2 | Male | 28 | 1.77 | 3.53 |
| | 2 | Female | 1 | 2.96 | 2.69 |
| | 2 | Female | 28 | 1.70 | 2.09 |

As shown in the table above, $AUC_{(0-t)}$ increased in a dose-proportional manner between 20 and 100 mg/kg/dose for females but increased in a more than dose proportional manner between 50 and 100 mg/kg/dose for males on Day 1. On Day 28, $AUC_{(0-t)}$ increased in a less than dose-proportional manner between 20 and 50 mg/kg/dose for both gender and increased in a slightly more than dose proportional manner between 50 and 100 mg/kg/dose. The exposure to acetaminophen on Day 28 did not change substantially but tended to decrease with the increase in dose.

The following table illustrates the gender ratios following administration of ivAPAP compared to Ofirmev® in rats (from the Applicant's submission):

**Table 37: APAP Exposure Sex Ratios in Rats**

Table 4.1: Mean Acetaminophen Gender Ratios in Sprague-Dawley Rat Plasma Following IV Infusion Administration of ivAPAP or Ofirmev

| Dose | Gender Comparison | Day | Ratio $C_{max}$ | Ratio $AUC_{(0-t)}$ |
|---|---|---|---|---|
| 20 | Female/Male | 1 | 0.965 | 1.33 |
| | | 28 | 1.05 | 1.40 |
| 50 | Female/Male | 1 | 0.750 | 1.16 |
| | | 28 | 1.28 | 1.22 |
| 100 | Female/Male | 1 | 1.01 | 0.845 |
| | | 28 | 1.23 | 0.723 |
| Ofirmev 100 | Female/Male | 1 | 1.09 | 0.915 |
| | | 28 | 0.825 | 0.613 |

As shown in the table above, there were no relevant sex differences. Accordingly, the incidence and severity of gross macroscopic observations, the organ weight parameters, and the incidence and severity of microscopic observations of each dose group in both females and males were combined.

**Dosing Solution Analysis**

Dose formulation and analysis was performed on all preparations of the proposed IV formulation of APAP. The following table illustrates the dose formulation pH, density, and osmolality results of the proposed IV formulation of APAP among the dose groups (from the Applicant's submission):

**Table 38: pH, Density and Osmolality Data**

Text Table 18
pH, Density and Osmolality Results: First Preparation

| Group No. | pH Results | Osmolality (mOsm/ kg) | Density Results (g/cm3) |
|---|---|---|---|
| 1 | 6.25 | 285 | 1.0035 |
| 2 | 5.89 | 285 | 1.0130 |
| 3 | 5.26 | 287 | 1.0127 |

The Applicant notes that since Groups 3, 4, and 5 received the same dose concentration (10 mg/mL), the pH, density, and osmolality measurements were given for Group 3 only. As shown in the table above, the groups received solutions that were comparable in pH, osmolality, and density.

# 7 Genetic Toxicology

There were no new genetic toxicology studies with IV APAP in this submission. The Applicant submitted a final study report for an Ames assay that evaluated (b) (4) (b) (4) (a drug substance impurity and drug product degradant), which is reviewed below.

## 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title:**

| | |
|---|---|
| Study no.: | 848-471-1364 |
| Study report location: | \\cdsesub1\evsprod\nda204957\0011\m3\32-body-data\32s-drug-sub\all-manufacturer\32s4-contr-drug-sub\32s43-val-analyt-proc\ph-sd-5875v1.pdf |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | April 25, 2016 |
| GLP compliance: | Yes. Under OECD Principles of GLP. FDA has a Memoranda of Understanding with (b) (4) |
| QA statement: | Yes. Signature provided on June 8, 2016. |
| Drug, lot #, and % purity: | (b) (4) Lot VG1598, 99.4% |

**Key Study Findings**

- *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* were incubated with (b) (4) (b) (4) mcg/plate of (b) (4)
- This is considered a valid study.
- Under the conditions of the study, (b) (4) is not mutagenic.
- Therefore, the drug substance specification for (b) (4) at NMT (b) (4) % is acceptable.

**Methods**

| | |
|---|---|
| Strains: | *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* |
| Concentrations in definitive study: | (b) (4) mcg/plate |
| Basis of concentration selection: | The doses tested were based on OECD 471 and ICH S2(R1) guidelines, a previous study, and the Sponsor's request. The concentration range in the previous study ( (b) (4) mcg/plate) did not show any inhibitory cytotoxic effects and any biologically relevant increases in revertant colony numbers following treatment with (b) (4) (b) (4) |
| Negative control: | Dimethyl sulfoxide (DMSO) and ultrapure water |
| Positive control: | Without metabolic activation: 4-nitro-1,2-phenylenediamine (TA98); sodium azide (TA100 and TA1535); 9-aminoacridine (TA1537); and methyl methanesulfonate (WP2 *uvr2*)<br>With metabolic activation: 2-aminoanthracene (all strains) |
| Formulation/Vehicle: | DMSO |
| Incubation & sampling time: | For each strain, a single colony of bacteria was grown on nutrient agar plates, isolated, inoculated in sterile nutrient broth, and grown overnight at 37°C. Each strain was incubated on plates with the test substance at the concentrations selected, with or without metabolic activation, for 48 hours at 37°C. The number of revertant colonies was then counted for each plate. |

The following table illustrates the types of mutations are repaired in the strains used in the study (from the Applicant's submission):

**Table 3: Genotypes of the Strains Used for Mutagenicity Testing**

| Strain | Genotype | | Mutations | | Main DNA target | Plasmid |
|---|---|---|---|---|---|---|
| | trp./his mutation | type of mutation | cell wall | DNA- repair | | |
| *S.ty.mur.* TA98 | *hisD3052* | Frameshift | *rfa* | *uvrB* | GC | pKM101 |
| *S.ty.mur.* TA100 | *hisG46* | Base pair substitution | *rfa* | *uvrB* | GC | pKM101 |
| *S.ty.mur.* TA1535 | *hisG46* | Base pair substitution | *rfa* | *uvrB* | GC | No |
| *S.ty.mur.* TA1537 | *hisC3076* | Frameshift | *rfa* | *uvrB* | GC | No |
| *E.coli* WP2*uvrA* | *trpE* | Base pair substitution | + | *uvrA* | AT | No |

Abbreviations: *S.ty.mur.*: *Salmonella typhimurium*; *E.coli*: *Escherichia coli*

## Study Validity

The study is considered valid for the following reasons: 1) the appropriate controls were used; 2) the appropriate strains were tested; 3) the positive control substances produced reliable positive results; 4) the highest concentration of X0002 (500 and 1000 mcg/plate) tested was appropriately selected due to cytotoxicity in the dose range-finding study; and 5) there was no evidence for a dose dependent increase in revertants following treatment with the vehicle control.

## Results

The following table illustrates the initial mutation test using (b) (4) (b) (4) (from the Applicant's submission):

**Table 39: Initial Mutation Test Results**

| Initial Mutation Test (Plate Incorporation Test) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Concentrations (µg/plate) | *Salmonella typhimurium* tester strains | | | | | | | | *Escherichia coli* | |
| | TA 98 | | TA 100 | | TA 1535 | | TA 1537 | | WP2uvrA | |
| | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 |
| [redacted] (b) (4) | | | | | | | | | | |

MR: Mutation Rate

As shown in the table above, there were no changes in the number of revertant colonies in any of the strains tested with and without S9 metabolic activation.

The following table illustrates the confirmatory mutation test using [redacted] (b) (4) (from the Applicant's submission):

**Table 40: Confirmatory Mutation Test Results**

| Confirmatory Mutation Test (Pre-Incubation Test) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Concentrations (µg/plate) | *Salmonella typhimurium* tester strains | | | | | | | | *Escherichia coli* | |
| | TA 98 | | TA 100 | | TA 1535 | | TA 1537 | | WP2uvrA | |
| | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 | -S9 | +S9 |
| [redacted] (b) (4) | | | | | | | | | | |

MR: Mutation Rate

As shown in the table above, there were no changes in the number of revertant colonies in any of the strains tested with and without metabolic activation.

Moreover, the number of revertant colonies is within the historical control range (see table below from the Applicant's submission):

**Table 41: Historical Controls for Mutation Test (2008-2015)**

**Table 18: Historical Control Values for Revertants/Plate (for the Period of 2008-2015)**

(b) (4)

[redacted]

Thus, under the conditions of this Ames assay, (b) (4) is not mutagenic.

# 8 Carcinogenicity

There were no new carcinogenicity studies with IV APAP in this submission.

# 9 Reproductive and Developmental Toxicology

There were no new reproductive and developmental toxicology studies with IV APAP in this submission.

# 10 Special Toxicology Studies

The Applicant submitted a blood compatibility assessment using their proposed drug product.

**Study Title: In Vitro Evaluation of the Influence of ivAPAP on Human Whole Blood Hemolysis, Plasma Flocculation and Platelet Aggregation**

| | |
|---|---|
| Study no.: | 6000344 STF |
| Study report location: | \\cdsesub1\evsprod\nda204957\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\6000344\6000344-final-main-report.pdf |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | April 25, 2016 |
| GLP compliance: | Yes. Under OECD Principles of GLP. FDA has a Memoranda of Understanding with (b) (4) |
| QA statement: | Yes. Signature provided on June 7, 2016. |
| Drug, lot #, and % purity: | ivAPAP, Lot STBJ5J677, 100%<br>Ofirmev®, Lot AAD4717, 100% |

**Platelet Aggregation:**
Platelet rich plasma (PRP) was prepared from whole blood samples collected from 3 male and 3 female donors. The following table illustrates the experimental design for testing platelet aggregation using the optical method (from the Applicant's submission):

Text Table 1
Experimental Design for Optical Method

| Group No. | Treatment | Final Test Item or Reference Comparator Item Concentration in the PRP Sample (mg/mL) | No. of Male /Female Donors | Experimental Conditions | |
|---|---|---|---|---|---|
| | | | | Agonist ADP 10 µM | Agonist Collagen 2 µg/mL |
| 1A | PRP Positive Control | 0 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 2A | 0.9% NaCl Negative Control | 0 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 3A | ReoPro® Inhibition Control | 0 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 4A | ivAPAP 10 mg/mL | 0.01 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 5A | ivAPAP 10 mg/mL | 0.1 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 6A | ivAPAP 10 mg/mL | 1 | 3 / 3 | Aliquot #1 | Aliquot #2 |
| 7A | Ofirmev® 10 mg/mL | 1 | 3 / 3 | Aliquot #1 | Aliquot #2 |

Following incubation period of 30 minutes at 37°C, the spiked PRP samples were loaded in the instrument prior to measurement of platelet aggregation.
Each of the above group was tested in duplicate for each experimental condition.

Platelets were prepared from each blood sample and then incubated with various concentrations of the proposed IV APAP formulation (0.01 to 1 mg/mL) for 30 minutes at 37°C. The following platelet aggregation parameters were measured (from the Applicant's submission):

The Group 4A to 7A ratio of aggregation amplitude and AUC over the Group 2A were calculated as in the following example:

> Group 4A to 7A Amplitude (%) of Donor 1 was multiplied by 100 and divided by the Group 2A Amplitude (%) of Donor 1.

The same calculation was done for the AUC results.

The following tables illustrate the effect of the proposed APAP formulation on platelet aggregation (from the Applicant's submission):

## Table 42: Platelet Aggregation Study Results

Text Table 8
Platelet Aggregation Amplitude (%) Mean Results of the ivAPAP or Ofirmev® Spiked Human Samples

| Group ID | ivAPAP or Ofirmev® Conc. (mg/mL) | Platelet Aggregation Amplitude (%) Group Mean Result ± SD | | | |
|---|---|---|---|---|---|
| | | Males (n = 4) | | Females (n = 3) | |
| | | ADP 10 µM | Collagen 2 µg/mL | ADP 10 µM | Collagen 2 µg/mL |
| 1A/ PRP Positive Control | 0 | 64.2 ± 17.04 | 79.0 ± 2.78 | 78.3 ± 3.55 | 78.7 ± 7.18 |
| 2A/ 0.9%NaCl Negative Control | 0 | 67.5 ± 15.60 | 76.8 ± 2.57 | 80.3 ± 5.13 | 74.3 ± 3.62 |
| 3A/ ReoPro® Inhibition Control | 0 | 0.2 ± 0.29 | 2.0 ± 2.18 | 0.0 ± 0.00 | 1.8 ± 2.75 |
| 4A/ivAPAP | 0.01 | 65.0 ± 15.26 | 77.5 ± 4.00 | 76.5 ± 4.50 | 76.7 ± 3.82 |
| 5A/ivAPAP | 0.1 | 57.5 ± 12.85 | 64.7 ± 7.82 | 68.8 ± 3.75 | 75.0 ± 6.73 |
| 6A/ivAPAP | 1 | 41.0 ± 18.30 | 11.5 ± 5.50 | 57.8 ± 9.41 | 22.0 ± 18.03 |
| 7A/Ofirmev® | 1 | 40.0 ± 15.21 | 12.2 ± 10.26 | 56.7 ± 7.11 | 22.7 ± 16.29 |
| Ratio (%) of Amplitude over the 0.9%NaCl Negative Control | | | | | |
| 4A/ivAPAP | 0.01 | 96.2 ± 1.68 | 101 ± 8.6 | 93.1 ± 1.67 | 103 ± 6.2 |
| 5A/ivAPAP | 0.1 | 85.4 ± 3.31 | 84.1 ± 8.85 | 83.8 ± 4.56 | 101 ± 9.0 |
| 6A/ivAPAP | 1 | 58.4 ± 15.85 | 14.9 ± 6.92 | 70.2 ± 9.34 | 30.4 ± 25.13 |
| 7A/Ofirmev® | 1 | 57.6 ± 10.75 | 15.7 ± 13.18 | 68.9 ± 7.08 | 31.2 ± 22.82 |

Text Table 9
Platelet Aggregation Area Under the Curve (%/min) Mean Results of the ivAPAP or Ofirmev® Spiked Human Samples

| Group ID | ivAPAP or Ofirmev® Conc. (µg/mL) | Platelet Aggregation AUC (%/min) Group Mean Result ± SD | | | |
|---|---|---|---|---|---|
| | | Males (n = 4) | | Females (n = 3) | |
| | | ADP 10 µM | Collagen 2 µg/mL | ADP 10 µM | Collagen 2 µg/mL |
| 1A/ PRP Positive Control | 0 | 298.4 ± 77.89 | 316.6 ± 40.60 | 359.5 ± 20.05 | 330.0 ± 22.79 |
| 2A/ 0.9%NaCl Negative Control | 0 | 317.8 ± 65.42 | 317.1 ± 31.36 | 365.3 ± 19.78 | 307.8 ± 16.82 |
| 3A/ ReoPro® Inhibition Control | 0 | 0.0 ± 0.00 | 2.0 ± 3.46 | 0.0 ± 0.00 | 3.8 ± 6.58 |
| 4A/ivAPAP | 0.01 | 305.7 ± 72.07 | 317.7 ± 23.10 | 356.8 ± 23.78 | 316.4 ± 18.43 |
| 5A/ivAPAP | 0.1 | 275.9 ± 69.82 | 253.8 ± 43.93 | 330.1 ± 14.98 | 299.8 ± 40.55 |
| 6A/ivAPAP | 1 | 182.4 ± 113.37 | 31.6 ± 26.54 | 278.5 ± 49.45 | 81.2 ± 70.58 |
| 7A/Ofirmev® | 1 | 179.2 ± 96.87 | 39.3 ± 45.51 | 271.1 ± 38.05 | 81.4 ± 66.79 |
| Ratio (%) of AUC over the 0.9%NaCl Negative Control | | | | | |
| 4A/ivAPAP | 0.01 | 95.7 ± 3.38 | 101 ± 11.9 | 98.9 ± 11.6 | 103 ± 5.6 |
| 5A/ivAPAP | 0.1 | 86.2 ± 5.38 | 79.7 ± 7.10 | 91.8 ± 7.29 | 97.5 ± 13.52 |
| 6A/ivAPAP | 1 | 53.6 ± 28.06 | 9.53 ± 7.449 | 76.9 ± 10.35 | 27.2 ± 23.99 |
| 7A/Ofirmev® | 1 | 53.4 ± 22.21 | 11.6 ± 13.13 | 75.0 ± 8.04 | 27.1 ± 22.51 |

At 0.01 mg/mL, the group mean amplitude and AUC results demonstrated that there was no inhibition of platelet aggregation observed in the male and female samples. At 0.1 mg/mL, the group mean amplitude and AUC results demonstrated a very slight inhibition of platelet aggregation observed in the male and female samples. At 1 mg/mL, the group mean amplitude and AUC results demonstrated that there was moderate inhibition of platelet aggregation observed in the female samples and high

inhibition in the male samples. It is noted that ivAPAP and Ofirmev at 1 mg/mL produced the same level of inhibitory effect on platelet aggregation. APAP is known to inhibit platelet aggregation in a dose-dependent manner (Munsterhjelm et al., 2005 and Martini et al., 2014).

**Hemolysis and Flocculation:**
Whole blood samples were collected and prepared from 3 male and 3 female donors. The following table illustrates the experimental design for testing hemolysis and flocculation (from the Applicant's submission):

Text Table 2
Experimental Design for Hemolysis and Flocculation

| Group No. | Treatment | Final Whole Blood Test Item or Reference Comparator Item Concentration (mg/mL) | No. of Male Donors | No. of Female Donors |
|---|---|---|---|---|
| 1H | Whole Blood Control | 0 | 3 | 3 |
| 2H | 0.9% NaCl Control | 0 | 3 | 3 |
| 3H | 20% Saponin Control | 0 | 3 | 3 |
| 4H | 20% Intralipid® Control | 0 | 3 | 3 |
| 5H | ivAPAP 10 mg/mL | 0.01 | 3 | 3 |
| 6H | ivAPAP 10 mg/mL | 0.1 | 3 | 3 |
| 7H | ivAPAP 10 mg/mL | 1 | 3 | 3 |
| 8H | Ofirmev® 10 mg/mL | 1 | 3 | 3 |

The prepared samples were then incubated for 1 hour at 37°C ± 1°C with concentrations of APAP (10 to 1000 mcg/mL). Percent hemolysis was determined from the following formula (from the Applicant's submission):

$$\% \text{ Hemolysis} = \frac{(100\text{-hematocrit }\%) \times \text{Plasma Hemoglobin}^{@}\ (g/dL)}{\text{Negative Control Whole Blood Hemoglobin}^{\#}\ (g/dL)}$$

@ Plasma hemoglobin from spiked sample.
# Negative control of the same donor.

The following turbidity (flocculation) parameters were determined (from the Applicant's submission):

> The Group 4H ratio of turbidity units over the Group 1H was calculated as in the following example:
>
> Group 4H turbidity units of Donor 1 were divided by the Group 1H Turbidity units of Donor 1.
>
> The turbidity index of each spiked sample (except for Group 3H and 4H) was calculated as follows:
>
> Turbidity units of spiked samples - turbidity units of negative control (0.9% NaCl Control), from the same donor.

The following table illustrates the results of the hemolysis and flocculation parameters measured (from the Applicant's submission):

## Table 43: Hemolysis Study Results

Text Table 10
Mean Results of the Spiked Male and Female Samples

| Parameter | Group No. | Treatment | Group Mean Result ± SD | |
|---|---|---|---|---|
| | | | Male | Female |
| Whole Blood Hemoglobin (g/dL) | 2H | Negative Control (0.9% NaCl) | 13.8 ± 0.7 | 11.7 ± 0.6 |
| Whole Blood Hematocrit (%) | 1H | Non-spiked Whole Blood | 44.9 ± 2.6 | 39.7 ± 1.1 |
| | 2H | Negative Control (0.9% NaCl) | 40.4 ± 1.8 | 34.9 ± 1.7 |
| | 3H | Positive Control (20% saponin) | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | 5H | ivAPAP - 0.01 mg/mL | 39.5 ± 2.3 | 35.0 ± 1.3 |
| | 6H | ivAPAP - 0.1 mg/mL | 39.9 ± 2.4 | 34.6 ± 2.1 |
| | 7H | ivAPAP - 1 mg/mL | 39.9 ± 1.9 | 34.6 ± 1.1 |
| | 8H | Ofirmev® - 1 mg/mL | 40.7 ± 2.0 | 34.4 ± 1.6 |
| Plasma Hemoglobin Conc. (g/dL) | 1H | Non-spiked Whole Blood | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | 2H | Negative Control (0.9% NaCl) | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | 3H | Positive Control (20% saponin) | 14.1 ± 0.9 | 11.7 ± 0.5 |
| | 5H | ivAPAP - 0.01 mg/mL | 0.0 ± 0.1 | 0.0 ± 0.0 |
| | 6H | ivAPAP - 0.1 mg/mL | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | 7H | ivAPAP - 1 mg/mL | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | 8H | Ofirmev® - 1 mg/mL | 0.0 ± 0.0 | 0.0 ± 0.0 |
| Plasma Hemolysis Index (Hemoglobin equivalent in mg/dL) | 1H | Non-spiked Whole Blood | 61 ± 14 | 39 ± 6 |
| | 2H | Negative Control (0.9% NaCl) | 42 ± 8 | 32 ± 5 |
| | 3H | Positive Control (20% saponin) | 11607 ± 560 | 10107 ± 574 |
| | 5H | ivAPAP - 0.01 mg/mL | 43 ± 1 | 36 ± 2 |
| | 6H | ivAPAP - 0.1 mg/mL | 42 ± 8 | 39 ± 5 |
| | 7H | ivAPAP - 1 mg/mL | 37 ± 6 | 26 ± 8 |
| | 8H | Ofirmev® - 1 mg/mL | 35 ± 3 | 26 ± 1 |
| Plasma Hemolysis Index (Hemoglobin equivalent in g/dL) | 1H | Non-spiked Whole Blood | 0.061 ± 0.014 | 0.039 ± 0.006 |
| | 2H | Negative Control (0.9% NaCl) | 0.042 ± 0.008 | 0.032 ± 0.005 |
| | 3H | Positive Control (20% saponin) | 11.607 ± 0.560 | 10.107 ± 0.574 |
| | 5H | ivAPAP - 0.01 mg/mL | 0.043 ± 0.001 | 0.036 ± 0.002 |
| | 6H | ivAPAP - 0.1 mg/mL | 0.042 ± 0.008 | 0.039 ± 0.006 |
| | 7H | ivAPAP - 1 mg/mL | 0.037 ± 0.006 | 0.026 ± 0.008 |
| | 8H | Ofirmev® - 1 mg/mL | 0.035 ± 0.003 | 0.026 ± 0.001 |
| Visual Plasma Hemolysis | 1H | Non-spiked Whole Blood | N for all samples | N for all samples |
| | 2H | Negative Control (0.9% NaCl) | N for all samples | N for all samples |
| | 3H | Positive Control (20% saponin) | $H^{+++}$ for all samples | $H^{+++}$ for all samples |
| | 5H | ivAPAP - 0.01 mg/mL | N for all samples | N for all samples |
| | 6H | ivAPAP - 0.1 mg/mL | N for all samples | N for all samples |
| | 7H | ivAPAP - 1 mg/mL | N for all samples | N for all samples |
| | 8H | Ofirmev® - 1 mg/mL | N for all samples | N for all samples |
| Hemolysis (%) | 2H | Negative Control (0.9% NaCl) | 0.2 ± 0.1 | 0.2 ± 0.1 |
| | 3H | Positive Control (20% saponin) | 101.9 ± 1.4 | 100.4 ± 1.0 |
| | 5H | ivAPAP - 0.01 mg/mL | 0.2 ± 0.0 | 0.2 ± 0.0 |
| | 6H | ivAPAP - 0.1 mg/mL | 0.2 ± 0.0 | 0.2 ± 0.0 |
| | 7H | ivAPAP - 1 mg/mL | 0.2 ± 0.1 | 0.1 ± 0.1 |
| | 8H | Ofirmev® - 1 mg/mL | 0.2 ± 0.1 | 0.2 ± 0.1 |
| Visual Plasma Flocculation | 1H | Non-spiked Whole Blood | N for all samples | N for all samples |
| | 2H | Negative Control (0.9% NaCl) | N for all samples | N for all samples |
| | 4H | Positive Control (20% Intralipid®) | $L^{+++}$ for all samples | $L^{+++}$ for all samples |
| | 5H | ivAPAP - 0.01 mg/mL | N for all samples | N for all samples |
| | 6H | ivAPAP - 0.1 mg/mL | N for all samples | N for all samples |
| | 7H | ivAPAP - 1 mg/mL | N for all samples | N for all samples |
| | 8H | Ofirmev® - 1 mg/mL | N for all samples | N for all samples |
| Plasma Turbidity Index (660 nm/700nm) | 1H | Non-spiked Whole Blood | 5 ± 2 | 5 ± 2 |
| | 2H | Negative Control (0.9% NaCl) | 6 ± 2 | 2 ± 1 |
| | 4H | Positive Control (20% Intralipid®) | 116 ± 35 [a] | 138 ± 52 [a] |
| | 5H | ivAPAP - 0.01 mg/mL | 1 ± 1 [b] | 1 ± 1 [b] |
| | 6H | ivAPAP - 0.1 mg/mL | 0 ± 0 [b] | 1 ± 1 [b] |
| | 7H | ivAPAP - 1 mg/mL | 0 ± 1 [b] | 2 ± 1 [b] |
| | 8H | Ofirmev® - 1 mg/mL | 1 ± 1 [b] | 2 ± 2 [b] |

N: No hemolysis or flocculation observed.
$L^{+}$: Slight flocculation (turbidity) observed (cloudy).
$L^{+++}$: Severe flocculation (turbidity) observed (lactescent).
$H^{+++}$: Severe hemolysis observed.
[a] Ratio of positive control over non-spiked plasma control.
[b] Result corrected for the negative control value.

As shown in the table above, there was no effect on hemolysis and flocculation from treatment with any of the concentrations of the proposed APAP formulation.

# 11 Integrated Summary and Safety Evaluation

The Applicant submitted a 28-day IV toxicology study in rats with their proposed formulation (ivAPAP) as well as the blood compatibility assessment of their proposed product and an Ames assay with the drug substance impurity (b) (4) (b) (4) There were no safety concerns with the formulation as there are no novel excipients and with drug substance and drug product specifications.

The extractable studies conducted are deemed acceptable (see quality review for details). From the extractable studies, leachable studies were performed. The leachables assessment resulted in 3 known compounds (b) (4) as well as several unknown compounds above the requested qualification threshold. In the toxicological risk assessment, (b) (4) and (b) (4) are adequately qualified but (b) (4) is not adequately qualified. Moreover, a total of 3 unknowns and 5 unknowns were detected in leachable studies with the PAB® container under normal and accelerated conditions, respectively. Although normally an approval issue, as this drug product container closure system has been used in other FDA-approved drug product formulations with comparable physicochemical properties and similar dose and duration, these deficiencies can be addressed post-marketing should the NDA be approved this cycle.

For the 28-day toxicology study, Sprague Dawley rats were administered IV doses of 0, 80, 200, and 400 mg/kg/day of ivAPAP as well as a 400 mg/kg/day of Ofirmev® four times a day for 28 consecutive days via an indwelling catheter placed in the vena cava at the level of the kidneys. The systemic NOAEL was 200 mg/kg/day (50 mg/kg/dose) based on moderate thrombus in the kidney, degeneration/atrophy of the testis, and cellular debris in the epididymis as well as moderate hemorrhage, severe thrombus, and moderate fibrosis of the liver at 400 mg/kg/day. The local NOAEL was 400 mg/kg/day administered at a concentration of 10 mg/mL as the proposed formulation did not present a greater risk than Ofirmev® and represents an exposure margin of 1. At the systemic NOAEL of 200 mg/kg/day, the average $C_{max}$ is 34.65 mcg/mL and the average $AUC_{0-t}$ is 42.6 mcg*h/mL on Day 1.

In the blood compatibility assessment of the proposed formulation ivAPAP, ivAPAP inhibited platelet aggregation, which is an expected pharmacology effect, but did not induce hemolysis of red blood cells or flocculation of proteins.

In the Ames assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* were incubated with (b) (4) (b) (4) mcg/plate of (b) (4) in a valid study. Under the conditions of the study, (b) (4) is not mutagenic.

Singla et al., 2012 studied the pharmacokinetics of Ofirmev® after a single dose IV infusion in plasma. The follow table illustrates the IV pharmacokinetic data (from Singla et al., 2012):

**Table 44: PK Data With Ofirmev®**

Table 1. Mean (%CV) Acetaminophen Plasma PK Parameters

| PK Parameter | IV (1,000 mg) | PO (1,000 mg) | PR (1,300 mg) | PR (Standardized to 1,000 mg) |
|---|---|---|---|---|
| *N* | 6 | 7 | 6 | 6 |
| Mean $C_{max}$ (μg/mL) | 21.6 (17.9) | 12.3 (45.2) | 7.90 (49.0) | 6.07 (49.0) |
| Median $T_{max}$ (range)* (hours) | 0.25 (0.25, 0.25) | 1.0 (0.50, 2.0) | 2.5 (2.0, 4.0) | 2.5 (2.0, 4.0) |
| Mean *t* ½ (hours) | 2.17 (20.0) | 2.53 (19.3)† | 3.00 (NC)‡ | 3.00 (NC)‡ |
| Mean $AUC_{0-6}$ (μg·h/mL) | 42.5 (16.5) | 29.4 (52.3) | 31.9 (29.2) | 24.5 (29.2) |
| Mean $AUC_{0-\infty}$ (μg·h/mL) | 50.0 (18.7) | 44.4 (35.4)† | 41.3 (NC)‡ | 31.8 (NC)‡ |
| Mean CL/F (L/hours) | 20.7 (19.8) | 24.6 (28.9)† | 32.5 (NC)‡ | 32.5 (NC)‡ |

*(Min, Max).
†*N* = 6.
‡*N* = 2 and mean (% CV).
NC, not calculated, % CV, coefficient of variation.

Following IV infusion with Ofirmev®, the $C_{max}$ of 21.6 mcg/mL and $AUC_{0\text{-}6hr}$ of 42.5 mcg*h/mL is comparable to the TK/PK findings at the NOAEL of 200 mg/kg/day on Day 1 in the submitted 28-day rat study. Thus, there is an exposure margin of approximately 1 for systemic toxicity comparing the proposed drug formulation ivAPAP with Ofirmev®.

From the nonclinical pharmacology toxicology perspective, we recommend approval. We have comments for the Applicant to address prior to any subsequent submission (see Executive Summary above).

# 12 Appendix/Attachments

**References**

Derelanko, MJ. 2008. The Toxicologist's Pocket Handbook. 2nd Edition. Informa Healthcare: New York.

Haworth S, Lawlor T, Mortelmans K, Speck W, and Zeiger E. 1983. Salmonella mutagenicity test results for 250 chemicals. *Envir Mutagen*, 5 (Supple 1):1-142.

Huang QG, Kong LR, Liu YB, and Wang LS. 1996. Relationships between molecular structure and chromosomal aberrations in in vitro human lymphocytes induced by substituted nitrobenzenes. *Bull Environ Contam Toxicol,* 57:349-353.

Martini AK, Rodriguez CM, Cap AP, Martini WZ, and Dubick MA. 2014. Acetaminophen and meloxicam inhibit platelet aggregation and coagulation in blood samples from humans. *Blood Coagulation and Fibrinolysis*, 25:831-837.

McCann J, Choi E, Yamasaki E, and Ames BN. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals. *Proc Natl Acad Sci U S A*, 72:5135-5139.

Munsterhjelm E, Munsterhjelm NM, Niemi TT, Ylikorkala O, Neuvonen PJ, and Rosenberg PH. 2005. Dose-dependent Inhibition of Platelet Function by Acetaminophen in Healthy Volunteers. *Anesthesiology*, 103:712-717.

National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of p-Nitrophenol (CAS No. 100-02-7) in Swiss Webster Mice (Dermal Studies). TR-417, 1-161. 1993.
Ref Type: Report

Shimizu M and Yano E. 1986. Mutagenicity of mono-nitrobenzene derivatives in the Ames test and rec assay. *Mutat Res*, 170:11-22.

Singla NK, Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, Ang R, and Royal MA. 2012. Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen. *Pain Practice*, 12(7):523-532.

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/s/

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I concur.