CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212854Orig1s000

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

Application number:	212854
Supporting document/s:	SDN 63 (Electronic Document Room Sequence number 63); SDN 70 (Electronic Document Room Sequence number 71)
Applicant's letter date:	May 13, 2021 (SDN 63); September 10, 2021 (SDN 70)
CDER Stamp Date:	May 13, 2021 (SDN 63); September 10, 2021 (SDN 70)
Product:	Naloxone HCl (5 mg/0.5 mL) injection
Indication:	Emergency treatment of known or suspected opioid over dosage
Applicant:	Adamis Pharmaceuticals Corp.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
DPT-N Reviewer:	Carlic K. Huynh, PhD
DPT-N Supervisor:	Newton H. Woo, PhD
DPT-N Deputy Director:	R. Daniel Mellon, PhD
Clinical Division Director:	Rigoberto A. Roca, MD
Project Manager:	Swati Patwardhan

Template Version: September 1, 2010

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Executive Summary:
This is a third cycle review. No nonclinical deficiencies were noted from the previous Complete Response Letter (dated November 13, 2020). There were no changes to the drug product formulation, impurity specifications, or to the primary container closure system since the last review cycle.

As specifications do not exceed ICH Q3A(R2) and Q3B(R2) qualification thresholds, the drug substance and drug product specifications are deemed acceptable. However, the CMC review team notified the nonclinical review team that the Applicant is seeking an expiry of (b) (4) but noted that a drug product degradant, (b) (4) was associated with stability data that was out of specification. The Applicant submitted an argument (b) (4) that the levels of this degradant at (b) (4)% are not a safety concern. Although it is acknowledged (b) (4) this scientific justification is not acceptable given that all drug product degradants under the scope of ICH Q3B(R2) (b) (4) The Applicant also stated (SDN 70) that QSAR data has been submitted addressing the genotoxicity potential of this degradant. However, this approach to conduct QSAR analysis that is outlined in ICH M7 only addresses the potential for mutagenicity and not clastogenicity of a compound and does not generally apply to drug substance or drug product impurities that exceed Q3A or Q3B qualification thresholds. Therefore, the out of specification level of (b) (4)% for (b) (4) is not adequately qualified. In order to support a degradant level greater than the qualification threshold of 0.5%, the Applicant should conduct a minimal genetic toxicology screen, which includes a point mutation assay and a chromosome aberration assay, as well as a repeat-dose toxicity study of appropriate duration in a single species.

Recommendations
Approvability
From a Pharmacology Toxicology nonclinical perspective, this NDA may be approved.

Additional Nonclinical Recommendations
Any impurity or degradation product (e.g., (b) (4)) that exceeds ICH thresholds should be adequately qualified for safety as recommended in ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:

a. You should complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you should conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

Refer to
Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*[1]

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*[2]

Labeling
The table below contains the draft labeling proposed by the Applicant with the changes proposed by this Reviewer and the rationale for the proposed changes. The reader is referred to the final action letter for the final drug product labeling.

Proposed	Suggested Revisions	Rationale/Comment
(b) (4)		

[1] https://www.fda.gov/media/71727/download
[2] https://www.fda.gov/media/71733/download

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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 NDA REVIEW AND EVALUATION

Application number:	212854
Supporting document/s:	SDN 45 (Electronic Document Room Sequence number 45)
Applicant's letter date:	May 15, 2020 (SDN 45)
CDER Stamp Date:	May 15, 2020 (SDN 45)
Product:	Naloxone HCl (5 mg/0.5 mL) injection
Indication:	Emergency treatment of known or suspected opioid over dosage
Applicant:	Adamis Pharmaceuticals Corp.
Clinical 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
Clinical Division Director:	Rigoberto A. Roca, MD
Project Manager:	Swati Patwardhan

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Executive Summary:
This is a second cycle review. The NDA was originally submitted on December 31, 2018. The original NDA resulted in a Complete Response (see Complete Response Letter dated November 22, 2019). There were no new nonclinical studies submitted in support of the proposed drug product. The first cycle review concluded with a Complete Response with a deficiency aimed at the lack of adequate extractable and leachable studies to support the safety of the container closure system. Specifically, the extraction studies conducted should establish an acceptable extractables leachables correlation that will assure adequate monitoring of the potential leachable compounds from the container closure system was well as providing a toxicological risk assessment for any leachable compound detected above the 5 mcg/day threshold.

The extractables study used 24-hour reflux in five solvents including a product simulation solvent (saline pH 4.0), isopropanol, hexane, and water at pH 2.0 and pH 11.0. These extraction solvents appear harsh (isopropanol and hexane) and cover physiologic conditions (water and saline). The Analytical Evaluation Threshold (AET) was based on a Safety Concern Threshold (SCT) of 5 mcg/day. The AET was (b) (4) mcg/g for the syringe and (b) (4) mcg/g for the stopper. The analytical methods used were able to detect a variety of compounds (volatile, non-volatile and semi-volatile). The reader is referred to the quality review for the adequacy of the extraction study and the extractable leachable correlation.

The leachable study was performed on 5 batches that were stored for up to 18 months under normal conditions (25°C/60% RH). The only leachable that was detected above the 5 mcg/day threshold is (b) (4) The safety of (b) (4) was provided by the toxicological risk assessment from the original submission. The toxicological risk assessment of (b) (4) was not changed in this submission except for the levels of (b) (4) detected to date. The levels of (b) (4) in the stability batches increased slightly and as a result, the safety margin decreased slightly (from (b) (4) x to (b) (4) x). Thus, there are no safety concerns with (b) (4)

The drug product specifications were revised and these meet ICH Q3A(R2) qualification thresholds and as such, there are no safety concerns with the drug product specifications.

From a nonclinical pharmacology toxicology perspective, the NDA may be approved.

Labeling:
The following table illustrates our recommended changes to the label:

Proposed	Suggested Revisions	Rationale/Comment
(b) (4)		

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(b) (4)

Background and Prior Regulatory History (Nonclinical):
Adamis Pharmaceuticals Corp. has developed a prefilled injectable device for intramuscular or subcutaneous administration of naloxone HCl (5 mg/0.5 mL). The Applicant has submitted an application via the 505(b)(2) pathway, relying upon the Agency's previous findings of safety and efficacy of (b) (4) Narcan® (NDA 16636).

The first cycle review concluded with a Complete Response. The following nonclinical deficiency was communicated with the Applicant (see Complete Response Letter from November 22, 2019):

7. You have not provided appropriate extractable/ leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

   To address this deficiency:
   Submit a revised toxicological risk assessment based on adequate extractable leachable data. To inform the risk assessment, conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

   a. Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.

   b. Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

   c. Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into

consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.

d. Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

On February 12, 2020, there was a post-action meeting with the Applicant that includes questions regarding the deficiencies in the November 22, 2019 Complete Response letter. The chemistry, manufacturing, and controls (CMC) review team concerns with the extractables leachables studies were discussed prior to discussions of the toxicological risk assessment for leachables. Because there was complete alignment on the methodology concerns raise by the CMC review team, the nonclinical team could not agree with most of the questions raised in that meeting. The following nonclinical responses were communicated with the Applicant (for discussion of the CMC issues, the reader is referred to the full Meeting Minutes dated March 10, 2020):

Question 12 (Comment 7a from CRL)
As mentioned above, we have eliminated the source of the laboratory contamination which previously generated GC-FID peaks that were incorrectly reported as leachables. We will follow Agency guidance and ICH Q3C (R5) for toxicological risk assessment of all leachables detected in stability samples. There are no extractables found and with the revised GC-FID method, there are no leachables in the Naloxone drug product. Please refer to previous responses 1 and 2 above.

Does the Agency agree that an acceptable extractable study has been executed and that an additional extractable study does not need to be performed because the extractable results correlate with the current leachable data generated after the revised GC-FID method was implemented?

FDA Response to Question 12
No, we do not agree. See our previous responses to the product quality questions.

Meeting Discussion
The preliminary comments were found to be adequate. No additional discussion

occurred.

Question 13 (Comment 7d from CRL)
We acknowledge and agree with this recommendation. Currently, there are no leachables on which to perform a toxicological risk assessment. If leachables are detected we will comply with the recommendation noted in Nonclinical, Comment 7d of the CRL.

Does the Agency agree that this information will be sufficient for resubmission of the application and fully address all the deficiencies listed in the Complete Response, Nonclinical, Sections 7a. - d.?

FDA Response to Question 13
No, we do not agree. See our previous responses to the product quality questions. Submit a toxicological risk assessment for any leachable detected at levels of 5 mcg/day or higher during the course of stability that is based on adequate extractable leachable data.

Meeting Discussion
The preliminary comments were found to be adequate. No additional discussion occurred.

The Applicant submitted a complete response to the complete response letter on May 15, 2020. The Applicant's responses to each part of the nonclinical deficiency noted in the complete response letter are outlined below. This section for the Applicant's response is followed by a review of the Applicant's submission of the extractable leachable assessment and the toxicological risk assessment.

Applicant's Response to Deficiency 7a:
The Applicant submitted an extraction study on the container closure components. The extractables from the container closure have not been observed as leachables during stability. The only leachable observed was (b) (4) which was assessed for toxicological risk.

Applicant's Response to Deficiency 7b:
The Applicant notes that the analytical methods used to detect extractables are the same methods used to detected leachables during release and stability testing. As such, if any of the extractable compounds were in the stability test samples then they would be detected by the leachable analytical methods.

Applicant's Response to Deficiency 7c:
The Applicant notes that leachables studies were conducted as part of stability testing and have identified all compounds in the drug product present at levels equal to or greater than 5 mcg/day and taken into consideration the maximum daily dose of the proposed drug product. There was only one leachable (b) (4) detected that was above the 5 mcg/day qualification threshold and a toxicological risk assessment was conducted on (b) (4). The risk assessment is based on the highest level of the leachable over the course of the proposed shelf-life.

Applicant's Response to Deficiency 7d:
The Applicant has submitted the toxicological risk assessment for one leachable [redacted]. A review of the Applicant's response to Deficiencies 7a, 7b, 7c and 7d is below.

Extraction Study:
An extraction study was performed using the stoppers and syringes. The extractables study used 24-hour reflux in five solvents including a product simulation solvent (saline pH 4.0), isopropanol, hexane, and water at pH 2.0 and pH 11.0. The Analytical Evaluation Threshold (AET) was based on a Safety Concern Threshold (SCT) of 5 mcg/day, a maximum daily dose of 10 mg/day, and an additional 50% uncertainly factor and the Applicant's AET is [redacted]mcg/mL. Individually, the AET was [redacted] mcg/g for the syringe and [redacted]mcg/g for the stopper. The non-volatile extractables were analyzed by LC-MS and quantified using HPLC. The volatile and semi-volatile extractables were analyzed by GC-MS and quantitated by GC-FID. The LOD and LOQ of the HPLC-DAD method are [redacted]ppm and [redacted] ppm, respectively. The LOD and LOQ of the GC-FID method are [redacted] and [redacted] ppm, respectively. For GC-FID and GC-MS analyses, [redacted] however, there were many extractables in the isopropanol and hexane solvents. [redacted] Extractable peaks above the method LOQ were quantitated and identified to the extent possible in a NIST library search and the majority were identified [redacted]. The following table illustrates the summary of the semi-volatile and volatile extractables above the LOQ from the stopper using isopropanol (IPA) and hexane solvents (from the Applicant's submission):

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(b) (4)

Reviewer's Comment:
The extraction study evaluates the stopper and syringe with appropriate solvents (i.e., water at pH 2.0 and 11.0, saline at pH 4.0, isopropanol, and hexane). The analytical methods detected a number of extractable compounds. The Applicant's AET of (b) (4) mcg/mL appears appropriate as it is based on a SCT of 5 mcg/day. The Reviewer's AET is 5 mcg/mL (5 mcg/day / 1 mL/day) = 5 mcg/mL), which is greater than the Applicant's AET and as such, the Applicant's AET is more conservative and was appropriately calculated. The extraction study has been found adequate per the CMC review team. The reader is referred to the quality review for details regarding the adequacy of the extraction study methodology.

Leachable Study:
Leachables were tested using 5 stability batches that were stored for up to 18 months under normal conditions (25°C/60% RH) and used the GC-FID method revision. The leachable study used a 5 mcg/day threshold. The concerns with the utility of the leachable study from the previous review cycle were adequately addressed as per the CMC review team. The reader is referred to the quality review for details regarding the adequacy of the leachable study methodology.

No leachable compounds were detected in any samples at any timepoints over the 5 mcg/day threshold level with the exception of (b) (4). It is noted that in the product, (b) (4) is observed as an impurity but (b) (4) was not observed as an extractable from any of the extraction study evaluating the primary container closure system components. (b) (4) was detected by the GC-FID method at similar levels across batches and time points, indicating that (b) (4) might be a process-equipment related leachable. (b) (4) was identified in process components/equipment by the supplier and not coming from any of the container closure components. (b) (4)

(b) (4) The reader is referred to the quality review for further details.

Toxicological Risk Assessment:
The only leachable compound that was detected above the 5 mcg/day threshold is (b) (4) and as such, the Applicant has submitted a toxicological risk assessment for (b) (4)

The Applicant submitted stability data using commercial lots that were stored for up to 18 months under normal conditions (25°C/60% RH) and the data are illustrated in the following table (from the Applicant's submission):

Table 1: Leachants in PPQ batches on Long-term Stability (25°C/60% RH)

(b) (4)

To date, the greatest amount of (b) (4) detected was (b) (4) ppm, which is (b) (4) %.

The proposed formulation is comprised of Naloxone HCl at a concentration of 10 mg/mL in NaCl and water for injection. The proposed formulation is packaged as two (b) (4) (5 mg in 0.5 mL each). Accordingly, the maximum daily dose of naloxone delivered via the proposed product is 2 injections or 10 mg/day and the maximum daily injection volume is 1 mL. (b) (4)

There was no new data in the toxicology risk assessment of (b) (4) that was submitted in the 1st cycle review (see nonclinical review dated October 23, 2019). The reader is referred to the above nonclinical review for details. The reviewer's PDE calculation has not changed and was previously determined to be (b) (4) mcg/day, which confers an exposure margin of (b) (4)
Thus, there are no safety concerns with (b) (4)

Drug Product Specifications:
The Applicant updated the drug product release specifications that are illustrated in the following table (from the Applicant's submission):

Test	Specification	Method Type	Method
(b) (4)			

The drug product stability specifications are illustrated in the following table (from the Applicant's submission):

Test	Method	Specification
		(b) (4)

The drug product specifications in the tables above meet ICH Q3B(R2) qualification thresholds of NMT 0.5% or 200 mcg TDI, whichever is lower, for drug products with a maximum daily dose of 10 to 100 mg. The specification for (b) (4) of NMT (b) (4) ppm results in a maximum daily exposure of (b) (4) which is below the 120 mcg/day threshold of genotoxic concern per ICH M7 for acute products. The specification for (b) (4) NMT (b) (4) ppm meets ICH M7 threshold of genotoxic concern for chronic products (1.5 mcg/day). As such, there are no safety concerns with the release and stability drug product specifications.

Conclusions and Recommendations:

This is the second cycle review for this Application. There were no new nonclinical studies submitted in support of the proposed drug product. The first cycle review concluded with a Complete Response with a deficiency aimed at the lack of adequate extractable and leachable studies to support the safety of the container closure system. Specifically, the extraction studies conducted should establish an acceptable extractables leachables correlation that will assure adequate monitoring of the potential leachable compounds from the container closure system was well as providing a

toxicological risk assessment for any leachable compound detected above the 5 mcg/day threshold.

The extractables study used 24-hour reflux in five solvents including a product simulation solvent (saline pH 4.0), isopropanol, hexane, and water at pH 2.0 and pH 11.0. These extraction solvents appear harsh (isopropanol and hexane) and cover physiologic conditions (water and saline). The Analytical Evaluation Threshold (AET) was based on a Safety Concern Threshold (SCT) of 5 mcg/day. The AET was (b) (4) mcg/g for the syringe and (b) (4) mcg/g for the stopper. The analytical methods used were able to detect a variety of compounds (volatile, non-volatile and semi-volatile). The reader is referred to the quality review for the adequacy of the extraction study methodology, targeting in the leachable study, and the extractable leachable correlation.

The leachable study was performed on 5 batches that were stored for up to 18 months under normal conditions (25°C/60% RH). The only leachable that was detected above the 5 mcg/day threshold is (b) (4) The safety of (b) (4) was provided by the toxicological risk assessment from the original submission. The toxicological risk assessment of (b) (4) was not changed in this submission except for the levels of (b) (4) detected to date. The levels of (b) (4) in the stability batches increased slightly and as a result, the safety margin decreased slightly (b) (4) Thus, there are no safety concerns with (b) (4).

The drug product specifications were revised and these meet ICH Q3A(R2) qualification thresholds and as such, there are no safety concerns with the drug product specifications.

From a pharmacology toxicology perspective, the proposed drug product is recommended for approval.

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/s/

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NEWTON H WOO
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RICHARD D MELLON
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I concur.

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:	212854
Supporting document/s:	SDN 1, 5, 7, 22, 23, 25, and 35
Applicant's letter date:	December 31, 2018 (SDN 1), March 29, 2019 (SDN 5), April 19, 2019 (SDN 7), July 8, 2019 (SDN 22), July 10, 2019 (SDN 23), July 19, 2019 (SDN 25), and September 4, 2019 (SDN 35)
CDER stamp date:	December 31, 2018 (SDN 1), March 29, 2019 (SDN 5), April 19, 2019 (SDN 7), July 8, 2019 (SDN 22), July 10, 2019 (SDN 23), July 19, 2019 (SDN 25), and September 4, 2019 (SDN 35)
Product:	Naloxone HCl (5 mg/0.5 mL)
Indication:	Emergency treatment of known or suspected opioid over dosage.
Applicant:	Adamis Pharmaceuticals Corp.
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:	Swati Patwardhan

Template Version: September 1, 2010

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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Adamis Pharmaceuticals Corp. has developed a prefilled injectable device for intramuscular or subcutaneous administration of naloxone HCl (5 mg/0.5 mL). The Applicant has submitted an application via the 505(b)(2) pathway, relying upon the Agency's previous findings of safety and efficacy of (b) (4) Narcan® (NDA 16636).

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted in this NDA. There were no safety issues with the formulation as there are no novel excipients, with the drug substance and drug product specifications as the specifications did not exceed ICH Q3A(R2) and Q3B(R2) qualification thresholds, and with the elemental impurities assessment as all levels of the elemental impurities were below ICH Q3D limits.

To support the local safety of the higher concentration of the naloxone formulation, a local tolerance study in New Zealand White rabbits (previously reviewed by Dr. Newton Woo) was conducted. Minimal necrosis and regeneration along the needle tract were observed in the treatment group (10 mg/mL naloxone); however, the incidence and severity were not different when compared to a group that received the highest currently approved naloxone concentration of 5 mg/mL. Given the results from the local tolerance study, there are no safety concerns from a local perspective with the Applicant's 10 mg/mL naloxone formulation. In terms of systemic safety of the formulation, the Applicant was asked in the 74-day letter to justify the systemic safety of the new formulation with nonclinical data or with prior clinical experience. The Applicant replied and argued the systemic safety of the new formulation through a clinical literature-based justification (refer to the Medical Officer's review for the systemic safety of the formulation).

The Applicant submitted an extractables/leachables evaluation to support the safety of the container closure system. However, the extractables/leachables assessment was deemed inadequate as the Chemistry, Manufacturing, and Controls (CMC) review team identified a number of deficiencies. Briefly, there was not an acceptable extractable leachable correlation as the extractables studies failed to detect several compounds observed in the leachable study. Given this lack of correlation, this Reviewer does not have confidence that the leachables assessment evaluated for all potential leachables. Further, there were several compounds that exceeded the qualification threshold of 5 mcg/day and there were several inconsistencies in the leachable data. As such, following consultation with the CMC review team, we agree that more robust extraction studies are needed to inform what compounds should be monitored for in the leachables evaluation and more robust leachables data will be required along with a risk assessment for all compounds that exceed the qualification threshold of 5 mcg/day.

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology Toxicology perspective, the NDA for the proposed drug product, Naloxone Hydrochloride (5 mg/0.5 mL), is recommended for a Complete Response.

Deficiencies:
You have not provided appropriate extractable leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

Information Needed to Resolve Deficiencies:
Conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

- Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.

- Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

- Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.

- Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

As the recommendation for this NDA submission is a Complete Response, labeling will be addressed in the subsequent resubmission. Exposure margins in the animal data (Sections 8.1 and 13.1) will need to be changed to reflect the dosing of the Applicant's proposed product (5 mg in 0.5 mL or 10 mg/mL compared to 0.02, 0.4, and 1 mg/mL in Narcan).

2 Drug Information

2.1 Drug

CAS Registry Number
51481-60-8

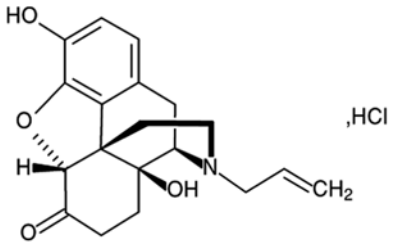
Generic Name
Naloxone hydrochloride

Code Name
N/A

Chemical Name
Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-,hydrochloride,(5)-, dihydrate 17-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dehydrate

Molecular Formula/Molecular Weight
$C_{19}H_{21}NO_4 \cdot HCl$ (b) (4)

Structure



Pharmacologic Class
Opioid antagonist (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and MFs

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company	Reviewer's Comment
16636	Narcan (Naloxone HCl)	DAAAP	0.4 and 1.0 mg/mL (IV, IM, or SC)	Withdrawn Effective (not for safety reasons)	August 20, 2010	For the complete or partial reversal of opioid depression, including respiratory depression	Adapt Pharma Operations, Ltd.	Referenced product
207534	Symjepi (Epinephrine)	DPARP	0.3 mg/0.3 mL (SC)	Approved	June 15, 2017	For the Emergency Treatment of Severe allergic Reaction (Type 1) including Anaphylaxis.	Adamis Pharmaceuticals Corp.	Submitted statement of right of reference and cross references to information and data

IND#	Drug Name	Div	Status	Indication	Company
136148	Naloxone HCl	DAAAP	Active (April 10, 2018)	Emergency treatment of known or suspected opioid over dosage	Adamis Pharmaceuticals Corp.

MF#	Subject of MF	Holder	Submit Date	Reviewer's Comment
			(b) (4)	This MF is directed at the drug substance for Naloxone HCl. The Applicant has revised the drug substance specification to meet ICH Q3A(R2) qualification thresholds and as such, the specifications are acceptable.
				Referenced by numerous approved products (NDAs and ANDAs).
				Referenced by numerous approved products (NDAs and ANDAs)

2.3 Drug Formulation

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

Table 2: Composition of Naloxone Hydrochloride Formulation and in Pre-filled Syringe

	Quantity of Syringe Contents (mg/ml)	Quantity per Dose (mg/0.5 mL)	Reference to Standard
Naloxone HCL (b) (4)	10 mg	5 mg	USP
Sodium Chloride	8.35 mg	4.17 mg	USP
Water for Injection	Q.S. to 1.0 mL	Q.S. to 0.5 mL	USP
HCL	As needed	As needed	NF, Ph. Eur., JP
(b) (4)			N/A

The proposed formulation is comprised of Naloxone HCl at a concentration of 10 mg/mL in NaCl and water for injection. There are no novel excipients in the proposed formulation. The proposed formulation is packaged as two (b) (4) (5 mg in 0.5 mL each). Accordingly, the maximum daily dose of naloxone delivered via the proposed product is 2 injections or 10 mg/day and the maximum daily injection volume is 1 mL.

2.4 Comments on Novel Excipients

There are no novel excipients in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

The following table illustrate the drug substance specifications (modified from the Applicant's submission):

Table 1: Specifications for Naloxone Hydrochloride (b) (4)

Tests	Acceptance Criteria	Method
(b) (4)		

The drug substance specification meet ICH Q3A(R2) qualification thresholds of NMT 0.15% or 1.0 mg per day intake (whichever is lower) for drug products with a maximum daily dose of ≤ 2 g/day. The specification for (b) (4) of NMT (b) (4) ppm results in a maximum daily intake of (b) (4) mcg/day (b) (4) (b) (4) of this impurity. (b) (4) contains a structural alert for genotoxicity but is below the genotoxic threshold of concern of 120 mcg/day for an acute use product and therefore the proposed specification is acceptable. The residual solvents, (b) (4) meet ICH Q3C limits. Thus, there are no nonclinical safety concerns with the drug substance or residual solvents specifications.

Drug Product

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

Table 1: Specifications for Naloxone Hydrochloride Drug Product

(b) (4)

At least 3 lots of the drug product were tested at different time points for up to 6 months of storage under normal (25ºC ± 2ºC/ 60% RH ± 5% RH) and accelerated (40ºC ± 2ºC/ 75% RH ± 5% RH) storage conditions and are summarized below (modified from the Applicant's submission):

Table 1: Drug Product Stability for 5 mg/0.5 mL Lot 18209

Protocol	18286	Product	Naloxone Injection		
Batch Number		Study Start Date	Storage Conditions		
P. 18209		07/23/18	25°C ± 2°C / 60% RH ± 5% RH		
Test	Method	Specification	Months		
			0	3	6
pH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Osmolality					
Related Substances					
Leachables					

Abbreviations: NT= Not tested, ND = Not detected

Table 2: Drug Product Stability for 5 mg/0.5 mL Lot 18209 -Accelerated

Protocol	18286	Product	Naloxone Injection						
Batch Number		Study Start Date	Storage Conditions						
P. 18209		07/23/18	40°C ± 2°C / 75±5% RH						
Test	Method	Specification	Months						
			0	1	2	3	4	6	
pH			(b) (4)						
Osmolality									
Related Substances									
Leachables									

Abbreviations: NT= Not tested, ND = Not detected

As the levels of drug product degradants are below ICH Q3B(R2) qualification thresholds of NMT 0.5% or 200 mcg TDI, whichever is lower, for drug products with a maximum daily dose of 10 to 100 mg for up to 6 months under accelerated storage conditions (40ºC ± 2ºC/ 75% RH ± 5% RH), there are no nonclinical safety concerns with the drug product specifications at release and during stability.

Container Closure System

The following figure illustrates the container closure (b) (4) for the proposed product (from the Applicant's submission):

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The proposed drug product solution is in direct contact with the glass barrel and the rubber stopper.

Extraction Studies:
The Applicant performed extraction studies on the rubber stopper that is in direct contact with the proposed drug product solution. The Applicant's Safety Concern Threshold (SCT) is set at 5 mcg/mL as recommended by the Division. (b) (4)

(b) (4)

The Applicant used a variety of extraction solvents that were selected as per USP <1663> and were shown in the following table (data from the Applicant's submission):

Extraction Solvent
Water (pH 2.0) acidic
Water (pH 6.73) neutral
Water (pH 11.0) basic
Isopropyl Alcohol/Water (50/50)
2% Nitric acid

The extraction conditions include reflux for 8 hours at high temperatures for each extraction solvent and reflect general practices. However, the reader is referred to the quality review for the definitive evaluation of the extraction methods.

The following analytical methods were used by the Applicant for the extraction studies (data from the Applicant's submission):

Analytical Method	Extractables	LOD	LOQ
LC-MS/HPLC-DAD	Non-volatile compounds	(b) (4)	
GC-MS/GC-FID	Volatile and Semi-volatile compounds		

(b) (4) These analytical methods appear to be of adequate sensitivity to detect extractables of at (b) (4) mcg/day.

The following table illustrate the extractables found in the glass syringe and rubber stopper (from the Applicant's submission):

Table 21: Summary of Extractables from the Glass Syringe and Stopper

Product Contact Component	Main Extractables
Glass Barrel	(b) (4)
Stopper	

Any extractable at less than (b) (4) ppm has not been included.

Leachables Study:
The reader is referred to the quality review for the adequacy of the leachable study methodology. Again, the Applicant's Safety Concern Threshold (SCT) is set at 5 mcg/mL (5 mcg/day). Stability lots were stored and leachables data were generated for the following 3-, 4-, and 6-month timepoint under accelerated storage conditions (40ºC ± 2ºC and 75% RH ± 5% RH) as well as 0-, 6-, 9-, 12-, 18-, 24-, and 36-month timepoint under normal storage conditions (25ºC ± 2ºC and 60% RH ± 5% RH). The Applicant did not provide a toxicological risk assessment for leachable compounds detected above the 5 mcg/day threshold.

The following table illustrates the leachable compounds detected at the 0-, 3-, 6-, and 9-month timepoint in at least 3 batches of the to-be-marketed drug product under long-term storage using normal and accelerated storage conditions (from the Applicant's submission):

Table 1: Leachants in PPQ And Confirmation batches on Long-term Stability (25°C/60% RH)

Lot Number	Time Zero	T= 3 month	T= 6 month	T= 9 month
	(b) (4)			
1838-022				
1838-031				
1838-032				
1915-022				

*Accelerated condition: 40°C/75% RH; NT: Not tested; ND: Not detected, TBD: To be determined.
**Average values are shown for duplicate values due to retest

As shown in the table above, none of the leachable compounds appear to increase over time.

The following table illustrates the maximum levels of leachables detected in the long-term stability lots (from the Applicant's submission):

Table 2: GC-FID Leachables in Long Term Stability Samples

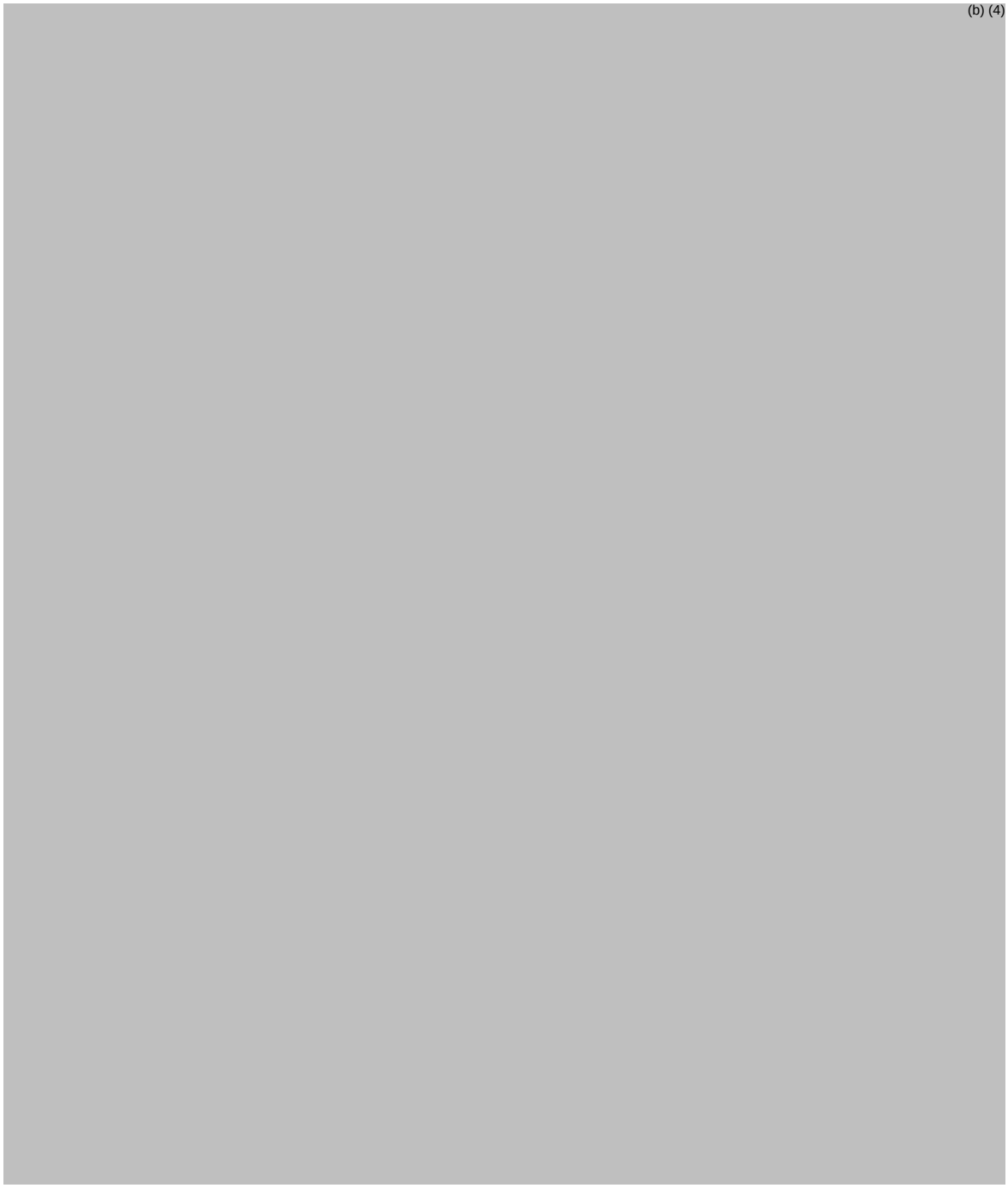
(b) (4)

As shown in the table above, (b) (4) were detected above the 5 mcg/day threshold.

Reviewer's Comments on the Extractables/Leachables Assessment:

It is important to note that none of the leachable compounds were identified in the extraction study. As such, there is a lack of an extractable leachable correlation. The quality review notes that more vigorous extractables studies to generate extractables profile to predict the leachables are needed. In addition, the CMC review team noted that there were inconsistencies between leachables data submitted to the Agency prior to and after August 16, 2019 as shown in the following table (from Dr. Jizhou Wang, Drug Product Reviewer, using data from the Applicant's submission):

(b) (4)



As shown in the table above, the leachables detected prior to and after August 16, 2019 are not the same under both the normal and accelerated storage conditions. We acknowledge that the Applicant used 3 commercial batches stored under both normal and accelerated storage conditions for up to 9 months to generate these leachables data. This Reviewer concurs with the conclusions of the quality review. The reader is referred to the quality review for further details.

Toxicological Risk Assessment:
The Applicant submitted a toxicological risk assessment of (b) (4)

(b) (4)

(b) (4) A study report for this rat toxicity study cannot be obtained via the reference in the toxicological risk assessment and as such, the data cannot be independently verified. No other toxicity data are available.

Reviewer's Comments on the Toxicological Risk Assessment:
We acknowledge the Applicant's toxicological risk assessment of (b) (4). Because the citation was not provided or able to be obtained, it cannot be independently evaluated. In addition to the information presented in the Applicant's toxicological risk assessment, (b) (4)

(b) (4)

(b) (4)

Since the extractable/leachable correlation is problematic and there are inconsistencies with the leachables data, a risk assessment for any identified leachable compound is questionable. More robust extractable and leachable studies are recommended by the CMC review team. As such, a more definitive toxicological risk assessment cannot be performed until more robust extractable and leachable studies have been conducted.

We acknowledge the Applicant used 3 commercial batches stored under both normal and accelerated storage conditions for up to 9 months to date. Moreover, a toxicological risk assessment must be performed for leachable compounds that exceed the 5 mcg/day threshold over the course of the stability under longer storage durations.

Elemental Impurities

The Applicant has submitted a risk assessment of potential elemental impurities as per ICH Q3D. The following table illustrates the outcome of this assessment (data from the Applicant's submission):

(b) (4)

As shown in the table above, the levels of each element in the elemental impurities assessment meet ICH Q3D limits. Thus, there are no nonclinical safety concerns for the elemental impurities.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed product is indicated for the treatment of known or suspected opioid overdose. The proposed product is for intramuscular and subcutaneous administration and must be administered by someone other than the patient. An initial injection is given (5 mg) and if a desired response is not obtained after 2 or 3 minutes, a repeated injection may be given. If there is still no response and additional doses are available, additional injections may be given every 2 or 3 minutes until emergency medical assistance arrives. The label is absent of a maximum daily dose of naloxone. The proposed product is for adults and pediatric patients over 1 year as well as under 1 year. For patients under 1 year, the proposed product is given to a pinched thigh muscle.

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency's previous findings of safety to Narcan® (NDA 16636). The pharmaceutical development of the proposed product was conducted under IND 136148. The concentration of naloxone in the proposed product is 10 mg/mL. At the filing meeting, the following nonclinical issues were communicated with the Applicant (see Filing Review Issues Identified dated March 13, 2019):

3. Several drug substance specifications and the drug product specification for (b) (4) exceed ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2), or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. …

4. Upon preliminary review of your extractables/leachables assessment, we see that a Safety Concern Threshold (SCT) of (b) (4) mcg/day was utilized. Amend your extractable/leachable assessment using a SCT of 5 mcg/day and provide evidence that your analytical methods used can detect compounds of at least 5 mcg/day for your proposed product. In general, the Division provides the following advice for leachable/extractables evaluations to assist Applicants in preparation for an NDA submission. …

5. An elemental impurities assessment as per ICH Q3D could not be located in your NDA submission. Provide the location or submit a complete risk assessment of elemental impurities for the drug product as per ICH Q3D that includes consideration of the process, equipment, excipients, and drug substance per USP <232/233>.

6. Based on your concentration and proposed dosing regimen, we anticipate that naloxone exposures with your drug product will exceed that of the referenced drug product. If use of your product results in systemic exposures (C_{max} or AUC) that

> exceed the highest labeled use with the reference product, an adequate safety justification is required to address the systemic safety of naloxone. In general, nonclinical studies are completed as per ICH M3(R2) to support safety. However, it may be possible to leverage prior clinical experience or literature that tested higher doses to justify the systemic safety in lieu of new nonclinical toxicology studies.

The Applicant has addressed all of these filing issues. An evaluation of the Applicant's response to Issue 6 is deferred to the Clinical Review team as the response is based on clinical data.

3 Studies Submitted

3.1 Studies Reviewed

A local tolerance study titled "Naloxone Hydrochloride: Local Tolerance Study Following Intramuscular Injection to New Zealand White Rabbits (GLP)" (Study 18-004, APC-6000) was submitted in support of the local safety of the proposed product in this NDA and was reviewed by Dr. Newton H. Woo at the time of the IND submission (see nonclinical review dated April 5, 2018 in IND 136148).

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

There were no previous reviews referenced.

4 Pharmacology

4.1 Primary Pharmacology

There were no primary pharmacology studies with intranasal naloxone submitted in this NDA.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies with intranasal naloxone submitted in this NDA.

4.3 Safety Pharmacology

There were no safety pharmacology studies with intranasal naloxone submitted in this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no dedicated PK/ADME studies with intranasal naloxone submitted in this NDA.

5.2 Toxicokinetics

There were no separate toxicokinetics studies done with intranasal naloxone submitted in this NDA.

6 General Toxicology

There were no single-dose and repeat-dose general toxicology studies done with intranasal naloxone submitted in this NDA.

7 Genetic Toxicology

There were no genetic toxicology studies with intranasal naloxone submitted in this NDA. The label for the referenced product NARCAN injection is shown below:

> NARCAN was weakly positive in the Ames mutagenicity and in the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in the *in vivo* rat bone marrow chromosome aberration study.

8 Carcinogenicity

There were no studies on the carcinogenicity of intranasal naloxone submitted in this NDA. The label for the referenced product NARCAN injection is shown below:

> Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with intranasal naloxone submitted in this NDA. The label for the referenced product NARCAN injection is shown below:

> Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category C

Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

10 Special Toxicology Studies

A local tolerance study in rabbits was submitted during the IND that was also submitted to this NDA. The study "Naloxone Hydrochloride: Local Tolerance Study Following Intramuscular Injection to New Zealand White Rabbits (GLP)" was previously reviewed by Dr. Newton Woo and is reproduced here (see nonclinical review dated April 5, 2018 for IND 136148).

Study title: Naloxone Hydrochloride: Local Tolerance Study Following Intramuscular Injection to New Zealand White Rabbits (GLP)

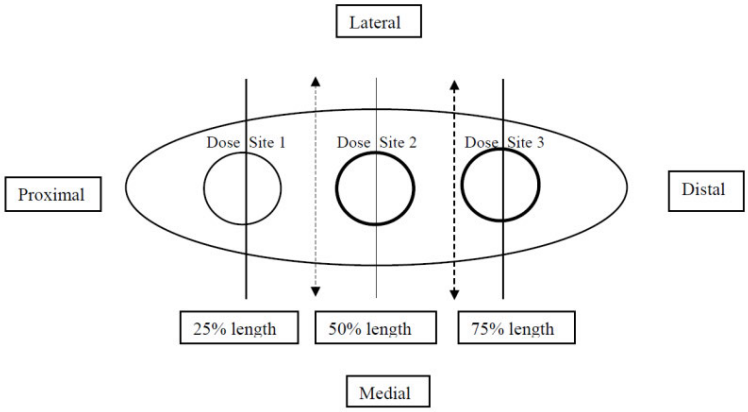
Study no.:	18-004 (APC-6000)
Study report location:	EDR (IND study report link) or EDR (NDA study report link)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 7, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Naloxone HCl 10 mg/mL, 02TOX07Feb2018-829, 100.6%; Naloxone HCl 5 mg/mL, 01tox07Feb2018-829, 101.5%

Key Study Findings

- There were no injection site findings reported to be treatment related.
- Minimal necrosis and regeneration along the needle tract were observed in the treatment group (10 mg/mL naloxone); however, the incidence and severity was not different when compared to a group that received the highest currently approved naloxone concentration of 5 mg/mL.

Methods

Doses: 0, 15 mg (test article), 6 mg (comparator)
Frequency of dosing: Single dose (3 injections)
Route of administration: IM to left quadriceps femoris muscle at three dose sites (see below)



Dose volume: Test article 0.5 mL/injection site (total 1.5 mL); Comparator 0.4 mL/injection site (total of 1.2 mL)
Formulation/Vehicle: 0.9% saline
Species/Strain: New Zealand White Rabbit/*Oryctolagus Cuniculus*
Number/Sex/Group: 3 for vehicle control and test article group
1 for comparator group
Age: 10-12 weeks of age at study initiation
Weight: 2.2 to 2.8 kg on Day 1
Satellite groups: Comparator arm testing approved concentration (5 mg/mL)
Unique study design: Included a comparator arm
Deviations from study protocol: There were no protocol deviations during the study.

Group	Animal No/sex	Test Formulation	Dosage Level (mg/animal)[1]	Dose Concentration (mg/mL)[2]	Dose Volume (mL/animal)	Dosing route and regimen
1	3 Males & 3 Females	0.9% Saline Solution (Vehicle Control)	-	-	1.5	IM, single dose in 3 injection sites of 0.5 mL
2	3 Males & 3 Females	Naloxone Hydrochloride (Test Article)	15	5 mg/0.5 mL	1.5	IM, single dose in 3 injection sites of 0.5 mL
3	1 Male & 1 Female	Naloxone Hydrochloride (Comparator)	6	2 mg/0.4 mL	1.2	IM, single dose in 3 injection sites of 0.4 mL

[1] Dosage level is expressed as the amount of Naloxone Hydrochloride delivered per animal
[2] Expressed as mg/ml of Naloxone Hydrochloride in the dosing solution

Observations and Results

Mortality

All animals were observed for mortality/moribundity twice daily (morning and afternoon).

There were no unscheduled deaths.

Clinical Signs

Detailed clinical observations were recorded once prior to dosing on Day 1, at least 4 h after doing on Day 1, and twice daily thereafter, at least 4 h apart. Animals were only observed once on Day 8, prior to necropsy.

There were a number of skin findings (abrasions, scabs, redness) that were attributed to the shaving procedure. Findings did not change over the course of the study and were not dose-dependent.

Injection Site Scoring

Injection sites were scored once prior to dosing on Day 1, at least 4 h after doing on Day 1, and twice daily thereafter, at least 4 h apart, and once on Day 8 (prior to necropsy), following the scale below.

SKIN OBSERVATIONS	SCORE
Erythema and Eschar	-
No Erythema	0
Slight Erythema	1
Slight but Well-Defined Erythema	2
Moderate to Severe Well-Defined Erythema	3
Severe Erythema with Eschar	4
Edema	-
No Edema	0
Slight Edema	1
Slight but Well-Defined Edema	2
Moderate Well-Defined Edema (edematous area raised approximately 1.0 mm)	3
Severe Edema (edematous area raised more than 1.0 mm and/or extending beyond area of exposure to test material)	4
Other Skin Observations:	-

There were no injection site findings attributed to treatment.

Body Weights

Body weights were recorded prior to dosing once during acclimation, once daily during the treatment and observation period, and prior to scheduled termination.

Body weight was not affected by treatment.

Histopathology

All surviving animals were euthanized for tissue collection on Day 8. At necropsy, a systemic examination of the animal's general physical condition, body orifices, and external and internal organs and tissues was performed. The left quadriceps femoris injection sites were collected, tissue partially slices to indicate separation of Dose Sites 1, 2, and 3 and retained in formalin.

Adequate Battery
Yes

Peer Review
No

Histological Findings
The left and right quadriceps femoris muscles were processed histologically. Microscopic examination was performed on these tissues in all animals to assess local tissue reaction included degeneration, necrosis, inflammation, hemorrhage, edema and fibrosis.

Microscopic findings present at the injection sites included minimal myocyte necrosis and minimal myocyte regeneration (see table below) and occurred in a linear pattern along the needle tract.

Summary of microscopic finding incidences*

Microscopic Finding	Males			Females		
	0	10 mg/mL	5mg/mL (comparator)	0	10 mg/mL	5mg/mL (comparator)
Myocyte necrosis, minimal	0/9	2/9	2/3	0/9	3/9	1/3
Myocyte regeneration, minimal	1/9	3/9	2/3	0/9	5/9	1/3

* based on total number of injection sites evaluated (9 for main study group = 3 injection sites x 3 animals; 3 for comparator group = 3 injection sites x 1 animal)

Reviewer Comment: Given that the findings were confined to the needle tract and that the incidence and severity of findings were not dose-dependent, this Reviewer is in agreement with the Sponsor that the findings reported above were likely related to the physical disruption of the muscle by the injecting needle.

Special Evaluation

Special stains were not required to further characterize lesions and changes.

Dosing Solution Analysis

Immediately following dosing on Day 1, two vials per formulation were retained and shipped for analysis. The purity levels of the submitted samples were within acceptable limits.

11 Integrated Summary and Safety Evaluation

No nonclinical studies were submitted in this NDA. There were no safety issues with the formulation as there are no novel excipients, the drug substance and drug product specifications as the specifications did not exceed ICH Q3A(R2) and Q3B(R2) qualification thresholds, and the elemental impurities assessment as all levels of the elemental impurities were below ICH Q3D limits.

A local tolerance study in New Zealand White rabbits was submitted in IND 136148 and was previously reviewed by Dr. Newton Woo. New Zealand White rabbits were administered the proposed product (10 mg/mL), the comparator Naloxone HCl (5 mg/mL), or control (0.9% saline). Minimal necrosis and regeneration along the needle tract were observed in the treatment group (10 mg/mL naloxone); however, the incidence and severity were not different when compared to a group that received the highest currently approved naloxone concentration of 5 mg/mL.

The extractables/leachables assessment was not performed adequately. The Chemistry, Manufacturing, and Controls (CMC) review team has a number of deficiencies. Briefly, there is the extractable leachable correlation is not adequate since the extractables studies failed to detect any of the leachables observed in the leachable study and there are inconsistencies in the leachable data. As such, more robust extractables studies to generate extractables profile to predict the leachables and more robust leachables studies to properly identify leachable compounds are needed.

From a Pharmacology Toxicology perspective, the proposed drug product, Naloxone Hydrochloride (5 mg/0.5 mL), is recommended for a Complete Response due to inadequate extractables leachables data that was submitted to support the safety of the container closure system.

12 Appendix/Attachments

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARLIC K HUYNH
10/23/2019 01:10:52 PM

NEWTON H WOO
10/23/2019 01:13:41 PM

RICHARD D MELLON
10/23/2019 01:15:41 PM